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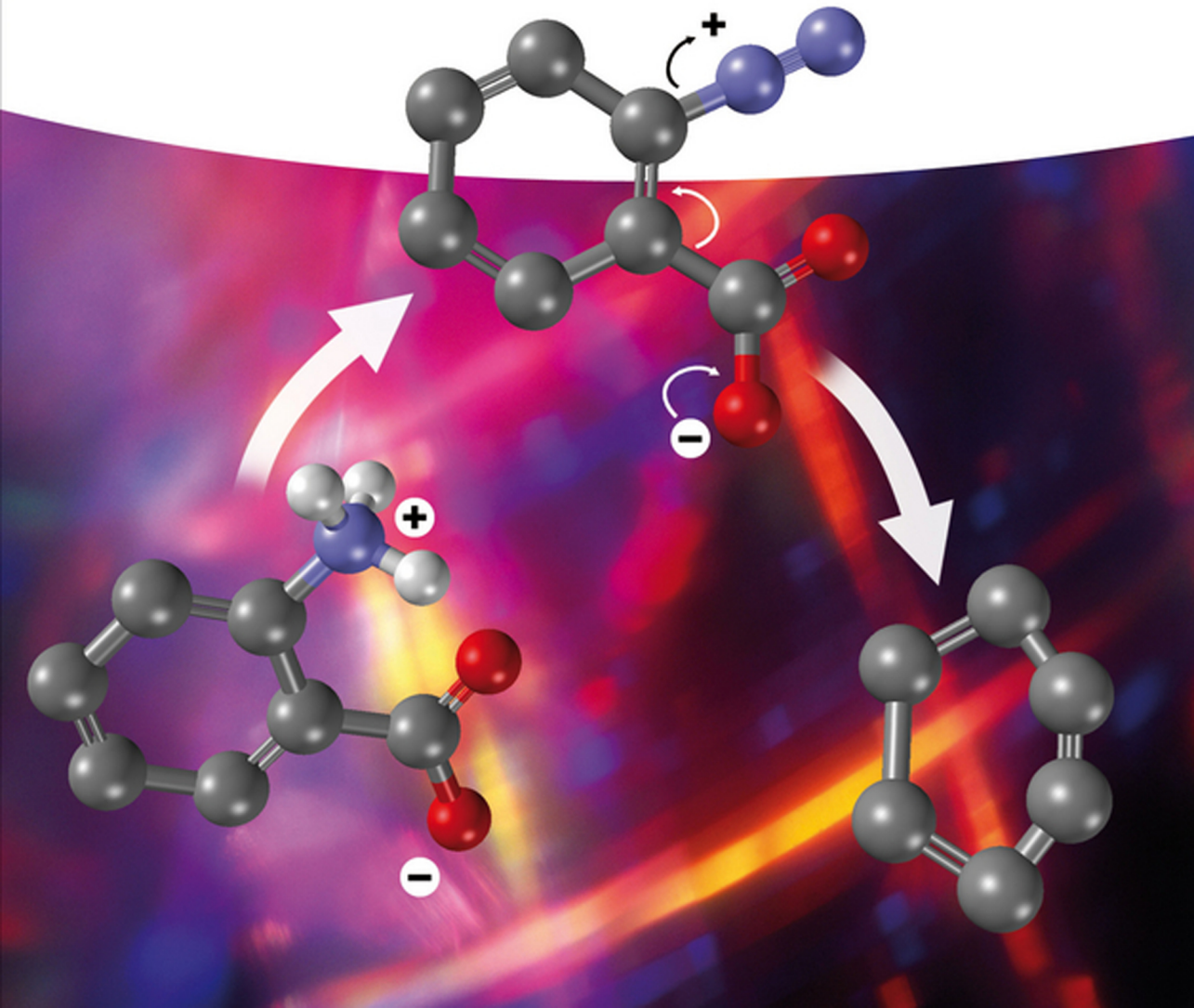
Maya Shankar Singh

Reactive Intermediates in Organic Chemistry

Structure, Mechanism, and Reactions



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Structure, Mechanism, and Reactions

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Contents

Preface

Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties, which attracts particular attention because of its immense importance to life and society. Organic synthesis is a creative science involving the construction and cleavage of bonds, the strategies for which represent the central theme in organic synthesis. More than any other branch of organic chemistry, synthesis has improved our understanding of the structure, dynamics, and transition of molecules. Most synthetic problems have more than one solution, and the trick is to judge which of these is likely to have the best chance of success. Even the most experienced chemists develop routes that work well on paper but fail miserably in the laboratory. However, there are some guidelines and principles that are helpful in designing a suitable route for a particular synthesis. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus to understand structure and mechanism of a particular reaction. For synthetic chemists it is very important to understand in detail what is going on when the molecules in the starting materials react with each other and create the molecules characteristic of the product. Knowledge about mechanisms makes it possible to develop better and less expensive methods to prepare products of technical importance.

Writing a textbook of any level is always a challenging mission. This book has been designed in view of the growing importance of intermediates in the synthesis of natural and/or non-natural molecules. The ideas of functionality and stereochemistry have their origins in the second half of the nineteenth century, and the concepts of bonding and reaction mechanism undoubtedly belong to the twentieth century. The goal of this text is to incorporate basic conceptual tools and recent advances in the area of organic synthesis and particularly in the field of reactive intermediates, which are the key steps of any transformation. A systematic understanding of the mechanisms of organic reactions is necessary as without it organic chemistry is chaos, and impossible to learn.

Theory, mechanism, synthesis, structure, and stereochemistry are discussed throughout the book in a qualitative to semiquantitative fashion. During the writing of this book I have always tried to anticipate the questions of a student and to challenge them to think about the subject, motivating them to understand and to realize why, rather than just memorizing material. Chemists present chemistry

in terms of structural diagrams and for this reason all reactions have been drawn using curly arrows; the handwriting of chemistry. Curved arrows and chemical reactions introduce students to the notational systems employed in all of the mechanistic discussions in the text. Such a course is frequently offered as a course material in organic chemistry at the undergraduate and beginning graduate level. I guess one will enjoy many fruitful hours of insight in the course of studying this book and I welcome your constructive comments on its content and approach. In attempting to accomplish these objectives, my approach is substantially different from currently available titles.

I have tried to put equal weight to the three basic fundamental aspects of the study of reactive intermediates, that is, reactions, mechanisms, and stereochemistry. The organization is based on these concepts, so that students can understand the large number of organic reactions based on relatively few principles. Accordingly, this book is divided into seven chapters. The first gives a brief introduction dealing with some basic, very frequently used terms, concepts of steric and electronic effects, and sites of chemical reactivity. The student is also told why such information will be important in the study of a particular reaction mechanism. Chapters 2–6 cover specific reactive intermediates in detail regarding their structure, geometry, generation, stability, and reactions. Chapter 7 gives a brief survey of the miscellaneous intermediates. End-of-chapter summaries review the major concepts of the chapter in a concise narrative format to help readers to understand the key points. The problems at the end of each chapter represent the application of concepts, rather than a review of material explicitly presented in the text. They are designed so that students can test themselves on the material just covered before they go on to the next section. I hope the level of difficulty will present a considerable challenge to students. These problems allow students to practice and test their mastery of core principles within each chapter. A concerted effort was made to make none of the problems so difficult that the student loses confidence.

I would greatly appreciate comments and suggestions from users that will improve the text or correct errors. I can only conclude by expressing my wish that others will enjoy using this text as much as I have enjoyed writing it. In particular, I want to thank the many wonderful and talented students I have had over the years, who taught me how to be a teacher and researcher. I also want to thank the dedicated people at Wiley-VCH, Germany, Dr. Anne Brennführer (Commissioning Editor), Lesley Belfit (Project Editor), and Claudia Nussbeck (Editorial Assistant), for their truly superior editorial ability and for keeping me happy and on track.

Finally, I am grateful to my wife Meera and my son Keshav whose contributions to the project are beyond measure, and so I thank them for their understanding, love, encouragement, and assistance during the lengthy process of writing this book.

1
Introduction

Chemistry is an old science that influences every aspect of life on earth (from toothpaste to life-saving medicines) because just about everything that we can touch and feel is made of chemicals, which is why it is known as the *mother science* or *central science*. The chemical cornucopia (a hollow basket filled with various kinds of festive materials) is truly impressive. While chemistry is, indeed, an old subject (~1000 BC), modern chemistry (Antoine-Laurent de Lavoisier (1743–1794), the ''Father of modern chemistry'') is ~230 years old, while organic synthesis is only about 150 years old. The essential feature of this central science is synthesis. The chemist who designs and completes an original and aesthetically pleasing synthesis is like the composer, artist, or poet, who with great individuality fashions new forms of beauty from the interplay of mind and spirit.

Chemistry occupies a unique middle position between physics and mathematics on the one side and biology, ecology, sociology, and economics on the other. It is said that chemistry is reducible into physics and finally mathematics. On the one hand, it deals with biology and provides explanations for how molecules determine the processes of life. On the other hand, it mingles with physics as well as mathematics, and finds explanations for chemical phenomena in the fundamental processes and particles of the universe:

> ''The greatest scientific advance of the last 50 years is the way biology is becoming a molecular science (chemistry) . . . .''

Chemistry is playing a vital role in every area of our increasingly technological society that links the familiar with the fundamental.

Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. It is the science of molecules, but organic chemistry is something more, that is, a tentative attempt to understand the chemistry of life. The task of the organic chemist is to make tools (molecules), that is, the art and science of constructing the molecules of nature available for various uses. Essentially all chemical reactions that take place in living systems, including in our own bodies, are organic reactions because the molecules of life – proteins, enzymes, vitamins, lipids, carbohydrates, and nucleic acids – all are organic compounds. All

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things originating from living things are organic but anything containing carbon is also organic. The food we eat, the wood to make our homes, the clothing we wear (whether natural cotton or polyester), gasoline, rubber, plastics, medicines, pesticides, herbicides, all are made from organic compounds. We can thank organic chemistry for making our life easier in the modern age, and furthermore a responsibility lies on the shoulders of synthetic organic chemists to make life even better.

Chemistry is a vibrant subject filled with light, colors, fragrance, flavors, action, and excitement; a subject that begs to be taught by the points of inquiry method. When you picked up this book, your muscles were performing chemical reactions on sugars to give you the energy you required. As you go through this book, your eyes are using an organic compound (11-*cis*-retinal) to switch visible light into nerve impulses. Gaps between your brain cells are being bridged by simple organic molecules (neurotransmitter amines) so that nerve impulses can be passed around your brain. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus to understand structure and mechanism. Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties.

To understand organic chemistry one must be familiar with two languages. One is the structure and representation of molecules. The second is the description of the reaction mechanism in terms of curly arrows. The first is static and the second dynamic. Synthesis is considered difficult because you need to have a grasp of lots of reactions. Well, if you have an understanding of simple basic organic chemistry plus a few special ''tools'' you can do a surprising amount and enjoy the challenge. A detailed understanding of reactive intermediates is at the heart of chemical transformations, and thus of modern synthetic chemistry. The term reactive further implies a certain degree of instability of the species. Reactive intermediates are typically isolable only under special conditions, and most of the information regarding the structure and properties of reactive intermediates comes from indirect experimental evidence. Reaction mechanisms are a fundamental and most important part of organic chemistry, telling us about the interaction between electron-deficient and electron-rich species. The functional group is the site of reactivity in a molecule. By looking at the structure of the functional group, it is possible to predict the kind of reactions it will undergo.

A chemical reaction at the molecular level is an event in which two molecules collide in such a way as to break one or more of their bonds and make one or more new bonds, and hence new molecules. The sequence and timing of the bond-breaking and bond-making processes will be important to our understandings of the reactions. To find out how molecules react with each other and how to predict their reactions we need to know the *reaction mechanism*. Organic chemistry encompasses a very large number of compounds (many millions). To recognize these actors (compounds), we turn to the roles they are inclined to play in the

scientific drama staged by the multitude of chemical reactions that define organic chemistry. We begin by defining some basic terms that will be used very frequently as this subject is elaborated:

Chemical reaction: A chemical reaction is a process that leads to the transformation of one set of chemical substances into another. Classically, chemical reactions encompass changes that strictly involve the motion of electrons in the forming and breaking of chemical bonds between atoms, and can often be described by a chemical equation. A transformation results in the change of composition, constitution, and/or configuration of a compound (referred to as the *reactant* or *substrate*) by making or breaking of carbon–carbon (C–C), carbon–hydrogen (C–H), and/or carbon–heteroatom (C–X) bond(s). Chemical reactions are described with chemical equations, which graphically present the starting materials, end products, and sometimes intermediate products and reaction conditions.

Reactant or substrate: The starting material undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.

Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic, small or large, or gas, liquid, or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.

Product(s): In a chemical reaction, substances (elements and/or compounds) called *reactants* are changed into other substances (compounds and/or elements) called *products*, the final form taken by the major reactant(s) of a reaction. Product(s) are formed during chemical reactions as reagents are consumed. Products have lower energy than the reagents and are produced during the reaction according to the second law of thermodynamics.

Reaction conditions: Reaction conditions summarize the experimental details relating to how transformations are carried out in laboratory settings; the optimum environmental conditions are needed, such as temperature, pressure, time, catalysts, and solvent under which a reaction progresses smoothly.

Catalysts: Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions. A catalyst may participate in multiple chemical transformations. Catalysts that speed up the reaction are called *positive catalysts*. Substances that slow a catalyst's effect in a chemical reaction are called *inhibitors*. Substances that increase the activity of catalysts are called *promoters*, and substances that deactivate catalysts are called *catalytic poisons*. Catalytic reactions have a lower rate-limiting free energy of activation than the corresponding uncatalyzed reaction, resulting in higher reaction rate at the same temperature.

Electrophile: An electron-deficient atom, ion, or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile. In general, electrophiles (literally *electron-lover*) are positively charged or neutral species that participate in a chemical reaction by accepting an electron pair in order to bond to a nucleophile. Because electrophiles accept electrons, they are Lewis acids.

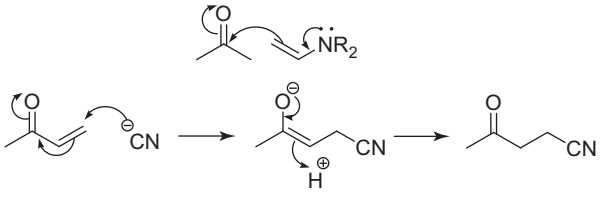
Nucleophile: An atom, ion, or molecule that has an electron pair that may be donated in bonding to an electrophile or Lewis acid; all nucleophiles are Lewis bases. **Nucleophilicity**, sometimes referred to as *nucleophile strength*, refers to a substance's nucleophilic character and is often used to compare the affinity of atoms.

The terms *nucleophile* and *electrophile* were introduced by Christopher Kelk Ingold in 1929, replacing the terms *cationoid* and *anionoid* proposed earlier by A.J. Lapworth in 1925.

1.1 Reaction Mechanism and Reaction Arrows

Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course. This is best accomplished by perceiving the reaction pathway or mechanism of a reaction. A detailed description of the changes in structure and bonding that take place during a reaction and the sequence of such events are called the *reaction mechanism*. Here, you will meet mechanisms, the dynamic language used by chemists to talk about reactions. A reaction mechanism should include a representation of plausible electron reorganization as well as the identification of any intermediate species that may be formed as the reaction progresses. Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and nonbonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a *mechanism*. In general, two kinds of curved arrows are used in drawing mechanisms. A curly arrow represents the actual movement of a pair of electrons from a filled orbital into an empty orbital, in either an intermolecular or intramolecular fashion. The tail of the arrow shows the source of the electron pair (highest occupied molecular orbital, HOMO) such as a lone pair or a pi (π) bond or a sigma (σ) bond. The head of the arrow indicates the ultimate destination of the electron-pair, which will either be an electronegative atom that can support a negative charge (a leaving group) or an empty orbital (LUMO, lowest unoccupied molecular orbital) when a new bond will be formed or an antibonding orbital (π^* or σ^*) when that bond will break.

A full head on the arrow indicates the movement or shift of an electron pair:



A partial head (fishhook) on the arrow indicates the shift of a single electron:

Chemists also use *other arrow symbols* for other purposes, and it is essential to use them correctly. These arrows include the reaction arrow: ⟶; the equilibrium arrow: ⇌; and the resonance arrow: ⟷.

Charge is conserved in each step of a reaction. If we start with neutral molecules and make a cation, we must make an anion too. Charge cannot be created or destroyed. If our starting materials have an overall charge plus (+) or minus (–) then the same charge must appear in the products.

It is a prerequisite for any mechanistic investigation that the reactants, all products, and the stoichiometry of the reaction are known. Many cases can be found in the literature where false mechanistic conclusions were drawn because this principle was neglected. Side products, even if very minor, can give useful hints concerning the mechanism as they are often derived from a common intermediate in a parallel reaction. Long-lived intermediates can be distinguished from products by analyzing the reaction mixture not only at the end but also as a function of the reaction time. Reactions where intermediates can be isolated in a normal workup are rather rare. More often, intermediates might be observable by spectroscopic techniques. The existence of short-lived intermediates or of intermediates occurring after the rate-determining step (RDS) can still be demonstrated by trapping reactions or by special techniques such as matrix isolation.

1.2
Properties and Characteristics of a Reaction

In an effort to understand how and why reactions of functional groups take place in the way they do, chemists try to discover just how different molecules and ions interact with each other as they come together. To this end, it is important to consider the various properties and characteristics of a reaction that may be

observed and/or measured as the reaction proceeds. The most common and useful of these are covered below.

1.2.1 Reactants and Reagents

Variations in the structure of the reactant and reagent may have a marked influence on the course of a reaction.

1.2.2 Product Selectivity

1) **Regioselectivity:** Regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions. It is often the case that addition and elimination reactions may proceed to more than one product. If one possible product out of two or more is formed preferentially, the reaction is said to be regioselective.
2) **Stereoselectivity:** Stereoselectivity is the property of a chemical reaction in which a single reactant forms an unequal mixture of stereoisomers during the non-stereospecific creation of a new stereocenter or during the non-stereospecific transformation of a preexisting one. The selectivity arises from differences in steric effects and electronic effects in the mechanistic pathways leading to the different products. Stereoselectivity can vary in degree but it can never be total since the activation energy difference between the two pathways is finite. If the reaction products are such that stereoisomers may be formed, a reaction that yields one stereoisomer preferentially is said to be stereoselective. An **enantioselective** reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme, or a chiral reagent. The degree of relative selectivity is measured by the enantiomeric excess (ee).
   A **diastereoselective** reaction is one in which one diastereomer is formed in preference to another (or in which a subset of all possible diastereomers dominates the product mixture), establishing a preferred relative stereochemistry. In this case, either two or more chiral centers are formed at once such that one relative stereochemistry is favored or a preexisting chiral center (which need not be optically pure) biases the stereochemical outcome during the creation of another. The degree of relative selectivity is measured by the diastereomeric excess (de).
   Stereoconvergence can be considered an opposite of stereoselectivity, when the reaction of two different stereoisomers yields a single product stereoisomer.
3) **Stereospecificity:** In chemistry, stereospecificity is the property of a reaction mechanism that leads to different stereoisomeric reaction products from different stereoisomeric reactants, or which operates on only one (or a subset) of the stereoisomers. This term is applied to cases in which stereoisomeric

reactants behave differently in a given reaction. The quality of stereospecificity is focused on the reactants and their stereochemistry; it is concerned with the products too, but only as they provide evidence of a difference in behavior between reactants.

4) **Chemoselectivity** is the ability of a reagent to react selectively with one functional group in the presence of another similar functional group. An example of a chemoselective reagent is a reducing agent that can reduce an aldehyde and not a ketone. In cases where chemoselectivity cannot be achieved, the functional group that needs to be prevented from participating in the reaction can be protected by converting it into a derivative that is unreactive to the reagent involved. The usual strategy employed to allow for such selective differentiation of the same or similar groups is to convert each group into a masked (protected) form, which is not reactive, but can be unmasked (deprotected) to yield the group when necessary.

1.2.3 Reaction Characteristics

1) **Reaction rates:** Some reactions proceed very rapidly, and some so slowly that they are not normally observed. Among the variables that influence reaction rates are temperature (reactions are usually faster at a higher temperature), solvent, and reactant/reagent concentrations. Useful information about reaction mechanisms may be obtained by studying the manner in which the rate of a reaction changes as the concentrations of the reactant and reagents are varied. This field of study is called *kinetics*.
2) **Intermediates:** Many reactions proceed in a stepwise fashion. This can be convincingly demonstrated if an intermediate species can be isolated and shown to proceed to the same products under the reaction conditions. Some intermediates are stable compounds in their own right; however, some are so reactive that isolation is not possible. Nevertheless, evidence for their existence may be obtained by other means, including spectroscopic observation or inference from kinetic results.

1.2.4 Factors that Influence Reactions

It is helpful to identify some general features of a reaction that have a significant influence on its facility. Some of the most important of these are:

1) **Energetics:** The potential energy of a reacting system changes as the reaction progresses. The overall change may be **exothermic** (energy is released) or **endothermic** (energy must be added), and there is usually an **activation energy** requirement as well. Tables of standard bond energies are widely used by chemists for estimating the energy change in a proposed reaction. As a

rule, compounds constructed of strong covalent bonds are more stable than compounds incorporating one or more relatively weak bonds.

2) **Electronic effects:** The distribution of electrons at sites of reaction (functional groups) is a particularly important factor. Electron-deficient species or groups, which may or may not be positively charged, are attracted to electron-rich species or groups, which may or may not be negatively charged. We refer to these species as electrophiles and nucleophiles, respectively. In general, *opposites attract and like repel*.

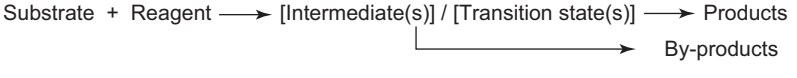
The charge distribution in a molecule is usually discussed with respect to two interacting effects: an **inductive effect**, which is a function of the electronegativity differences that exist between atoms (and groups), and a **resonance effect**, in which electrons move in a discontinuous fashion between parts of a molecule. Other factors that influence a reaction include:

1) **Steric effects:** Steric effects arise from the fact that each atom within a molecule occupies a certain amount of space. If atoms are brought too close together there is an associated cost in energy due to overlapping electron clouds and this may affect the molecule's preferred shape (conformation) and reactivity. When they are crowded together, van der Waals repulsions produce an unfavorable **steric hindrance**. Steric hindrance occurs when the large size of groups within a molecule prevents chemical reactions that are observed in related molecules with smaller groups. Steric hindrance may influence conformational equilibria, as well as destabilizing transition states of reactions. When a Lewis acid and Lewis base cannot combine due to steric hindrance, they are said to form a frustrated Lewis pair.

   The structure, properties, and reactivity of a molecule depend on straightforward bonding interactions including covalent bonds, ionic bonds, hydrogen bonds, and lesser forms of bonding. This bonding supplies a basic molecular skeleton that is modified by repulsive forces. These repulsive forces include the steric interactions described above. Basic bonding and steric factor are at times insufficient to explain many structures, properties, and reactivity. Thus steric effects are often contrasted and complemented by electronic effects implying the influence of effects such as induction, conjunction, orbital symmetry, electrostatic interactions, and spin state. There are more esoteric electronic effects but these are among the most important when considering structure and chemical reactivity.
2) **Stereoelectronic effects:** Stereoelectronic effects are simply the chemical and kinetic consequences of orbital overlap. In many reactions atomic or molecular orbitals interact in a manner that has an optimal configurational or geometrical alignment. Departure from this alignment inhibits the reaction. Stereoelectronic effects guide the geometry and reactivity pattern of most functional groups.
3) **Solvent effects:** The nature of the solvent used in reactions often has a profound effect on how the reaction proceeds. Solvent effects are the group of effects that a solvent has on chemical reactivity. Solvents can have an effect on solubility,

stability, and reaction rates. Thus, choosing the appropriate solvent allows for thermodynamic and kinetic control over a chemical reaction. Most reactions are conducted in solution and the solvent selected for a given reaction may exert a strong influence on its course. A solute dissolves in a solvent when it forms favorable interactions with the solvent. This dissolving process depends upon the free energy change of both solute and solvent. The free energy of solvation is a combination of several factors. Different solvents can affect the equilibrium constant of a reaction by differential stabilization of the reactant or product. The ionization equilibrium of an acid or a base is affected by a solvent change. The effect of the solvent is not only due its acidity or basicity but also because of its dielectric constant and its ability to preferentially solvate and thus stabilizes certain species in acid–base equilibria. A change in the solvating ability or dielectric constant can thus influence the acidity or basicity.

Many organic reactions seem at first glance to be highly complex, taking place in several stages involving formation of one or more transient intermediates, which undergo further reaction until the final product is reached. Such reactions are termed *multistep reactions*. A description of the step-by-step process, that is, its sequence of steps and the details of electron movement, bond breaking and making, and the timing by which reactants are changed into products is called the *mechanism of the reaction*. The mechanism will be clearer if ''curved arrows'' are used to show the movement of the electrons from an electron-rich center to an electron-deficient center. The organic starting material, in which a change of functional group is involved, is called the *substrate* or *reactant*, which is attacked by the **reagent**. The reagent is very commonly an inorganic or very simple organic substance and is used to create the desired transformation in the substrate:



For chemists it is very important to understand in detail what is going on when the molecules in the starting materials react with each other and create the molecules characteristic of the product. This is the process of determining the mechanism of the reaction. Knowledge about mechanisms makes it possible to develop better and less expensive methods to prepare products of technical importance.

Reactive intermediates are short lived and their importance lies in the assignment of reaction mechanisms on the pathway from the starting substrate to stable products. The lifetimes of these intermediates range from 10^{-12} s upwards. These intermediates may be formed by attack of various reagents on substrates, by dissociation of organic compounds, or by promotion of molecules to excited states by absorption of light or interaction with high-energy radiation. These reactive intermediates are, in general, not isolated but are detected by spectroscopic methods or trapped chemically or their presence is confirmed by indirect evidence. These intermediates may be formed by attack of various reagents on substrates, by

dissociation of organic compounds, or by promotion of molecules to excited states by absorption of light. Many of the reactions of organic chemistry proceed by way of reactive intermediates according to the following schematic equation:

$$\text{Starting material} \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} \text{Intermediate(s)} \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} \text{Product(s)}$$

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]}$$

where K_{eq} is equal to the relative concentrations of products and reactants at equilibrium. If the products are more stable (have lower free energy) than the reactants, there will be a higher concentration of products than reactants at equilibrium ($K_{eq} > 1$). In contrast, if the reactants are more stable than the products, there will be a higher concentration of reactants than products at equilibrium ($K_{eq} < 1$). In most of the cases of interest to us in this book $k_2 > k_1$ otherwise the intermediate would represent an isolable compound or a species in rapid equilibrium with reactants. In general, reactive intermediates correspond to a relatively shallow dip in a free energy versus reaction coordinate diagram and they can either proceed to products faster than returning to starting material, that is, $k_2 > k_{-1}$, or vice versa, $k_{-1} > k_2$.

Much effort has been expended in certain famous test cases such as with ''nonclassical'' carbocations in deciding whether an intermediate actually exists. It is usually considered that a reactive intermediate is significant if the depth of the free energy well containing it is sufficient to prevent every molecular vibration along the reaction coordinate proceeding back to reactants or forward to products. Generally, the rate of a multistep reaction depends on the slowest step (i.e., highest energy step) in a multistep chemical reaction and is called the *rate-limiting step* or *rate-determining step* of the reaction that controls the overall rate of the reaction. The rate of a reaction is dependent on the following three factors:

1) The number of effective collisions taking place between the reacting molecules in a given period of time. The greater the number of collisions, the faster the reaction.
2) The fraction of collisions that occur with sufficient energy to get the reacting molecules over the energy barrier (not all collisions between molecules lead to chemical change).
3) The fraction of collisions that occur with the proper orientation.

There are two ways of speeding reactions up: (i) we can heat the reactants so that a higher proportion of them have the activation energy on collision; (ii) we can add a suitable catalyst to the reaction mixture. The rate of a reaction in solution is almost always dependent on the nature of the solvent. Two characteristics of the solvent play a part in determining the relative free energies of reactant and transition state, and therefore the rate of the reaction. First, energy is needed to separate the unlike charges and the amount of energy decreases as the dielectric

constant of the solvent increases. Second, the solvating power of the solvent is important. The transition state can be stabilized by solvation of both the developing positive and the developing negative ions with protic solvents.

Whenever a reaction can give more than one possible products, two or more reactions are in competition. One reaction predominates when it occurs more rapidly than the competing reactions. The rate of a chemical reaction can be defined as the number of reactant molecules converted into products in a given time. As the reactants change into products, they pass through an unstable state of maximum free energy, called the *transition state* or *activated complex* that is not stable, having transient existence, and cannot be isolated. The transition state is a molecular complex in which reactants have been forced together in such a way that they are ready to collapse into products. The structure of the transition state is between the structure of the reactants and the structure of the products. The transition state represents an energy maximum on passing from reactants to products; it is not a real molecule, having partially formed/broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules. *Intermediates* are molecule or ion that represent a localized energy minimum having fully formed bonds and existing for some finite length of time with some stability. The transition state has a higher energy than either the reactants or products. The energy required to reach the transition state from the reactant energy minimum is defined as the *activation energy*. This activation energy, also called the *energy barrier* for a reaction, is the minimum energy molecules must have if they are to react. A reaction coordinate diagram describes the energy changes that take place in each of the steps (Figure 1.1).

The field of chemistry that describes the properties of a system at equilibrium is called *thermodynamics*. It is helpful to look at the driving forces that cause a given reaction to occur such as the changes in energy content of products versus reactants (thermodynamics) and the pathway, and rate by which the molecules

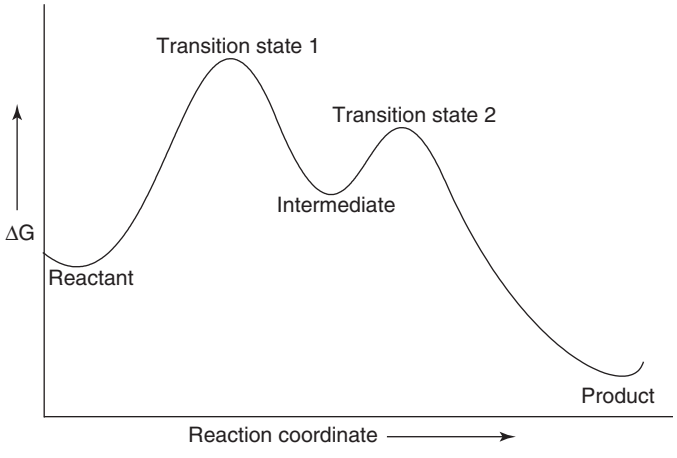


Figure 1.1 Reaction profile showing the reaction intermediate where $k_2 > k_{-1}$.

become transformed from reactants into products (kinetics). Thermodynamics and kinetics are important features in describing how various energy contents affect reactions. Free energy has both enthalpy (bond energy) and entropy (disorder) components. Enthalpy changes are almost always important in chemical reactions, but entropy changes are usually significant in organic reactions only when the number of product molecules differs from the number of reactant molecules. The product that is forms fastest is called the *kinetic product* and the most stable product is called the *thermodynamic product*. Thus, the nitration of methylbenzene is found to be *kinetically controlled*, whereas the Friedel–Crafts alkylation of the same species is often *thermodynamically controlled*. The form of control that operates may also be influenced by the reaction condition; thus the sulfonation of naphthalene with concentrated H_2SO_4 at 80 °C is essentially *kinetically controlled*, whereas at 160 °C it is *thermodynamically controlled*.

Selectivity means that one of several reaction products is formed preferentially or exclusively, for example, reaction product **A** is formed at the expense of reaction product **B**. Selectivities of this type are usually the result of a *kinetically controlled reaction process*, or "**kinetic control**." This means that they are usually not the consequence of an equilibrium being established under the reaction conditions between the alternative reaction products **A** and **B**. In this latter case one would have a *thermodynamically controlled reaction process*, or "**thermodynamic control**." If the reactions leading to the alternative reaction products are one step, the most stable product is produced most rapidly, that is, more or less selectively. This type of selectivity is called *product-development control*.

From the value of K_{eq} we can calculate the change in free energy. The difference between the free energy content of the products and the free energy content of the reactants at equilibrium under standard conditions is called the *Gibbs standard free energy change* ($\Delta G°$). If $\Delta G°$ is negative, that is, less than zero, the reaction will be an **exergonic reaction** (the transition state is similar to the *starting material* with respect to energy and structure) and if $\Delta G°$ is positive, that is, greater than zero, the reaction will be an **endergonic reaction** (the transition state is similar to the *product* with respect to energy and structure). The Gibbs standard free energy change ($\Delta G°$) has an enthalpy ($\Delta H°$) component and an entropy ($\Delta S°$) component:

$$\Delta G^{o} = \Delta H^{o} - T\Delta S^{o}$$

The enthalpy term ($\Delta H°$) is the heat given off or the heat absorbed during the course of the reaction, usually given in kilocalories (or kilojoules) per mole, and T is the absolute temperature. Heat is given off when bonds are formed, and heat is consumed when bonds are broken. A reaction with a negative $\Delta H°$ is called an *exothermic reaction* (weaker bonds are broken and stronger bonds are formed) and a reaction with a positive $\Delta H°$ is called an *endothermic reaction* (stronger bonds are broken and weaker bonds are formed). Reactions tend to favor products with the lowest enthalpy (those with the stronger bonds). Entropy ($\Delta S°$) is defined as the degree of disorder, which is a measure of the freedom of motion or randomness in a system. Restricting the freedom of motion of a molecule causes a decrease in entropy. For example, in a reaction in which two molecules come together to

form a single molecule, the entropy in the product will be less than the entropy in the reactants, because two individual molecules can move in ways that are not possible when the two are bound together in a single molecule. In such a reaction, the $\Delta S°$ will be negative. For a reaction in which a single molecule is cleaved into two separate molecules the products will have greater freedom of motion than the reactants, and $\Delta S°$ will be positive. A reaction with a negative $\Delta G°$ is said to have a favorable driving force. Negative values of $\Delta H°$ and positive value of $\Delta S°$ contribute to make $\Delta G°$ negative, that is, the formation of products with stronger bonds and with greater freedom of motion causes $\Delta G°$ to be negative.

For a spontaneous reaction, there must be an increase in entropy overall (i.e., the entropy change of the universe must be positive). The universe to a chemist consists of the reaction (system) that we are studying and its surroundings. It is comparatively easy to measure entropy changes of the reaction, but those of the surroundings are more difficult to determine directly. Fortunately, the change in entropy of the surroundings usually results from the heat released to, or absorbed from, the reaction. Heat released to the surroundings (an exothermic reaction) will increase the entropy of the surroundings while absorption of heat (an endothermic reaction) will lead to a decrease in entropy of the surroundings. Thus we can determine whether a reaction is spontaneous from the entropy and enthalpy changes of the reaction (Table 1.1).

The sign of $\Delta G°$ for a reaction tells us whether the starting materials or products are favored at equilibrium, but it tells us nothing about how long it will take before equilibrium is reached. If $\Delta G°$ for a reaction is *negative*, the products will be favored at equilibrium. If $\Delta G°$ for a reaction is *positive*, the reactants will be favored at equilibrium. If $\Delta G°$ for a reaction is 0, the equilibrium constant for the reaction will be 1. A small change in $\Delta G°$ makes a big difference in equilibrium constant K.

The functional groups determine the way the molecule works both chemically and biologically. Understanding chemical reactions in greater detail requires numerous different pieces of information, such as structural parameters, orbital interactions, energetic details, effect of media, and other external perturbations. One of my basic goals is to answer questions on stereoselectivity, catalysis, stability and reactivity of reactive intermediates, kinetic and thermodynamic aspects of chemical transformation, and so on. Many of the reactive intermediates of organic chemistry are charged species, such as **carbocations** (carbenium and carbonium ions) and **carbanions**, but there is an important subgroup of formally neutral

Table 1.1 Factors affecting the spontaneity of a reaction.

ΔH	ΔS	ΔG	Result
Negative	Positive	Always negative	Spontaneous
Positive	Negative	Always positive	Non-spontaneous
Positive	Positive	Negative at high T	Spontaneous at high T
Negative	Negative	Negative at low T	Spontaneous at low T

Table 1.2 Common reactive intermediates and their relationships.

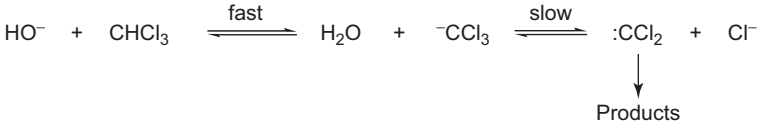
Type	C	N	O
-Onium ion	R_5C^+ carbonium ion	R_4N^+ ammonium ion	R_3O^+ oxonium ion
Neutral molecule	R_4C	R_3N	R_2O
Anion	R_3C^- carbanion	R_2N^- amide anion	RO^- alkoxide
Radical	$R_3C^\bullet$ carbon radical	$R_2N^\bullet$ aminyl radical	$RO^\bullet$ oxyl radical
-Enium ion	R_3C^+ carbenium ion	$R_2N^\bullet$ nitrenium ion	RO^+ oxenium ion
-Ene	R_2C : carbene	RN : nitrene	: O : oxene

electron-deficient reactive intermediates. For example, a carbon-containing reactive center can be either trivalent, with a single nonbonding electron, that is, a carbon centered **radical**, or divalent with two nonbonding electrons, that is, a **carbene**. Neutral reactive intermediates such as radicals, carbenes, nitrenes, and arynes occupy a fascinating place in the history of organic chemistry. First regarded as mere curiosities, neutral reactive intermediates ultimately came under the intense scrutiny of physical organic chemists from a mechanistic point of view. This concise text concentrates on how these electron-deficient species now play a key role in synthetic chemistry research. Important reactions are clearly and simply laid out with carefully chosen examples that illustrate their use in organic synthesis. Table 1.2 gives a comparison of various neutral reactive intermediates and their relationship to corresponding cations and anions.

There are many other kinds of reactive intermediates, which do not fit into the previous classifications. Some are simply compounds that are unstable for various possible reasons, such as structural strain or an unusual oxidation state, and are discussed in Chapter 7. This book is concerned with the chemistry of carbocations, carbanions, radicals, carbenes, nitrenes (the nitrogen analogs of carbenes), and miscellaneous intermediates such as arynes, *ortho*-quinone methides, zwitterions and dipoles, anti-aromatic systems, and tetrahedral intermediates. This is not the place to describe in detail the experimental basis on which the involvement of reactive intermediates in specific reactions has been established but it is appropriate to mention briefly the sort of evidence that has been found useful in this respect. Transition states have no real lifetime, and there are no physical techniques by which they can be directly characterized. Probably one of the most direct ways in which reactive intermediates can be inferred in a particular reaction is by a kinetic study. Trapping the intermediate with an appropriate reagent can also be very valuable, particularly if it can be shown that the same products are produced in the same ratios when the same postulated intermediate is formed from different precursors.

A classic example of the combined uses of kinetic and product-trapping studies is that of Hine and coworkers in their work on the hydrolysis of chloroform under basic conditions. The observation that chloroform undergoes deuterium for hydrogen exchange (in D_2O) faster than hydrolysis and further that the rate

of hydrolysis is retarded by addition of chloride ion is strong evidence in favor of the mechanism shown. Further circumstantial evidence for dichlorocarbene formation is provided by trapping experiments, for example, with alkenes, giving 1,1-dichlorocyclopropanes as products (Scheme 1.1).



Scheme 1.1

Organic structures can be determined accurately and quickly by spectroscopic methods. Mass spectrometry determines mass of a molecule and its atomic composition. NMR spectroscopy reveals the carbon skeleton of the molecule, whereas IR spectroscopy determines functional groups in the molecules. UV-visible spectroscopy tells us about the conjugation present in a molecule. Spectroscopic methods have also provided valuable evidence for the intermediacy of transient species. Most of the common spectroscopic techniques are not appropriate for examining reactive intermediates. The exceptions are visible and ultraviolet spectroscopy, whose inherent sensitivity allows them to be used to detect very low concentrations; for example, particularly where combined with flash photolysis when high concentrations of the intermediate can be built up for UV detection, or by using matrix isolation techniques when species such as *ortho*-benzyne can be detected and their IR spectra obtained. Unfortunately, UV and visible spectroscopy do not provide the rich structural detail afforded by IR and especially ^{1}H and ^{13}C NMR spectroscopy. Current mechanistic studies use mostly stable isotopes such as ^{2}H, ^{13}C, ^{15}N, ^{17}O, and ^{18}O. Their presence and position in a molecule can be determined by NMR. Mass spectroscopy, although much more sensitive than NMR, usually allows us to determine the degree of labeling but the position of the label can be identified only in favorable cases (via fragmentation).

In the case of transient species with unpaired electrons such as free radicals, and the triplet states of carbenes or nitrenes, electron spin resonance (ESR) spectroscopy can provide unique evidence about the structure of the intermediate. Useful information about intermediates in reactions involving radical pair coupling can also be obtained by a technique known as chemically-induced dynamic nuclear polarization (CIDNP). However, detailed discussions of ESR and CIDNP are outside the scope of this book and for further information suitable text books on physical organic chemistry or the references given in the Further Reading section should be consulted.

Besides the kinetics of a reaction there are several other ways of studying reactions. The final mechanism deduced for a reaction must explain the following:

products and side products;
intermediates observable where possible;

kinetics;
stereochemical results;
isotope studies;
relative reactivity of different reagents;
relative reactivity of different substrates;
effect of different solvents.

So far, we have looked at the following aspects: why molecules generally do not react with each other; why sometimes molecules do react with each other; how in chemical reactions electrons move from full to empty orbitals, which is the key to reactivity; molecular shape and structure determine reactivity; charge attraction and orbital overlap bring molecules together; the right orientation to use any attraction; charge is conserved in each step of a reaction and representing the movement of electrons in chemical reactions by curly arrows, which are vital for learning reaction mechanism.

You cannot learn the whole subject of reactive intermediates, there is just too much of it. You can learn trivial things like the name of intermediates but that does not help you to understand the principles behind the subject. You have to understand the principles and fundamentals because the only way to tackle organic reaction mechanisms is to learn to work it out. That is why I have provided end-of chapter problems. The end-of chapter problems should set you on your way but they are not the end of the journey to understanding. They are to help you discover if you have understood the material presented in each chapter. You are probably reading this text as part of a university/college course and you should find out what kind of examination problems your university/college uses and practice them, too. This first chapter gives a general introduction, illustrating material that will subsequently be covered in detail. The remaining six chapters with their special topics take up specific classes of reactions and discuss their mechanisms and applications. The criteria used to select these classes of reactions are (i) the reactions are highly important in synthetic organic chemistry and (ii) a fair amount is known about their mechanisms. It is hoped that the choice of topics made will indicate both the scope and the depth of current mechanistic theories.

1.3 Summary

- The electrons in any atom are grouped in energy levels whose energies are universally proportional to the inverse square of a very important number n. This number is called the *principal quantum number* and it can have only a few integral values ($n = 1, 2, 3 \ldots$). The energy levels also depend on the type of atom. Electrons in atoms are best described as waves.
- The 1s orbital is spherically symmetrical and has no nodes. The 2s orbital has one radial node and the 3s orbital two radial nodes. They are both spherically symmetrical.

- The bonding MO (molecular orbital) is lower in energy than the AOs (atomic orbitals) and the antibonding MO is higher in energy than the AOs.
- All normal compounds of carbon have eight electrons in the outer shell ($n = 2$) of the carbon atom, all shared in bonds. It does not matter where these electrons come from; just fit them into the right MOs on sp, sp^2, or sp^3 atoms.
- All normal compounds of nitrogen have eight electrons in the outer shell ($n = 2$) of the nitrogen atom, six shared in bonds and two in a lone pair. Similarly, all compounds of oxygen have eight electrons in the outer shell ($n = 2$) of the oxygen atom, four shared in bonds and four in lone pairs.
- The *activation energy*, also called the *energy barrier* for a reaction, is the minimum energy molecules must have if they are to react.
- Nucleophiles do not really react with the nucleus but with empty electronic orbitals. In a reaction mechanism, nucleophiles donate electrons and electrophiles accept electrons.
- For any reaction molecules must approach each other so that they have enough energy to overcome the repulsion and have the right orientation and suitable symmetry to use any attraction.
- Curly arrows are used to represent the reaction mechanisms, which show the movement of electrons within molecules. A curly arrow shows the movement of a pair of electrons.
- If you make a new bond to uncharged H, C, N, or O you must also break one of the existing bonds in the same step. Make sure that overall charge is conserved in your mechanism.
- Conjugation focuses on the sequence of alternating double and single bonds, while delocalization focuses on the molecular orbitals covering the whole system. Electrons are delocalized over the whole of a conjugated system.
- The stronger the acid HA, the weaker is its conjugate base, A^- (the more stable the conjugate base, the stronger the acid) and the stronger the base A^-, the weaker its conjugate acid AH.
- A transition state is a structure that represents an energy maximum on passing from reactant to products, which cannot be isolated. It is not a real molecule in that it may have partially formed or broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules.
- An intermediate is a molecule or ion that represents a localized energy minimum – an energy barrier must be overcome before the intermediate forms something more stable.

Problems

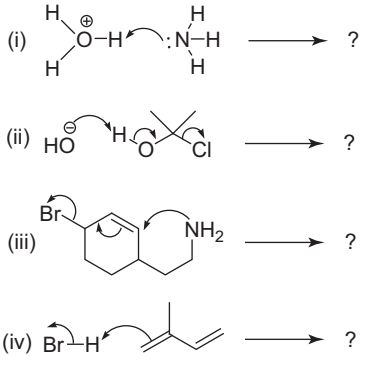
1. Draw a reaction diagram profile for a one-step exothermic reaction. Label the parts that represent the reactants, products, transition state, activation energy, and heat of reaction.

2. Draw a reaction energy diagram for a two-step endothermic reaction with a rate-limiting second step.
3. Consider the following reaction:

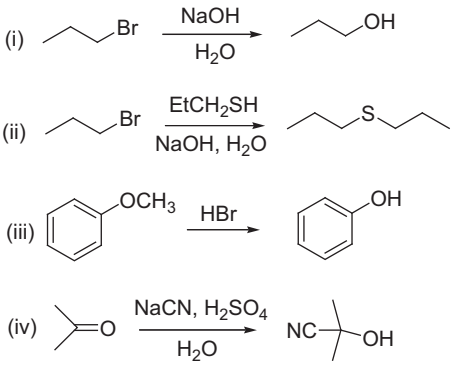
$$CH_4 + Cl^{\bullet} \rightarrow {}^{\bullet}CH_3 + HCl$$

This reaction has activation energy (E_a) of + 4 kcal mol^{-1}(+17 kJ mol^{-1}) and a $\Delta H°$ of +1 kcal mol^{-1}(+4 kJ mol^{-1}). Draw a reaction energy diagram for this reaction.

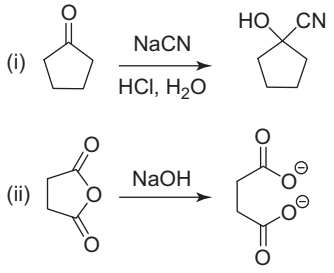
4. Complete the following mechanisms by drawing the structure of the products in each case.



5. Draw mechanisms for the following reactions.



6. Explain the following terms with appropriate examples: regioselectivity, chemoselectivity, stereoselectivity, transition state, intermediate, and activation energy.
7. Draw transition states and intermediates for the following reactions and fit each on an energy profile diagram.



8. The equilibrium between a carbonyl compound and its hydrate usually favors the aldehyde or ketone. Explain why and draw an energy profile to express this.
9. Hemiacetal formation is catalyzed by acid or base, but acetal formation is possible only with an acid. Explain why with suitable examples.

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2
Carbocations

2.1
Introduction

In many cases, reactions proceed via so-called intermediates, which have in general very short lifetimes. One type of reactive intermediates is the so-called ''*carbocations*.'' Charged atoms and groups of atoms are common in inorganic chemistry. All of us know about table salt, which consists of positively charged sodium ions (cations) and negatively charged chloride ions (anions). The opposite is true for the large number of organic compounds, especially hydrocarbons, which are composed of only two elements, carbon and hydrogen. Carbocations have been well established as intermediates in numerous synthetic transformations. In such cases these intermediates had to have an extremely short lifetime, a billionth of a second or less, and due to their high reactivity their concentrations had to be very low. Their existence has been indicated by measurements of reaction rates and observations of the spatial arrangement of the atoms in space. For such purposes, a variety of ingenious experiments have been carried out. However, nobody was able to see these carbocations, not even with the most powerful microscopes or by spectroscopic methods. These techniques can be regarded as extensions of human vision. Consequently, there was no evidence for the existence of carbocations, in other words whether they were a reality independent of human consciousness or were only created by human imagination to describe the experimental results. Because it was not possible to detect carbocations with spectroscopic methods, different scientists interpreted their experiments differently, and a scientific feud took place in organic chemistry during the 1960s and 1970s.

Through a series of brilliant experiments **Professor George Olah** solved the problem. He created methods to prepare long-lived carbocations in high concentrations, which made it possible to study their structure, stability, and reactions with spectroscopic methods. He achieved this by using special solvents, which did not react with the cations. He observed that in these solvents, at low temperatures, carbocations could be prepared with the aid of superacids (acids 18^{10} times stronger than concentrated sulfuric acid). Through Olah's pioneering work he and the scientists who followed in his footsteps could obtain detailed knowledge about the structure and reactivity of carbocations. Olah's discovery resulted in a complete

Reactive Intermediates in Organic Chemistry: Structure, Mechanism, and Reactions, First Edition.
Maya Shankar Singh.

Figure 2.1 Carbenium and carbonium ions.

revolution for scientific studies of carbocations, and his contributions occupy a prominent place in all modern textbooks of organic chemistry.

Olah found that there are two groups of carbocations, namely, trivalent ones called *carbenium ions*, in which the positive carbon atom is surrounded by three atoms, and those in which the positive carbon is surrounded by five atoms, called *carbonium ions* (Figure 2.1). The disputed existence of these pentacoordinated carbocations was the reason for the scientific feud. By providing convincing proof that pentacoordinated carbocations exist, Olah demolished the dogma that carbon in organic compounds could at most be tetracoordinated, or bind a maximum of four atoms. This had been one of the cornerstones of structural organic chemistry since the days of Kekulé in the 1860s.

Olah found that the superacids were so strong that they could donate a proton to simple saturated hydrocarbons, and that these pentacoordinated carbonium ions could undergo further reactions. This fact has contributed to a better understanding of the most important reactions in petrochemistry. His discoveries have led to the development of methods for the isomerization of straight chain alkanes, which have low octane numbers when used in combustion engines, to produce branched alkanes with high octane numbers. Furthermore, these branched alkanes are important as starting materials in industrial syntheses. Olah has also shown that with the aid of superacids it is possible to prepare larger hydrocarbons with methane as the building block. With superacid catalysis it is also possible to crack heavy oils and liquefy coal under surprisingly mild conditions.

2.2 History

The history of carbocations dates back to 1891 when G. Merling reported that he added bromine to tropylidene (cycloheptatriene) and then heated the product to obtain a crystalline, water-soluble material, C_7H_7Br. He did not suggest a structure for it; however, Doering and Knox convincingly showed that it was tropylium (cycloheptatrienylium) bromide (Figure 2.2). This ion is predicted to be aromatic by the Hückel rule.

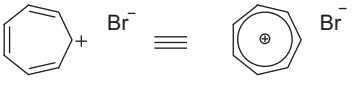
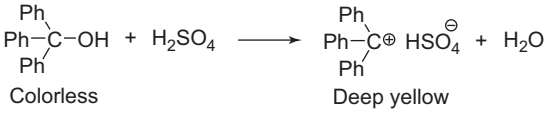


Figure 2.2 Tropylium bromide.

In 1902 Norris and Kehrman independently discovered that colorless triphenylmethanol gave deep yellow solutions in concentrated sulfuric acid (Scheme 2.1). Triphenylmethyl chloride similarly formed orange complexes with aluminum and tin chlorides. Adolf von Baeyer recognized in 1902 the salt-like character of the compounds formed. He dubbed the relationship between color and salt formation **halochromy**, of which malachite green is a prime example.



Scheme 2.1 Reaction of triphenylmethanol with conc. H_2SO_4.

Carbocations are reactive intermediates in many organic reactions. This idea, first proposed by Julius Stieglitz in 1899 (on the constitution of the salts of imidoethers and other carbimide derivatives), was further developed by Hans Meerwein in his 1922 study of the Wagner–Meerwein rearrangement. Carbocations were also found to be involved in the S_N1 reaction and E1 reaction and in rearrangement reactions such as the Whitmore 1,2 shift. The chemical establishment was reluctant to accept the notion of a carbocation and for a long time the *Journal of the American Chemical Society* refused articles that mentioned them.

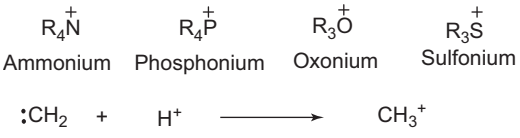
The first NMR spectrum of a stable carbocation in solution was published by Doering *et al*. It was the heptamethylbenzenonium ion, made by treating hexamethylbenzene with methyl chloride and aluminum chloride. The stable 7-norbornadienyl cation was prepared by Story *et al*. by reacting norbornadienyl chloride with silver tetrafluoroborate in sulfur dioxide at −80 °C. The NMR spectrum established that it was nonclassically bridged (the first stable nonclassical ion observed). In 1962 Olah directly observed the *tert*-butyl carbocation, by nuclear magnetic resonance, as a stable species on dissolving *tert*-butyl fluoride in magic acid. The NMR of the norbornyl cation was first reported by Schleyer *et al*. and it was shown to undergo proton scrambling over a barrier by Saunders *et al*.

2.2.1
Carbonium Ions and Carbenium Ions

A carbocation was previously often called a *carbonium ion* but questions arose concerning the exact meaning. In present day chemistry, a carbocation is any positively charged carbon atom. Two special types have been suggested: carbenium ions, which are trivalent, and carbonium ions, which are pentavalent or hexavalent. University level textbooks only discuss carbocations as if they are carbenium ions, or discuss carbocations with a fleeting reference to the older phrase of carbonium ion or carbenium and carbonium ions.

Carbocations play a key role in many chemical processes and the study of carbocations as transient or long-lived species has directly influenced the understanding of bonding and solvation, which are fundamental aspects of chemistry.

The strengths of acids, as measured by pK_a values, range from very weak ones such as hydrocarbons to acids that are much stronger than sulfuric acid. Acids with acidities greater than sulfuric acid are called *superacids*. Carbocations are most important reactive intermediates, having a formal positive (+) charge on carbon. During much of the recent history of organic chemistry, a structure with a positively charged carbon atom was called a carbonium ion, a term reminiscent of other positively charged species, such as ammonium, phosphonium, sulfonium, and so on (hypervalent cations: having a higher than usual valency, Scheme 2.2). However, these latter terms all refer to species formed by adding a positively charged atom such as a proton to an atom with a nonbonded pair of electrons to form the positively charged ion. Most carbocations, in contrast, are formed by removing a substituent and its electron pair from the carbon, leading to a hypovalent (having less than its usual valency) cation. To keep the nomenclature of organic chemistry consistent, it was proposed that a species such as CH_3^+ should be thought of as being the addition product of methylene and a proton, so it should more properly be termed a *carbenium ion*, and that is the term now in general use for species in which a trivalent carbon atom bears a positive charge. However, the more general term *carbocation* is used instead.



Scheme 2.2 Hypervalent and hypovalent cations.

To continue the analogy of adding the suffix *-ium* to the term for a neutral species, George Olah (born in Hungry in 1927 but emigrated to the USA and awarded the Nobel Prize for his work on cations in 1994) proposed that the term *carbonium ion* refer to a species that could be considered to be formed by adding a positive charge to a neutral, tetravalent carbon atom. Such a species in which a carbon atom appears to be bonded to more than four atoms at once is known as a *hypercoordinate carbon compound*. Figure 2.3 shows the bonding in a methanonium ion, CH_5^+ as suggested by Olah. In one possible ''nonclassical'' structure, the added proton is

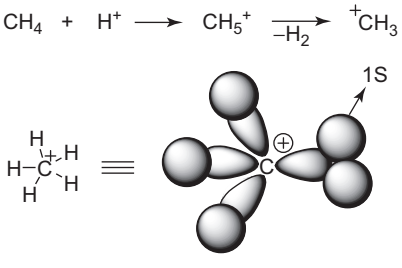
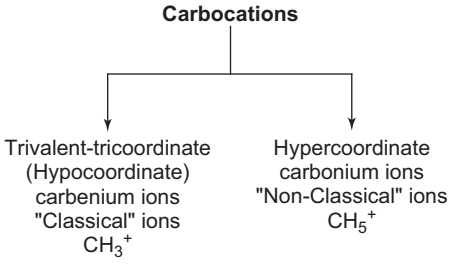


Figure 2.3 Representation of the structure of CH_5^+.

Table 2.1 Relationship between hypovalent and hypervalent carbocations.

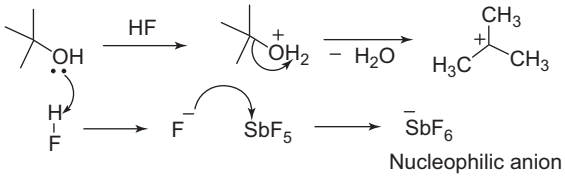


Property	CH_3^+	CH_5^+
Number of bonds to C^+	3	5
Electrons in outer shell	6	8
Empty orbital	Yes, a p orbital	No
Electron-deficient	Yes	No

associated side-on with the electron density of one of the C–H bonds of methane. Hypervalent ions are unstable and undergo loss of H_2 to give hypovalent species.

Table 2.1 shows the relationship between the two types of carbocations.

A **carbenium ion** can be represented by a single Lewis structure involving only two-electron, two-center bonds. A **carbonium ion** cannot be represented adequately by a single Lewis structure. Such a cation contains one or more carbon or hydrogen bridges joining two-electron deficient centers. The bridging atoms have coordination numbers higher than usual, typically five or more for carbon and two or more for hydrogen. Such ion contains two-electron, three-center bonds. Despite the conceptual model that gave rise to the name, carbenium ions are usually formed by heterolytic dissociation of a bond to carbon. In particular, around 1900 it was observed that triarylmethyl halides could be dissolved in SO_2 to yield electrically conducting solutions, which suggested that carbon atoms could be positively charged. Olah was able to make carbocations from alcohols. He treated *tert*-butanol with SbF_5 and HF in liquid SO_2 (Scheme 2.3).



Scheme 2.3 Generation of *tert*. butyl cation.

The proton NMR of this cation (in liquid SO_2 at −70 °C) showed just one signal for the three methyl groups at 4.15 ppm, quite far downfield for C–Me groups. The ^{13}C spectrum also showed downfield Me groups at 47.5 ppm, but the key evidence was the shift of the central carbon atom, which came at an amazing 320.6 ppm, downfield from anything we have met before. This carbon is much deshielded – it is positively charged and electron deficient.

Such charged intermediates require more energy for formation in the gas phase than would the corresponding trivalent carbon radicals because energy is required both to break the bond to carbon and to separate the charged ions. The additional energy may be small in solution, especially with very polar solvent molecules to solvate and stabilize the ions, but it can be considerable in the gas phase. However, we must remember that the stabilization afforded by polar solvents is accompanied by perturbation of the environment of the cation, so any investigation of the cation is necessarily an investigation of both the ion and its environment.

2.3 Structures and Geometry of Carbocations

Carbocations are electron-deficient species that are the most important intermediates in several kinds of reactions. A common model for carbocation structure is a planar species exhibiting sp^2 hybridization, as shown in Figure 2.4 for methyl cation. The p-orbital that is not utilized in the hybrids is empty and is often shown bearing the positive charge since it represents the orbital available to accept electrons. There is a vacant p orbital perpendicular to the plane of the molecule; this is the LUMO (lowest unoccupied molecular orbital). In all reactions of carbocations there is an interaction between this LUMO and the HOMO (highest occupied molecular orbital) of another molecule. A structure with an empty p orbital should be more stable than a structure in which an orbital with s character is empty. In general, a carbocation is a purely ionic species.

The sp^2-hybridized model is consistent with the observed geometry for the *t*-butyl carbocation, which has been determined through both NMR and X-ray crystallographic studies to be planar, with 120° bond angles about the central carbon atom. Other evidence in support of planar structure for carbocations is the racemization of chiral alkyl halides under solvolysis conditions. If somehow the structure of a molecule deviates from a 120° bond angle and sp^2 hybridization in the corresponding carbocation, the carbocation will not be formed. This is why Ph_3CCl in liquid SO_2 is ionized readily whereas analogous bridged 1-bromotriptycene does not ionize in SO_2. However, larger bridgehead carbocations can exist, for example, the adamantyl cation has been synthesized (Scheme 2.4).

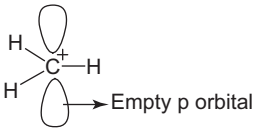
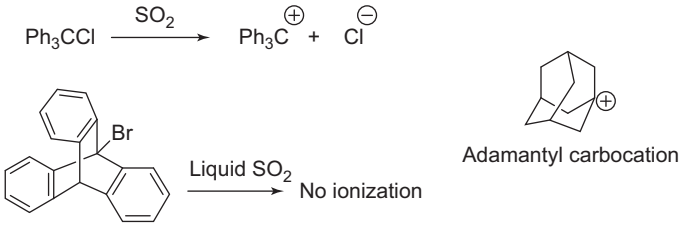


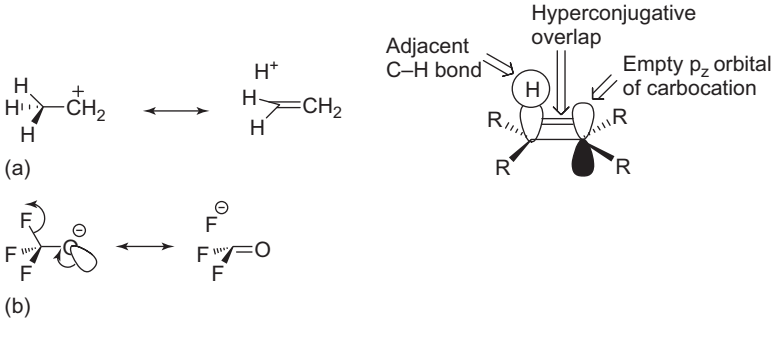
Figure 2.4 Methyl cation.



Scheme 2.4 Planar and non-planar carbocations

The ΔH for heterolytic dissociation of alkanes in the gas phase varies with the alkyl groups as follows: methyl > ethyl > *iso*-propyl > *tert*-butyl, which is consistent with the generalization that the ease of formation of carbocations is 3° > 2° > 1°. Alkyl groups are electron donating relative to hydrogen. Yet, how can a carbon atom be electron donating relative to hydrogen when both have essentially the same electronegativity? We can explain some, but not all, of the results by saying that a sp^3-hybrid orbital on carbon has a Pauling electronegativity of 2.5, while a sp^2-hybrid orbital on carbon is about 0.25 units more electronegative. This expectation that the energy of a system is lowered due to electron polarization through a σ bond system is known as *induction*.

We may also explain the electron-donating ability of a methyl or other alkyl group in terms of *hyperconjugation* (σ conjugation into empty p orbital), a lowering of the energy of a system by delocalization of electrons through π bonds involving sp^3-hybridized carbon atoms adjacent to the carbocation center. In molecular orbital terms, hyperconjugation is the overlap of the filled sigma orbitals of the C–H bonds adjacent to the carbocation with the empty ''p'' orbital on the positively charged carbon atom (Scheme 2.5a). This electronic ''spillover'' helps delocalize the positive charge onto more than one atom. The more alkyl substituents, the more sigma bonds there are for hyperconjugation. Note that it is not the sigma bonds that are directly attached to the carbocation that are involved in hyperconjugation; these orbitals are perpendicular to the empty ''p'' orbitals and cannot overlap with it. Rather, it is the sigma bonds one atom removed from the positively charged carbon



Scheme 2.5 (a) Stabilization of carbocation by hyperconjugation with an adjacent methyl group; (b) negative hyperconjugation.

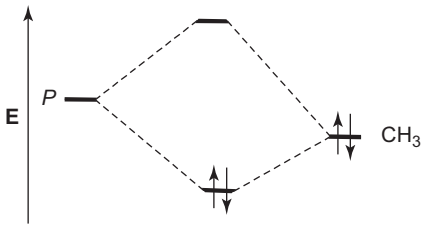


Figure 2.5 PMO description of stabilization of carbocation by methyl group.

atom that help to stabilize it. These bonds can rotate into an ''eclipsed'' conformation with the empty ''p'' orbital, thus interacting with it. Since the overlap supplies electron density to the electron-deficient carbocation carbon, we predict that increasing the number of hyperconjugative interactions increases carbocation stability.

A somewhat similar result can be obtained by applying PMO (perturbation molecular orbital) theory to the problem. Figure 2.5 shows the PMO description for the interaction of an empty p-orbital with a π (CH_3) localized methyl group orbital. The net effect is to distribute the electron density from the methyl portion of the molecule into a new orbital that has density on both the methyl group and the adjacent CH_2 group, thus delocalizing the positive charge and stabilizing the carbocation. Clearly, neither the valence bond notion of hyperconjugation nor the MO description gives us justification for declaring the methyl to be electron donating by induction.

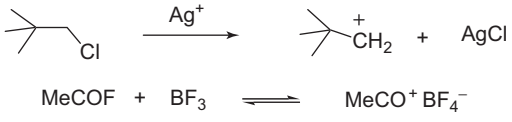
Negative hyperconjugation describes the stabilization of anionic species by σ-delocalization, involving σ^*-orbitals as acceptors. An example is the trifluoromethoxide anion (Scheme 2.5b), which usually observed as a highly reactive species but is stable enough in the solid state for the crystal structure to be determined. The C–O bond though nominally a single bond has almost the same length as the ordinary C=O double bond; while the C–F bonds are significantly longer than normal. The simplest explanation is that there is strong σ-delocalization of the nonbonding electrons on O^- into the antibonding orbitals of the C–F bonds; the pattern of bond lengths is accounted for by the major contribution from the no-bond resonance structure (Scheme 2.5b). Thus, the anomeric effect, negative hyperconjugation, and hyperconjugation are three terms describing, in different situations, basically the same effects.

2.4 Generation of Carbocation

Carbocations (stable or unstable) may be generated in various ways. The most common way is the removal of an electronegative atom or group along with its pair of electrons attached to carbon. The leaving group may be a stable, neutral atom or molecule. Factors that generally affect carbocation formation are the nature of the leaving groups, structural factors, solvent effects, salt effects, and isotope effects.

2.4.1
From a Halide

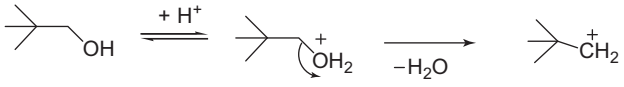
Carbocations may be generated from a halide by using a strongly ionizing solvent or by adding a Lewis acid such as silver ion, BF_3, $AlCl_3$, and so on. The catalytic effect of Ag^+ can be complicated, however, by the fact that the precipitated silver halide may itself act as a heterogeneous catalyst (Scheme 2.6). Such ionization reactions are controlled by two factors within the molecule. The first is the polarizability (leaving group ability) of the C–X bond. The greater this polarizability is, the faster the ionization step. The second factor is the stability of the generated carbocation.



Scheme 2.6

2.4.2
From an Alcohol

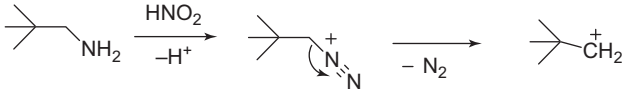
By treatment with acid, protonation of lone-pair electrons occurs, resulting in conversion into a better leaving group that promotes heterolysis (Scheme 2.7). Solvolysis reactions are promoted by polar solvents such as dimethyl sulfoxide (DMSO), DMF (dimethylformamide), THF (tetrahydrofuran), and so on. These solvents stabilize the transition state as well as the ions formed.



Scheme 2.7

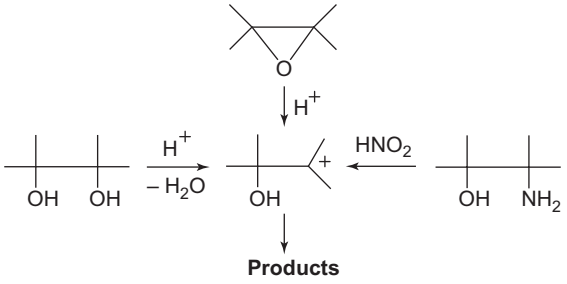
2.4.3
From an Amine

Amines are treated with nitrous acid to give diazonium ion that loses molecular nitrogen to form a carbenium ion (Scheme 2.8).



Scheme 2.8

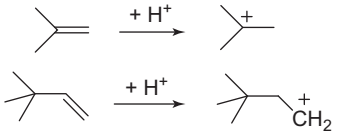
Note that there could be more than one route for the generation of a given carbocation (Scheme 2.9).



Scheme 2.9

2.4.4 From an Alkene

Carbocations may also be formed from alkenes by protonation (Scheme 2.10).



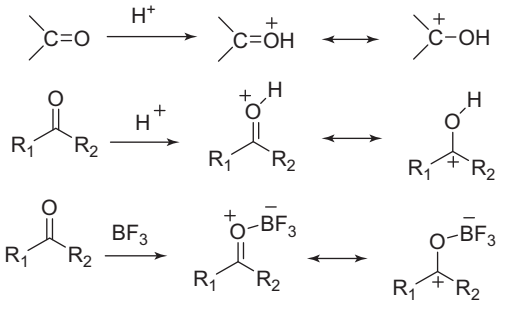
Scheme 2.10

2.4.5 From Carbonyl Compounds

The reaction of aldehydes and ketones with an acid catalyst gives the corresponding oxygen-stabilized cation. Protonation of carbonyl compounds also gives carbocations (Scheme 2.11). Here, note that carbocations are positively charged species. They are much more likely to be formed in acidic than in basic media; in fact, carbocations are never seen under conditions that are strongly basic.

2.4.6 Solvent Effects

Any property of a solvent system that can lower the energy of activation for heterolytic bond cleavage will favor carbocation formation, such as (i) the dielectric constant – a rough measure of the ability of the solvent to separate oppositely charged ions; (ii) hydrogen-bonding ability; (iii) acid–base properties; and (iv) nucleophilicity: as the nucleophilicity of a solvent decreases, the likelihood of discrete carbocation formation increases. As the ionic concentration of a solvent



Scheme 2.11

system increases, the overall polarity of the medium also increases. Increased solvent polarity favors ionization of neutral molecules.

2.5 Carbocation Stability

If electrons were money, carbocations would be the beggars of organic chemistry. Packing a mere six valence electrons, these electron-deficient intermediates figure prominently in many reactions we meet in organic chemistry, such as:

- nucleophilic substitution (S_N1) and elimination (E1) reactions;
- additions of electrophiles to double and triple bonds;
- electrophilic aromatic substitution;
- additions to carbonyl compounds and enolate chemistry (albeit in masked form).

Although generations of organic chemists have used the rates of nucleophilic substitution reactions as a means of judging the stability of carbocations, this approach is fraught with error:

- Most 2° substrates do not react by the S_N1 pathway.
- One is never sure of the extent to which cations that do form are differentially stabilized by dipolar or more specific interactions with the solvent.

Two methodologies exist for more direct measurement of carbocation stabilities:

1) The formation of carbocations in hyperacid media allows us to study the properties of carbocations.

Ned Arnett has adapted this methodology to allow measurement of the enthalpy of reaction for the process:

$$R - X \rightarrow R^{\oplus} + X^{\ominus}$$

in $SbS_5/FSO_3H/SO_2ClF$ at $-40\,^{\circ}C$

Some differences in the degree of ion pairing, and therefore in solvation energies, undoubtedly exist, but the results seem reasonable.

2) The solvent can be eliminated completely by making use of mass spectrometry, particularly ion cyclotron resonance.

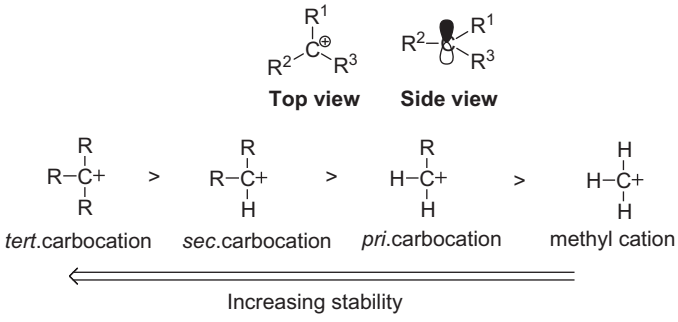
One can, for example, measure the enthalpy of protonation of an alkene to a carbocation, or the ionization of a free radical to a carbocation.

During the 1920s and 1930s, a group of three chemists, that is, Hans Meerwein from Germany, "the father of modern carbocation chemistry," Sir Christopher Ingold of England, and Frank Whitmore of the United States proposed alkyl cations as intermediates in many organic reactions. Carbocations are classified according to the number of alkyl substituents that are bonded to the positively charged carbon: a **primary carbocation** has one alkyl substituent bonded to the positively charged carbon, a **secondary carbocation** has two, and a **tertiary carbocation** has three. According to the laws of electrostatics, the stability of a charged system is increased by dispersal of the charge. Any factor that tends to spread out the positive charge of the electron-deficient carbon must stabilize a carbocation.

Three main structural factors help to stabilize carbocations:

1) neighboring carbon atoms;
2) neighboring carbon–carbon multiple bonds;
3) neighboring atoms with lone pairs.

The greater the number of alkyl substituents bonded to the positively charged carbon, the more stable the carbocation will be. The order of relative stability of carbocations is: tertiary ~ benzylic > allylic ~ secondary > primary ~ vinyl > phenyl. The nature of electron release by alkyl groups is not very clear. It may be an inductive effect, a resonance effect (hyperconjugation), or a combination of the two. When we refer to the inductive effect of the alkyl groups, it should be clear that this might well include a contribution from hyperconjugation.



Alkyl groups decrease the concentration of positive charge on a carbon, thereby increasing the carbocation stability (Figure 2.6). Alkyl groups decrease the concentration of positive charge because they are more readily polarized than are hydrogens. Alkyl substituents also stabilize carbocations by hyperconjugation. Hyperconjugation occurs only if the σ bond orbital and the empty p-orbital have the appropriate orientation. A charged species is more stable if its charge is spread out (delocalized) over more than one atom. The more stable the carbocation, the faster

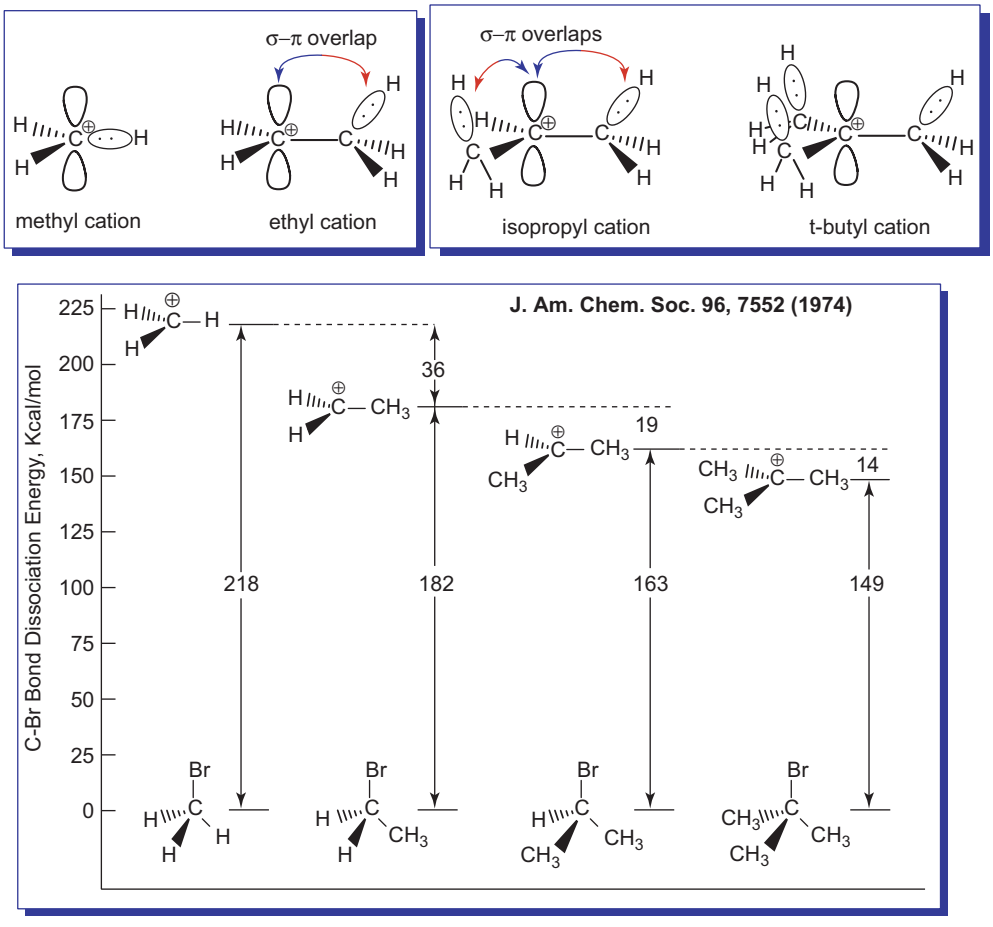


Figure 2.6 Relative stabilities of carbocations in quantitative terms.

it is formed. The energy difference between 1°, 2°, and 3° cations is approximately 11–15 kcal mol^{-1}.

We can get a more quantitative feel for the relative stabilities of alkyl carbocations by examining data for the enthalpy of ionization (gas phase) for various alkyl chlorides: Of course, each of these reactions is much more endothermic in the gas phase than it would be in solution, where solvent molecules of appropriate polarity characteristics could help to stabilize the electrically charged products of the ionization reaction. (This is why "ionizing solvents" are often used for reactions that involve charged intermediates.) Nevertheless, the data clearly reflects the order of carbocation stability that we have already established: tertiary carbocations are the easiest (least endothermic) to form, the secondary, then primary, and the methyl carbocation is the most difficult to form.

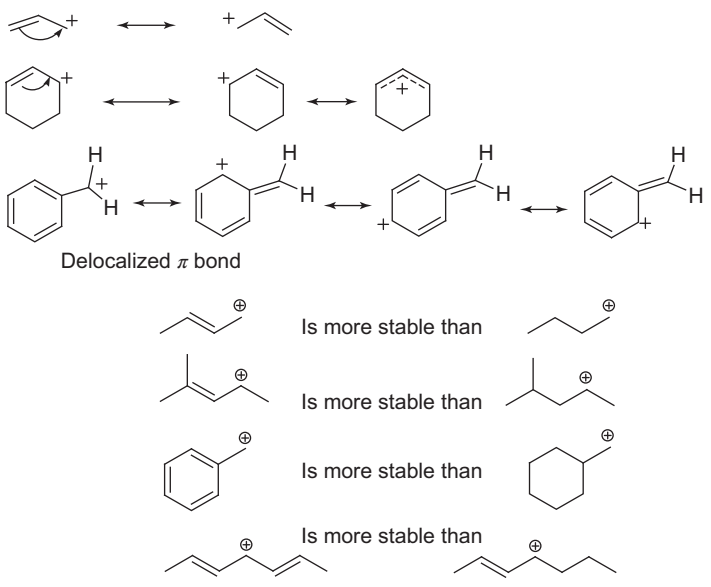


Figure 2.7 Effect on carbocation stability of resonance stabilization by conjugation with pi bonds.

There are basically two types of carbocations: (i) those that are *not* stabilized by resonance effects (simple alkyl carbocations) and (ii) those that *are* stabilized by resonance, which usually occurs either through lone pair (nonbonding) electrons on adjacent atoms or through conjugated π-bonding electrons (e.g., **allylic** and the **benzylic** carbocations, Figure 2.7).

If the positive charge is in conjugation with a double bond the stability is greater because of increased delocalization due to resonance and because the positive charge is spread over more than one atom. More effective stabilization is provided by genuine conjugation with π or lone-pair electrons. The allyl cation has a filled orbital containing two electrons delocalized over all three atoms. The benzyl cation is about as stable as the allyl cation but lacks its ambiguity of reaction.

When considering the importance of hyperconjugation versus resonance as the more important stabilizing feature, resonance usually wins out. For example, a primary carbocation with resonance is more stable than a secondary carbocation without resonance. A secondary carbocation with resonance is usually more stable than a tertiary carbocation without resonance.

Several benzylic cations have been obtained in solution as SbF_6^- salts. Diarylmethyl and triarylmethyl cations are still more stable. Arylmethyl cations are further stabilized if they have electron-donating substituents in *ortho* or *para* positions. The stability of such cations can be further increased if electron-donating substituents feed into the π-system. Triarylmethyl cations are propeller-shaped, even though the central carbon atom and the three ring carbons connected to it are in a plane. The three benzene rings cannot be all in the same plane because of steric hindrance.

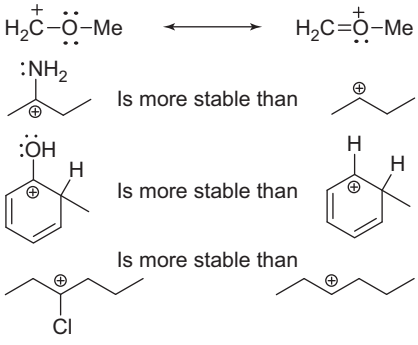


Figure 2.8 Effect on carbocation stability of resonance stabilization through lone pair (non-bonding) electrons.

The methoxymethyl cation can be obtained as a stable solid, $MeOCH_2^+$ SbF_6^- (Figure 2.8).

If a benzyl cation is substituted with electron-donating groups its stability may increase. For instance, *p*-methoxybenzyl chloride undergoes solvolysis at 10 000 times the rate of benzyl chloride in 67% aqueous acetone, but *m*-methoxybenzyl chloride has only two-third the rate of benzyl chloride. This is because the positive charge can be stabilized by the *p*-methoxy group but not the *m*-methoxyl (Figure 2.9a). The latter is destabilizing, probably because of a field effect from the carbon–oxygen dipole. Stabilization by delocalization can also occur through aromatization. For example, 1-bromocyclohepta-2,4,6-triene (tropylium bromide) is a crystalline solid (mp 208 °C) that is highly soluble in water, giving bromide ions in solution, that is, it is an ion pair. The reason for this behavior is that the cyclic cation has 6π electrons delocalized in three molecular orbitals spread over the seven carbon atoms. Thus, it is a Hückel $(4n + 2)$ π system exhibiting aromaticity (Figure 2.9b).

In addition to the tropylium cation, several long-lived carbenium ions are known. Three of the more interesting of these are shown below. For each of these, several

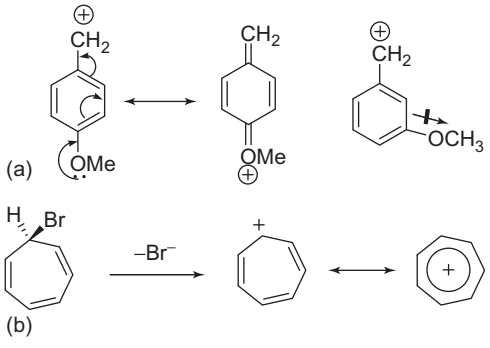


Figure 2.9 Carbocation charge stabilization through (a) conjugation and (b) aromatization.

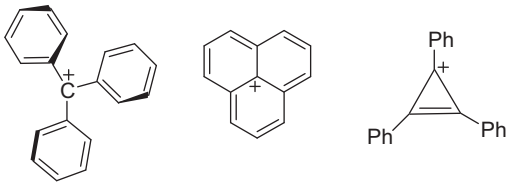


Figure 2.10 Examples of long-lived carbenium ions.

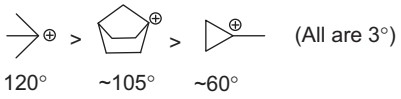


Figure 2.11 Preference of carbocations for planar geometry (120° inter-bond angles).

resonance structures may be drawn, showing that in all the cases the positive charge is delocalized over several atoms. In the case of the triphenylcarbenium ion, owing to a considerable amount of steric interference between the *ortho*-hydrogens, one benzene ring must be twisted out of the plane containing the three bonds to the central carbon atom. On the basis of spectral evidence, it is believed that all the three rings are so twisted to give ''propeller like'' conformation (Figure 2.10).

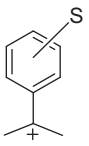
Carbocations prefer a planar geometry; any structural feature that interferes or prevents the attainment of 120° inter-bond angles will hinder (retard) carbocation formation (Figure 2.11).

2.6 Detection of Carbocations

The study of carbocations illustrates many of the ways in which reactive intermediates are studied. In particular, both ^{1}H and ^{13}C NMR have been among the primary instrumental methods applied to the structure and properties of carbocations. A pioneer in the field was Olah, who found that under appropriate conditions organic precursors dissolved in superacid media (such as SO_2ClF-SbF_5 solution, often at low temperature) gave solutions with spectra consistent with the presence of relatively long-lived carbocations.

Generally, ^{13}C NMR chemical shifts for carbenium ions are observed at very low field. For example, the chemical shift for the 3° carbon atom in isobutane is 25.2 ppm, whereas the chemical shift for the corresponding carbon atom in $(CH_3)_3C^+$ is 330.0 ppm (in SO_2ClF-SbF_5 solution). This large shift appears to result from decreased shielding due to the decreased electron density at the carbenium center. Studies of substituent effects on carbocation shifts reinforce this view. For example, the ^{13}C NMR shifts of the benzylic carbon atoms in the series of carbocations shown in Figure 2.12 range from 219 ppm for *p*-methoxy to 269 ppm for *p*-CF_3.

Intuitively, we might expect electron-donating alkyl substituents on a carbenium center to increase the local electron density and thus the shielding at that site,



S	$\delta^{13}C$
4-OCH_3	219
4-CH_3	243
4-H	255
4-CF_3	269

Figure 2.12 ^{13}C NMR chemical shifts of substituted carbocations.

leading to a smaller downfield shift in the carbon resonance. Surprisingly, however, there is evidence to suggest that alkyl substitution may lower the energy of a carbocation without decreasing the deshielding of the carbenium carbon atom. The ^{13}C NMR chemical shift for C2 of the isopropyl carbocation is −125.0 ppm from the signal for CS_2, while that of the 3° carbon atom of the *t*-butyl carbocation is −135.4 ppm from the signal for CS_2. Thus, substitution of hydrogen on C2 by a methyl group appears to deshield the carbocation, suggesting electron withdrawal, not donation. In fact, extended Hückel calculations indicate that the charge on the C2 of isopropyl is +0.611, while that of the central carbon atom of *t*-butyl is +0.692. Thus, in contrast to our expectation that the methyl group is electron donating relative to hydrogen, both theory and experiment indicate that the carbenium ion center has a greater positive charge with the methyl substituent present.

Treatment of benzene with $HF/SbF_5/SO_2ClF/SO_2F_2$ (an exotic and strongly acidic mixture) at −134 °C leads to protonation of benzene, producing the simplest arenium ion that could be studied by ^{13}C NMR spectroscopy. Signals for the carbon atoms *ortho* and *para* to the site of protonation are shifted dramatically downfield because of delocalization of positive charge to these positions. The NMR spectrum of allylic cation reveals a plane of symmetry, which confirms that the positive charge is spread over two carbons. The large shift of 224 ppm for these cations indicates very strong deshielding (i.e., lack of electrons). The middle carbon shift of 142 ppm is almost typical of a normal double bond (Figure 2.13).

2.7 Fate of Carbocations

As mentioned above, carbocations feature in many reactions, such as nucleophilic substitution (S_N1) and elimination (E1), additions of electrophiles to double and triple bonds, electrophilic aromatic substitution, and additions to carbonyl compounds and enolate chemistry (albeit in masked form).

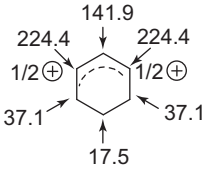


Figure 2.13 ^{13}C NMR spectrum of an allylic cation.

There are two properties of cations that must be considered before considering their reaction with a nucleophilic species: regioselectivity in formation of the cation and migration of the substituents (rearrangement). Although a carbocation undergoes various different reactions, the common goal of all of them is to provide a pair of electrons to complete the octet of the positively charged carbon atom since a carbocation is just a type of electrophile. There are three major reaction pathways by which carbocations react to give the stable products. They may (i) combine with a nucleophile, (ii) lose a proton or other electrofugal leaving group, or (iii) undergo rearrangement.

2.7.1 Reaction with a Nucleophile

The carbocation may react with an electron-rich species (neutral or anionic), that is, with a nucleophile (known as S_N1) to give the stable compound. The carbon–halogen bond breaks heterolytically without any assistance from the nucleophile, forming a carbocation. The carbocation then reacts with the nucleophile to form the substitution product, that is, an ionization mechanism (Scheme 2.12).

Treatment of an alkene with formaldehyde in the presence of an acid gives a 1,3-diol together with an α,β-unsaturated alcohol or cyclic acetal (**Prins reaction**) (Scheme 2.13).

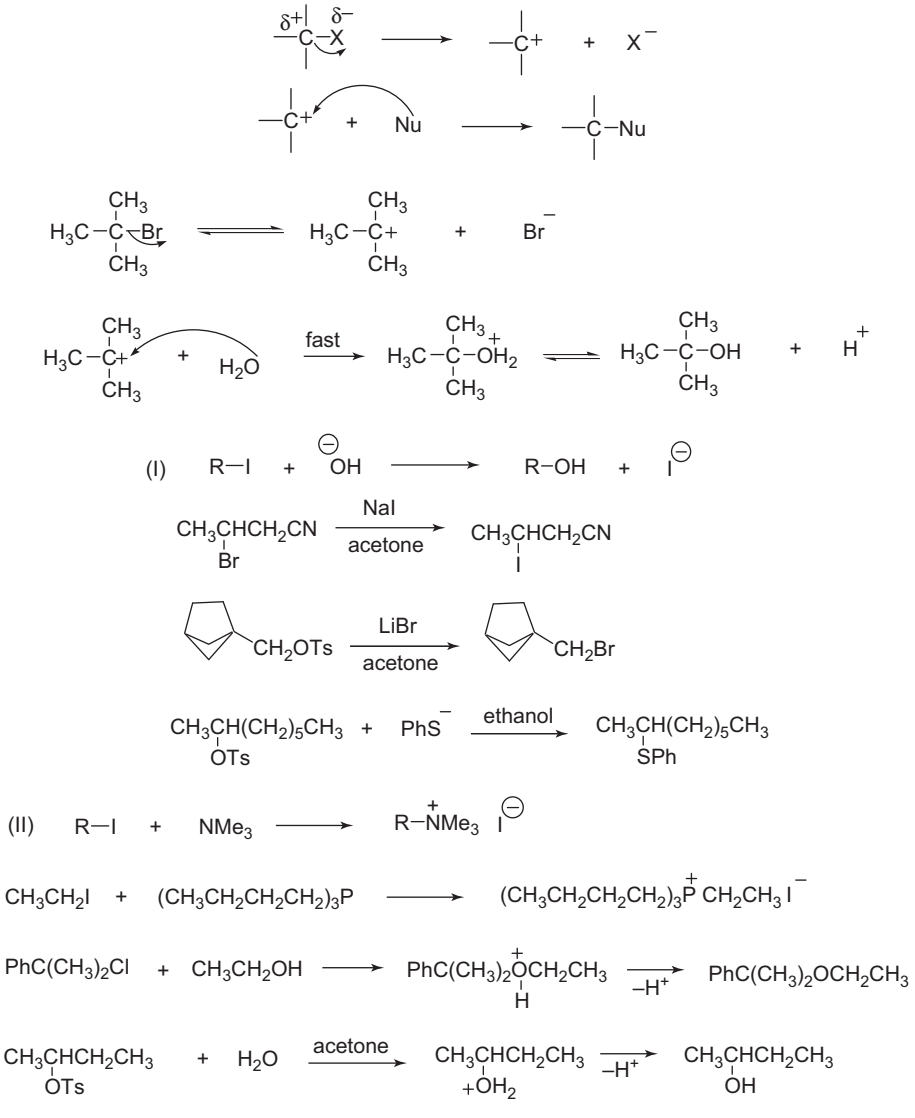
2.7.2 Elimination of a Proton

The carbocation may eliminate a proton or another electrophile from the adjacent atom (known as *E1*) to yield a stable compound (Scheme 2.14).

If one carries out the substitution reaction with a solution of sodium hydroxide, the reaction stops being a substitution and an alkene is formed instead. Overall, HBr has been lost from the alkyl halide, and the reaction is called an *elimination* (Scheme 2.15).

For some elimination reactions only one product is possible. For others, there may be a choice of two (or more) alkene products that differ either in the location or stereochemistry of the double bond. We shall now discuss the factors that control the stereochemistry (geometry) and regiochemistry (i.e., where the double bond is) of the alkenes, starting with E1 reactions (Scheme 2.16).

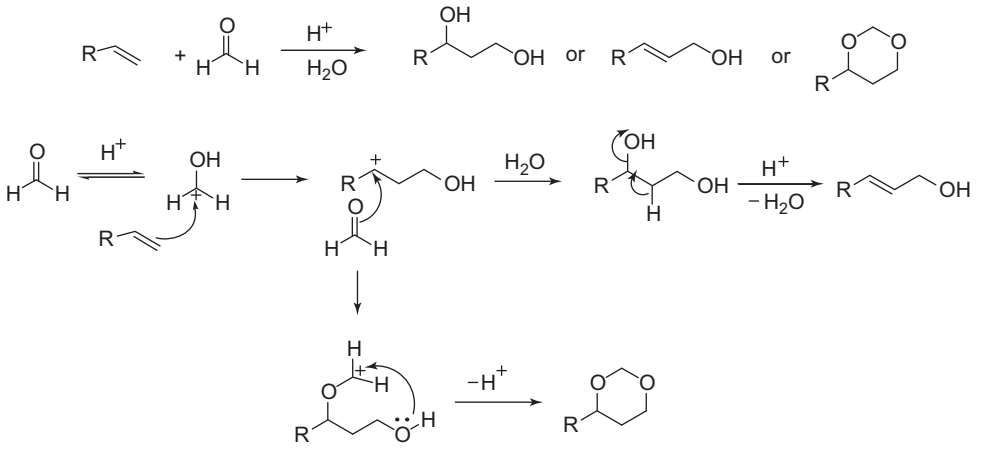
For steric reasons, (*E*)-alkenes (and transition states leading to (*E*)-alkenes) are usually lower in energy than (*Z*)-alkenes (and the transition state leading to them) because the substituents can get farther apart from one another. A reaction that can choose what it forms is therefore likely to favor the formation of (*E*)-alkenes. For alkenes formed by E1 elimination, this is exactly what happens: the less hindered (*E*)-alkene is favored. Carbocations can also lead to two other pathways, which do not yield to stable products but, instead, to other carbocations, that is, rearrangement and addition to an unsaturated linkage, for which the whole spectrum of reaction types is still open.



Scheme 2.12

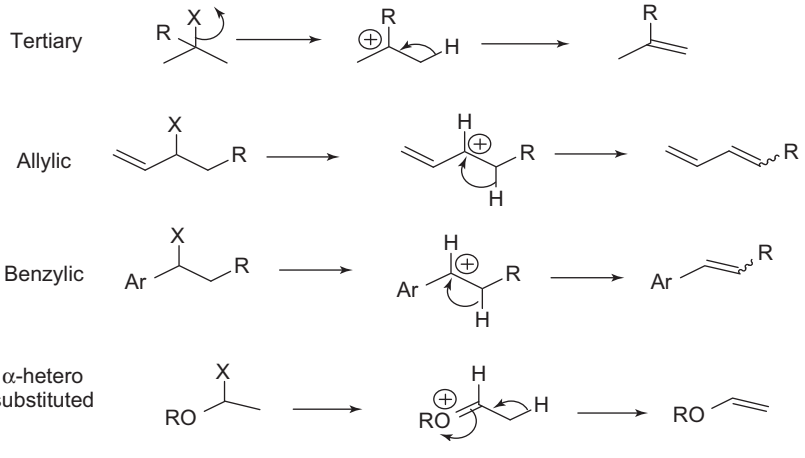
2.7.3 Rearrangements of Carbocations

Carbocations can be stabilized by the migration of hydrogen, alkyl, or aryl groups. Both stereochemistry and migratory aptitude can be factors in determining the extent of migration of the different groups. The rearrangement of *n*-butyl to *sec*-butyl carbenium ion is well known. This kind of rearrangement is a key



Scheme 2.13

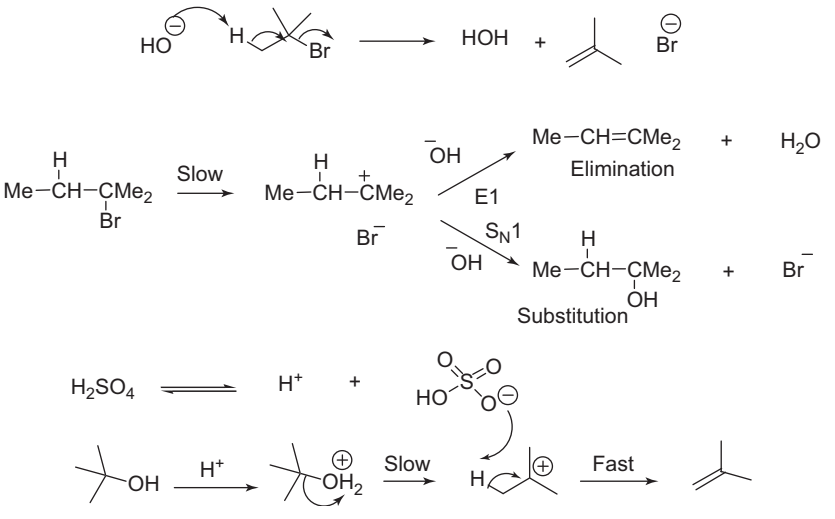
Substrates that readily eliminate by E1



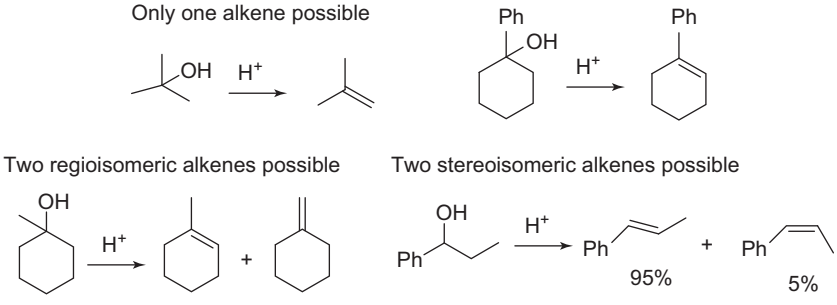
Scheme 2.14

step in common chemical reactions such as the formation of the 2-butenes by acid-catalyzed dehydration of 1-butanol, or the formation of *sec*-butyl benzene from the reaction of benzene with 1-chlorobutane in the presence of $AlCl_3$. Similarly, when an electrophile adds to 3-methyl-1-butene the *sec*-carbocation initially formed rearranges to give the *tert*-carbocation. A methyl group can also shift with its pair of electrons to give a more stable carbocation. The driving force for the rearrangements resides in the greater stability of a tertiary over a secondary or a primary carbocation (Scheme 2.17).

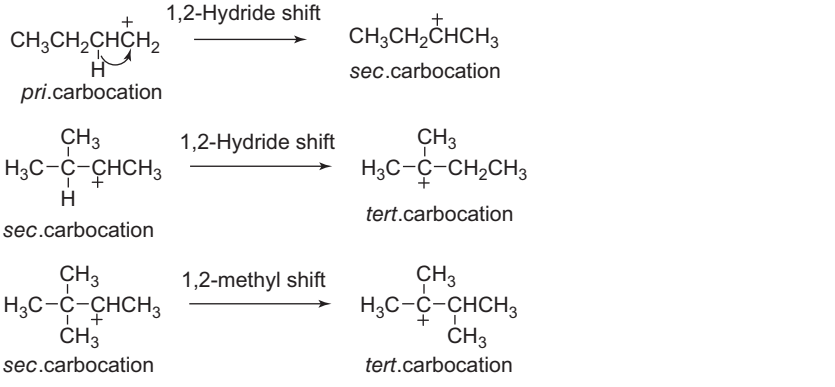
For this purpose of course, you cannot carry out a shift that is larger than 1,2. There are no 1,3 or 1,4 or higher shifts (Scheme 2.18).



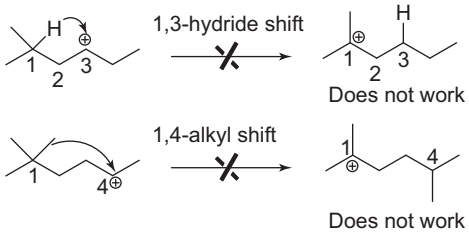
Scheme 2.15



Scheme 2.16



Scheme 2.17



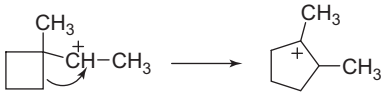
Scheme 2.18

In the absence of special electronic effects, alkyl groups show a clear dependence on the size of the migrating group. In general, smaller groups migrate before larger ones:

$$H > Me > CHMe_2 > CMe_3$$

It is difficult to give an absolute scale for migratory aptitude, however, since migratory aptitude is inevitably linked to the stability of the cation being formed.

Carbocation rearrangements also can occur by ring expansion, which is another type of 1,2-shift (Scheme 2.19).



Scheme 2.19

We might not expect to see rearrangement from a 3° carbocation, since it is not evident how a more stable carbocation could be formed. However, there is evidence that carbocations have a surprising facility for rearrangement, even if the rearrangement is not evident from the chemical reaction. For example, the proton NMR spectrum of the cyclopentyl carbocation (Figure 2.14) at −70 °C is a singlet (indicating the equivalence of all the protons), not the multiplet expected for a system with three sets of magnetically nonequivalent protons. Similarly, the ^{13}C NMR spectrum indicates one carbon signal coupled with nine equivalent protons. Apparently a rearrangement takes place rapidly on the NMR time scale so that all nine protons in the molecule are equivalent. A study of the line broadening of the ^{13}C NMR spectrum of cyclopentyl carbocation by Saunders revealed an isomerization rate of $3.1 \times 10^7\ s^{-1}$ at −139 °C, with a $\Delta G^{\#}$ of 3.1 kcal mol^{-1}.

We might expect that the isopropyl cation would be immune to the 1,2 hydride shift exhibited by the cyclopentyl cation, since a simple hydride shift would convert

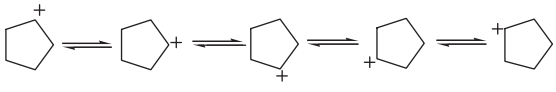


Figure 2.14 Equilibration of protons due to rapid rearrangement in the cyclopentyl carbocation.

a 2° carbocation into a 1° carbocation in an endothermic process. Nevertheless, scrambling of hydrogen atoms in the isopropyl cation was inferred by Saunders from proton NMR spectra, and the E_a for the reaction was determined to be 16.4 kcal mol^{-1}. More surprising than the proton rearrangement is the rearrangement of the carbon skeleton. Olah observed that a sample of isopropyl cation labeled at the 2-position with ^{13}C underwent carbon skeletal rearrangement with a half-life of 1 h at −78 °C, and after several hours the label was evenly distributed along the carbon chain.

The situation for the *sec*-butyl cation is even more interesting. We might expect it to behave in the same way as the cyclopentyl cation, that is, to undergo degenerate rearrangement between the two 2° carbocations at a rapid rate. At −110 °C the proton NMR spectrum of this species showed two sets of protons, consistent with expectation. However, warming the sample to −40 °C led to coalescence of the two peaks, indicating scrambling of all nine protons in the ion. (Heating the sample above −40 °C led to isomerization to the *t*-butyl cation.) Saunders suggested that the proton scrambling reaction arises through isomerization of the *sec*-butyl cation to a protonated methylcyclopropane, followed by opening to an isomerized *sec*-butyl cation.

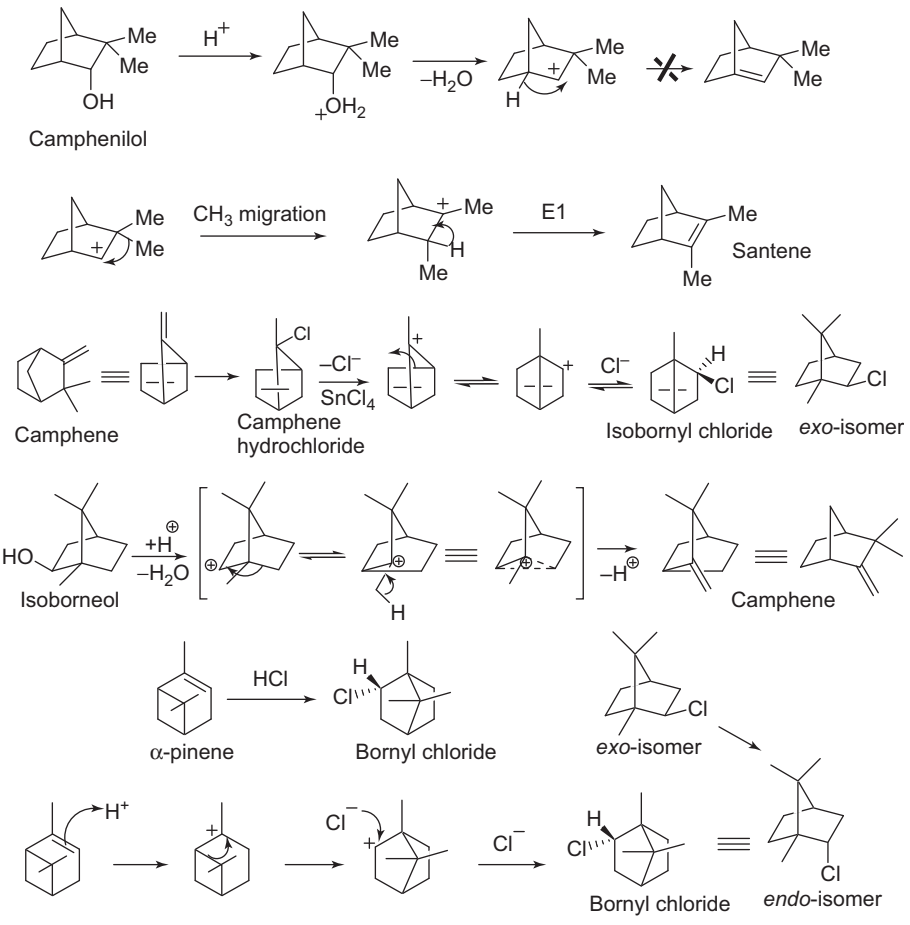
In alicyclic systems, the relief of strain can provide a powerful driving force for rearrangement. The classical examples are the transformation of camphenilol into santene and camphene hydrochloride into isobornyl chloride. Isobornyl chloride the *exo*-isomer (i.e., chlorine atom on the side opposite to the migrating bridge) is the sole product, which slowly rearranges to the thermodynamically more stable *endo*-isomer (bornyl chloride). Bornyl chloride is also obtained by treatment of α-pinene with HCl. The strained four-membered ring in the carbocation expands to the less strained five-member analog, despite the fact that the former contains a tertiary and the latter a secondary carbocation (Scheme 2.20).

In cyclic systems that enforce sufficient structural rigidity or conformational bias, the course of the rearrangement is controlled by stereoelectronic factors. The carbon substituent that is *anti* to the leaving group is the one that undergoes migration. In the *trans*-decalin derivative below, the hydroxyl group is held in the equatorial position because the ring system cannot flip. In this situation there is no hydrogen *anti* to the hydroxyl, but two of the ring carbon atoms are in the appropriate *anti* position for rearrangement (that migrates which leaves the more stable carbocation) and, in the presence of acid, ring contraction takes place (Scheme 2.21).

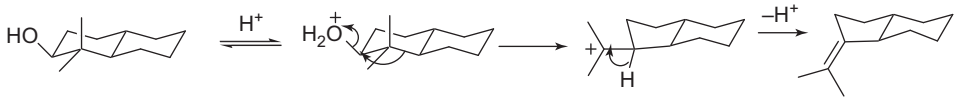
Wagner–Meerwein rearrangements of cations are similar in detail to those in which hydrogen atoms migrate. For example, in the solvolysis of 1-bromo-2,2-dimethylpropane heterolytic cleavage of the C–Br bond leads not to the primary cation but to the more stable tertiary cation (Scheme 2.22).

This cation is produced when a methyl group migrates from C2 to C1 as the C–Br bond is broken. The simultaneous migration of the alkyl group and departure of the leaving group to form a tertiary cation is, therefore, faster than the simple loss of the leaving group to form a primary cation.

The products observed are those that result from further reaction of rearranged (tertiary) cation. The alcohol results from reaction of the tertiary cation with water, forming an oxonium ion. Loss of a proton generates the product alcohol with a



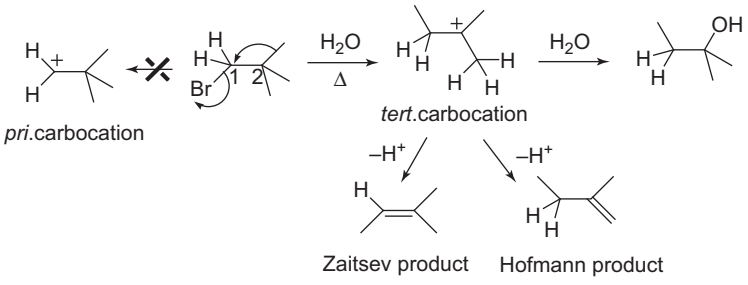
Scheme 2.20



Scheme 2.21

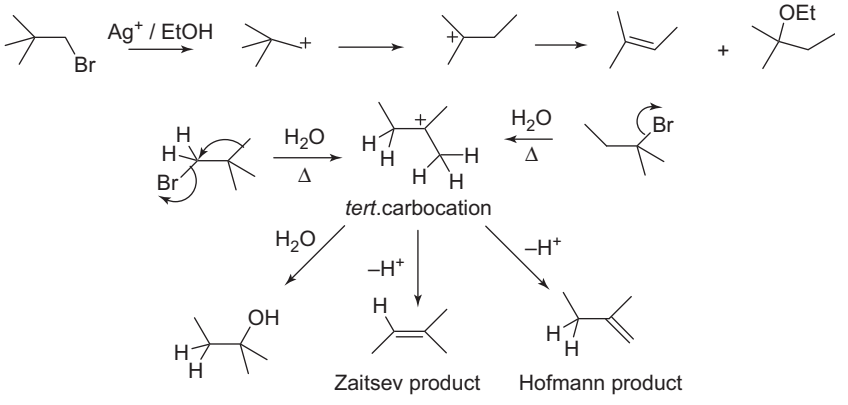
rearranged carbon skeleton. Alternatively, the cation can lose a proton from either of two different adjacent sites to give either the Zaitsev or Hofmann elimination product. All three observed products derive from the rearranged cation, whose carbon skeleton differs from that of the starting material because of migration of methyl group from C2 to C1 in a Wagner–Meerwein rearrangement.

When a more stable intermediate can be formed by migration of an alkyl group or hydrogen, rearrangement nearly always occurs. The products formed depend on the structure of the intermediate cation, no matter how this cation is initially formed.



Scheme 2.22

For example, the products obtained from the solvolysis of 2-bromo-2-methylbutane are the same as those from the solvolysis of 1-bromo-2,2-dimethylpropane. When a driving force for cation rearrangement exists, migration of an alkyl group almost always takes place faster than trapping of a less stable cation by solvent or another nucleophile (Scheme 2.23).

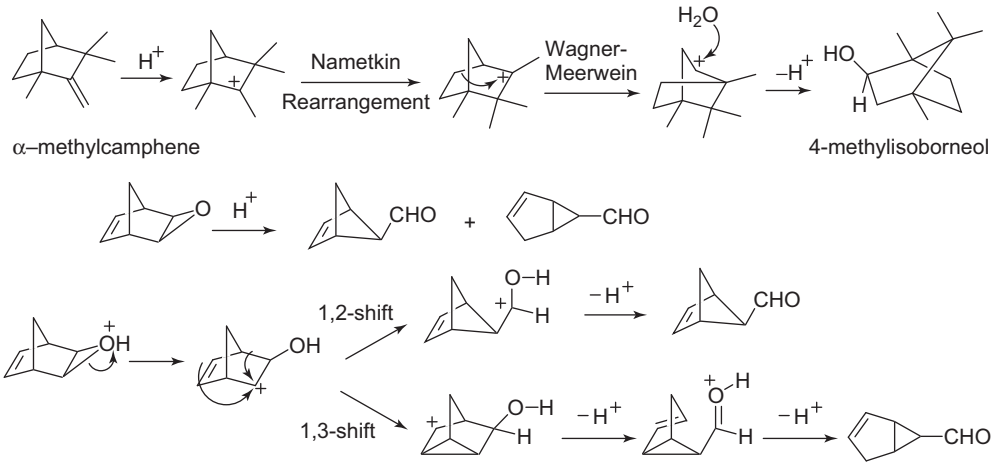


Scheme 2.23

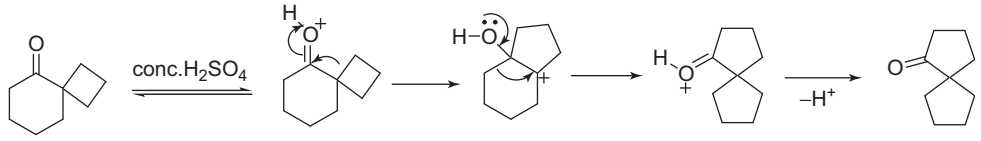
This particular type of Wagner–Meerwein shift has special recognition due to its importance in the field of terpene chemistry. For example, the conversion of α-methylcamphene into 4-methylisoborneol involves both a Nametkin and a Wagner–Meerwein rearrangement. In the *Meinwald rearrangement* both 1,2- and 1,3-shifts occur to give different products (Scheme 2.24).

A carboxonium ion may become less stable than a carbenium ion only when ring-strain effects dominate. In such cases carbenium ions can be generated from carboxonium ions by way of a Wagner–Meerwein rearrangement. Thus, the decrease of ring strain can provide a driving force strong enough to overcompensate for the conversion of a more stable into a less stable cationic center (Scheme 2.25).

The stabilization of a carbocationic center by an adjacent carbon–silicon bond (sometimes called the *β-effect*) can be used to control the course of carbocation rearrangement and carbocation-induced cyclizations.

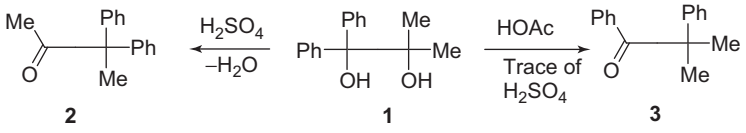


Scheme 2.24



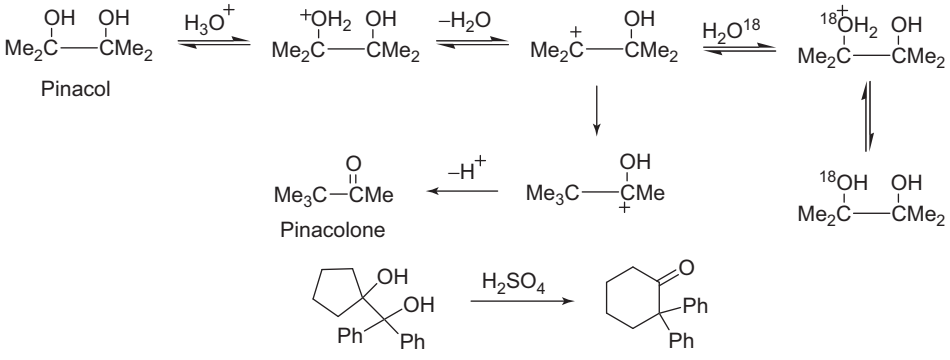
Scheme 2.25

Glycols in which the four R groups are not identical can give rise to more than one product depending on which group migrates, which depends on the reaction conditions as well as on the nature of the substrate. Thus, the action of cold, concentrated H_2SO_4 on **1** produces mainly 3,3-diphenyl-2-butanone (**2**) (methyl migration), while treatment of **1** with AcOH containing a trace of H_2SO_4 gives mainly **3** (phenyl migration) (Scheme 2.26).



Scheme 2.26

Of the two OH groups, the one which forms the more stable carbocation is protonated preferentially. This factor takes precedence over the migratory aptitude factor. Further evidence for carbenium ion formation in the pinacol rearrangement has been obtained by oxygen-exchange experiments. Partial rearrangement of pinacol to pinacolone has been carried out in acidic solutions containing H_2O^{18} (Scheme 2.27).



Scheme 2.27

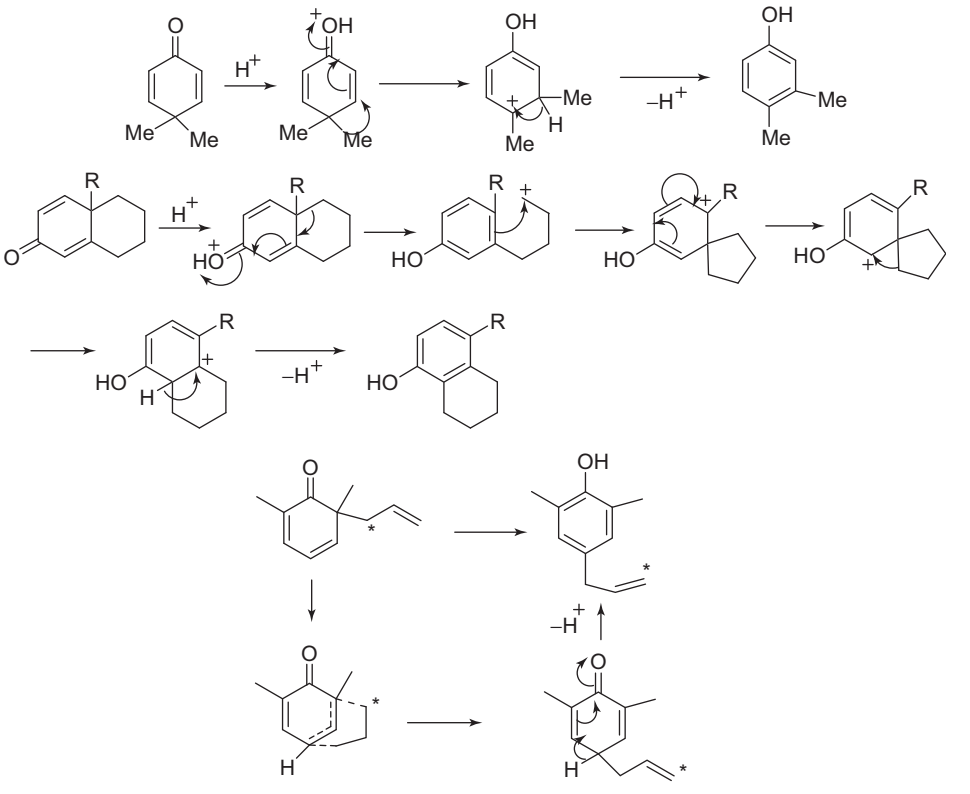
1,2-Rearrangement of carbenium ions occurs quantitatively only if:

- the new carbenium ion is substantially better stabilized electronically by its substituents than the old carbenium ion;
- the new carbenium ion is substantially more stable than the old carbenium ion because of other effects such as reduces ring strain;
- or the new carbenium ion is captured in a subsequent, irreversible reaction.

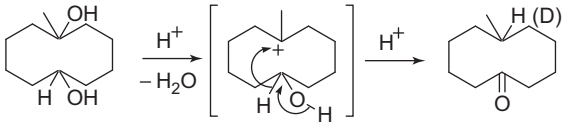
Transformation of a dienone into phenol in the presence of acid is known as the *dienone–phenol rearrangement*. As the name implies, this reaction results in the transformation of a quinoid structure into a benzenoid ring. It may be considered as a reverse pinacol rearrangement, since pinacol and semipinacol rearrangements are driven by the formation of a carbonyl group. The dienone in acetic anhydride solution is treated with a catalytic amount of sulfuric acid at room temperature. The protonated carbonyl compound rearranges to a tertiary carbocation, which rapidly undergoes elimination of H^+ to become aromatic. Thus, the driving force for the overall reaction is the creation of an aromatic ring in the product. In this rearrangement the migration terminus is not the carbon of a protonated carbonyl group, but rather a carbon in conjugation with it (Scheme 2.28).

Just as alkyl groups may undergo 1,2-shifts, hydride is also a candidate for such rearrangements. Hydride migrations involving more than neighboring centers in open chain substrates appear generally to be highly disfavored and most 1,*n*-hydride shifts can be accounted for by several 1,2-hydride shifts occurring in series. However, hydride rearrangements over large distances are well documented in medium ring (8–11-membered) carbocycles and are termed *transannular hydride migrations*. For example, 1-methylcyclodecane-1,6-diol on treatment with acid rearranges to form 6-methylcyclodecanone with none of the alternative product resulting from methyl migration being detected (Scheme 2.29).

As further evidence of the reluctance of alkyl groups to undergo transannular shifts, cyclodecane-1,6-diol does not form any ketone on acid treatment. More distant hydride shifts can also be studied, such as 1,4 and 1,5 hydride shifts.

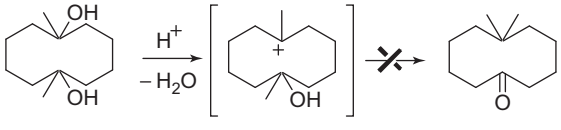


Scheme 2.28



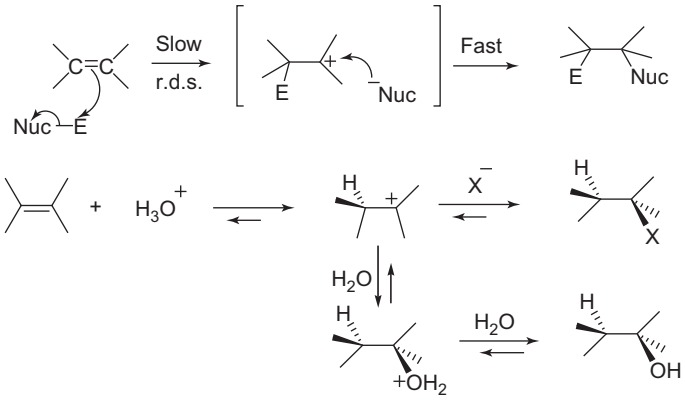
Scheme 2.29

These arrangements, though, are too fast to give secondary cation intermediates (Scheme 2.30).



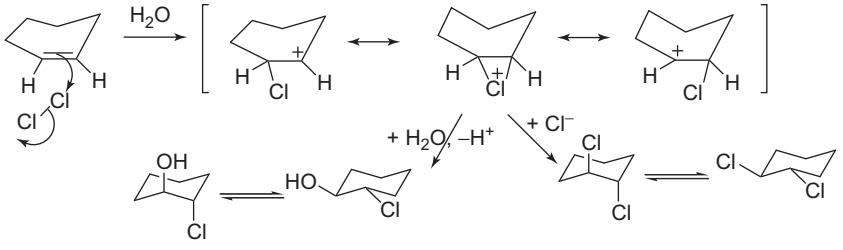
Scheme 2.30

In electrophilic addition, of course, the overall process is completed by the addition of a nucleophile (Scheme 2.31).



Scheme 2.31 Mechanism of electrophilic hydration and addition of HX to a simple alkene using H_3O^+ X^- in aqueous solution.

Nucleophilic capture of the chloronium ion by a water molecule (followed by proton loss) gives the chlorohydrin as shown (and its enantiomer) (Scheme 2.32). A *halohydrin* is an organic molecule that contains both an OH group and a halogen.

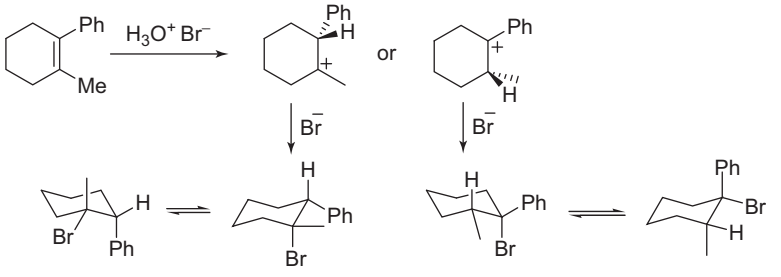


Scheme 2.32

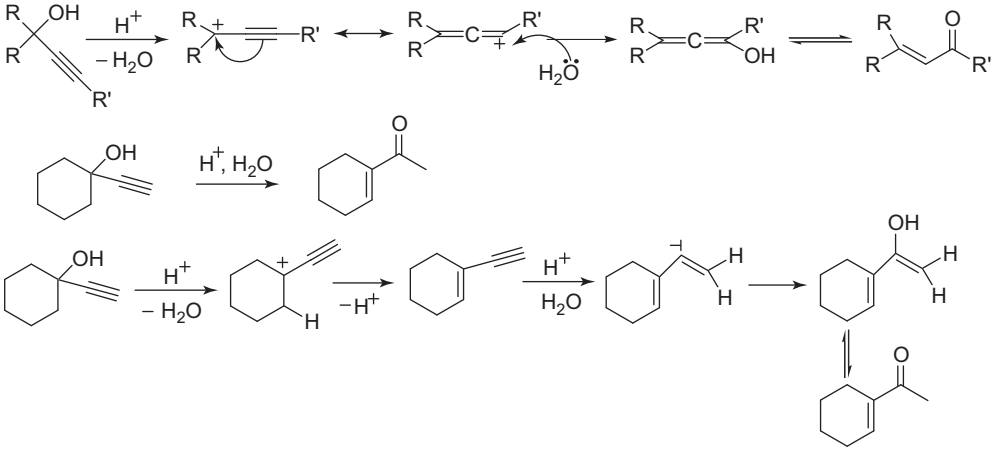
Protonation from above the plane at C1 and at C2 gives tertiary carbenium ions, which are both relatively stable, but the phenyl group allows extensive π-delocalization of the positive charge and, consequently, the ion with its charge adjacent to Ph is more stable and formed preferentially (Scheme 2.33).

Capture of carbenium ion by bromide ion from the face opposite to the one bearing the proton (i.e., the normal *anti* addition) gives the product of the reaction; the alternative route is not followed. Protonation from below the plane of the ring will lead to the enantiomeric product.

The isomerization of secondary and tertiary α-acetylenic alcohols to α,β-unsaturated carbonyl groups occurs via a 1,3-shift, when the acetylenic group is terminal. The products are aldehydes, whereas the internal acetylenes give ketones. The acid-catalyzed rearrangement of tertiary α-acetylenic (terminal) alcohols, leading to the formation of α,β-unsaturated ketones, is known as the *Rupe rearrangement* (Scheme 2.34).



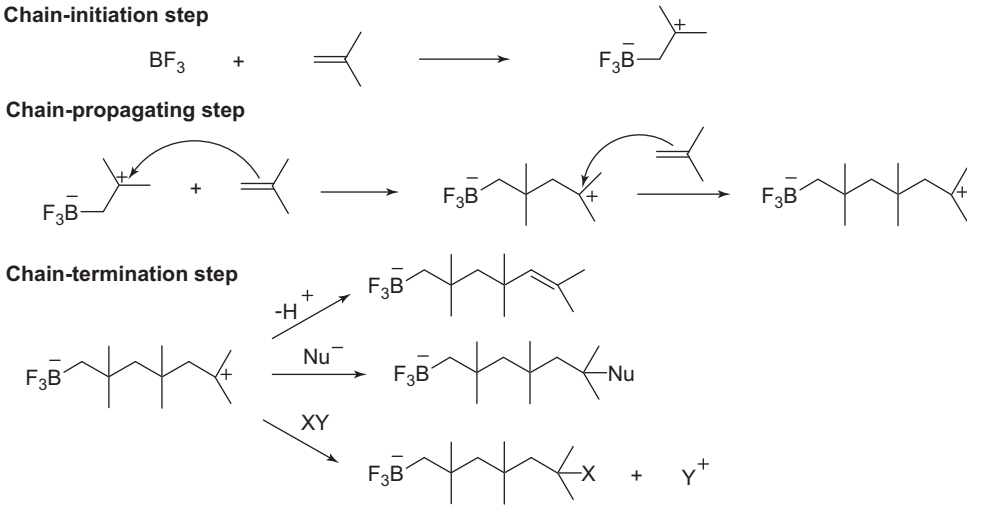
Scheme 2.33 Regioselectivity in the addition of HBr to 2-methyl-1-phenylcyclohexene using concentrated hydrobromic acid.



Scheme 2.34

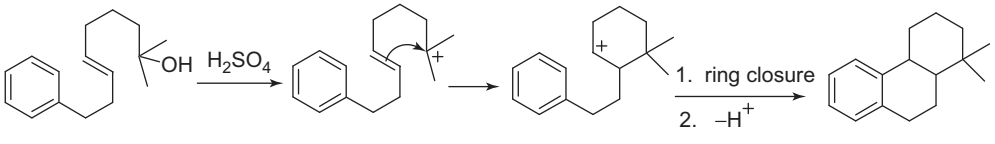
2.7.4
Cationic Polymerization

In cationic polymerization, the initiator is an electrophile that adds to the alkene, generating a cation. The initiator most often used in cationic polymerization is a Lewis acid, for example, BF_3 or $AlCl_3$. The advantage of such an initiator is that it does not have an accompanying nucleophile that may cause chain termination. Cationic polymerization can be terminated by loss of a proton, by addition of a nucleophile that reacts with the propagating site, or by a chain transfer reaction with the solvent (XY). The carbocation intermediate formed during the reaction can undergo rearrangement to a more stable carbocation. Monomers that are best able to undergo polymerization by a cationic mechanism are those with electron-donating substituents that can stabilize the positive charge at the propagating site (Scheme 2.35).



Scheme 2.35

In polyenes even tandem additions are possible. The best known and the most impressive example is the biomimetic synthesis of the steroid structure (Scheme 2.36).



Scheme 2.36

2.8 Nonclassical Carbocations

There has been considerable debate among organic chemists concerning the role of nonclassical structures as intermediates in reactions under normal conditions in solution. While alkyl groups do not usually undergo σ participation in acyclic or unstrained ring systems, there is much evidence to suggest that this does occur in strained rings. The species formed contain a two-electron, three-center bond and are known as "*nonclassical carbenium ions*." Nonclassical carbocations are a special type of carbocations that have the positive charge delocalized by a double or triple bond that is not in an allylic position, or by a single (σ) bond. Perhaps the "classic" example of such a nonclassical ion is the 2-norbornyl cation. However, not all researchers accepted this description, and the 2-norbornyl ions were also described as a pair of rapidly equilibrating classical (carbenium) ions (Figure 2.15).

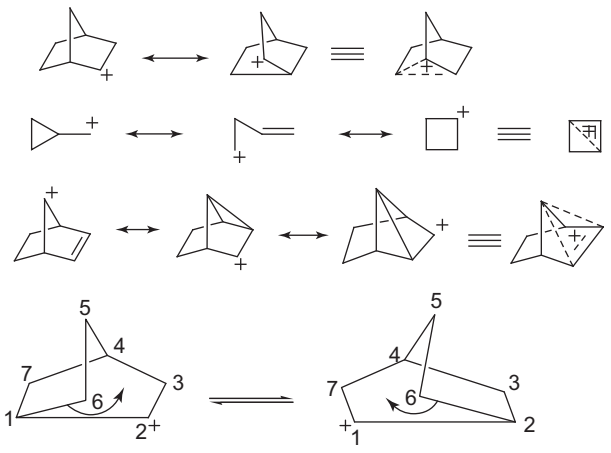


Figure 2.15 Rapidly equilibrating classical carbocation model for the 2-norbornyl cation.

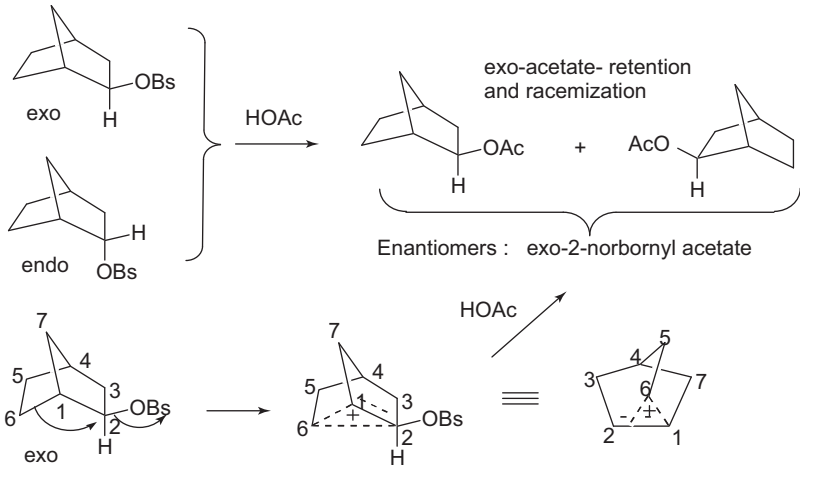
As with other carbocations, NMR spectroscopy has been utilized to determine the structure of the 2-norbornyl cation. The ^{13}C NMR spectrum at −70 °C showed three peaks: one at +101.8 ppm ($J = 53.3$ Hz) was assigned to carbon atoms 1, 2, and 6; another at +162.5 ppm ($J = 140$ Hz) was assigned to carbon atoms 3, 5, and 7; and a third at +156.1 ppm ($J = 153$ Hz) was assigned to carbon atom 4. We expect carbon atoms 1 and 2 to be equivalent, whether we think the carbocation is classical or nonclassical, but their equivalence with carbon atom 6 is a surprise. Apparently there is a rapid hydride shift that interconverts these positions.

During the acetolysis of *exo*- and *endo*-norbornyl brosylates it is found that solvolysis of the *exo*-isomer is 350 times faster than for the *endo*-isomer; both isomers give only the *exo*-acetate and optically pure *exo*-brosylate gives 100% racemic product while an optically pure *endo*-brosylate gives 93% racemic *exo*-acetate (Scheme 2.37).

The C_6–C_1 bond is situated at the rear side of the ionizable group and the σ electrons attacks the carbon bearing the ionizable group, thus facilitating the ionization. This leads to a nonclassical carbenium ion, which reacts with acetic acid to yield the racemic mixture of acetates. No such anchimeric assistance is available to the *endo*-isomer, which undergoes slow acetolysis through classical carbenium ions.

These results were interpreted as implying that the reaction of the *exo*-substrate occurred solely via a nonclassical carbocation, while the *endo*-substrate reacted by initial formation of a classical carbenium ion, which then rearranged to the nonclassical carbocation, but not before a small amount had reacted with solvent (attack being sterically directed to the *exo*-face).

Further support for the nonclassical structure of the 2-norbornyl cation came from an application of ^{13}C NMR spectroscopy based on the difference of the total chemical shift of a carbocation and the corresponding alkane. Differences in total chemical shift of 350 ppm or more suggest classical carbocations, while differences

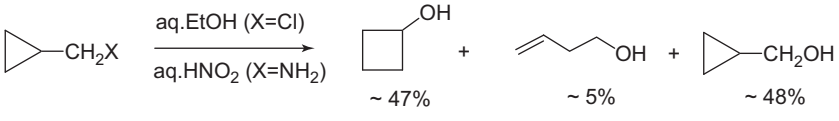


Scheme 2.37

of less than 220 ppm indicate nonclassical, bridged carbocations. For example, the sum of the total ^{13}C NMR chemical shift of propane is 47 ppm, while the sum for the 2-propyl cation is 423 ppm. The difference, 376 ppm, indicates that the 2-propyl cation is a classical ion. For the 2-norbornyl systems the total of the ^{13}C shifts is 408 ppm, while the total for norbornane is 233 ppm. The difference, 175 ppm, was taken as evidence for a nonclassical structure.

The conclusion that the 2-norbornyl cation is a nonclassical carbocation has been strengthened by the experimental determination of its infrared spectrum when the cation is generated in a cryogenic SbF_5 matrix. The experimental IR spectra agree with those calculated for a nonclassical structure.

Another system, which has attracted much interest, is that of the cyclopropylmethyl cation, for similar reasons to the 2-norbornyl systems: namely, the great ease of solvolysis of cyclopropylmethyl substrates accompanied by formation of rearrangement products. Of particular interest is that regardless of the method of generation of the cationic species the ratio of products is always very similar. Both hydrolysis of cyclopropylmethyl chloride under conditions favoring S_N1 substitution and diazotization of cyclopropylamine produce cyclobutanol and but-3-en-1-ol as well as cyclopropylmethanol in approximately 47%, 5%, and 48% yields respectively. Moreover, diazotization of cyclobutylamine also produces the same three alcohols in the same ratios (Scheme 2.38).



Scheme 2.38

So far the data might be interpreted by invoking a set of very rapidly interconverting classical carbocations, but the difference in rates of solvolysis of cyclopropylmethyl derivatives compared with the corresponding 2-methyl-1-propyl derivatives (106 : 1) appears to demand α-participation. The scheme involving the formation of nonclassical bicyclobutonium ions proposed by Roberts is generally accepted to explain all the features of this system. This envisages the initial formation of two equivalent three-center carbocations by methylene-assisted loss of the leaving group, followed by equilibration of these structures through a whole array of equivalent intermediates. These subsequent equilibriums result in ultimate scrambling of the carbon atoms.

Participation of a π bond to generate nonclassical carbocation has been shown during the acetolysis of tosylates **4–6**. Among the norbornyl derivatives the *anti*-tosylate (**6**) on acetolysis reacts 10^{11} times faster than its saturated analog (**4**) while **5** has 10^4 times greater reactivity than **4** (Figure 2.16).

The fastest rate of acetolysis of *anti*-tosylate, **6** compared to **4** proves the removal of the tosyl group with strong *anchimeric assistance* by the double bond. The resulting nonclassical carbocation, that is, bridged ion, can only react with acetate ion from the side opposite to the neighboring group, with retention of configuration. In the *syn*-isomer **5** the rate is slower because the double bond is not properly situated for participation. Compound **8** reacts 10^{14} times faster than **7** because the developing p-orbital of the carbocation in **8** is orthogonal to the participating bond of the cyclopropane ring (Figure 2.17).

A more distant methoxy group from the leaving group is found in 4-MeO alkyl sulfonate, which reacts with alcohols 4000 times faster than the *n*-butyl sulfonate (Scheme 2.39).

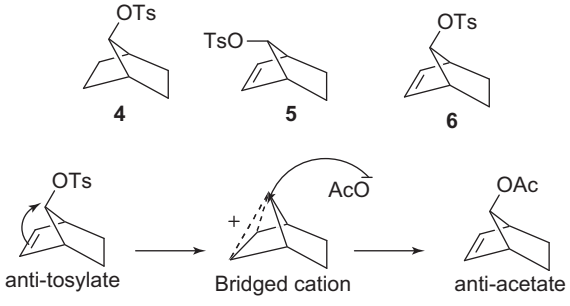


Figure 2.16 Participation of a π bond in generating a nonclassical carbocation.

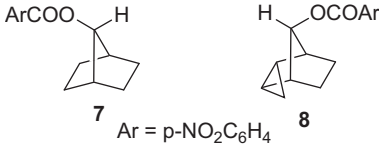
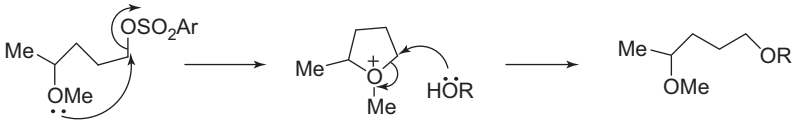


Figure 2.17 Compound **8** reacts 10^{14} times faster than **7** owing to anchimeric assistance.



Scheme 2.39

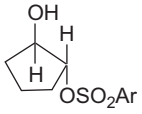


Figure 2.18 *trans*-2-Hydroxycyclopentyl arene sulfonates.

The OH group in *trans*-2-hydroxycyclopentyl arene sulfonates acts as a neighboring group when the leaving group is tosylate but not when the leaving group is nosylate (*p*-$NO_2.C_6H_4SO_2O$, -*ONs*); apparently, this is because the nosylate group leaves so fast that it does not require assistance. Neighboring group lends anchimeric assistance only when there is sufficient demand for it (Figure 2.18).

Aryl participation is more common than simple alkene participation. Again π-electrons are involved, but the reaction is now electrophilic aromatic substitution with a delocalized intermediate, often called a *phenonium ion*. A phenonium ion is symmetrical that can be attacked on either atom in the three-membered ring to give the same product (Scheme 2.40).

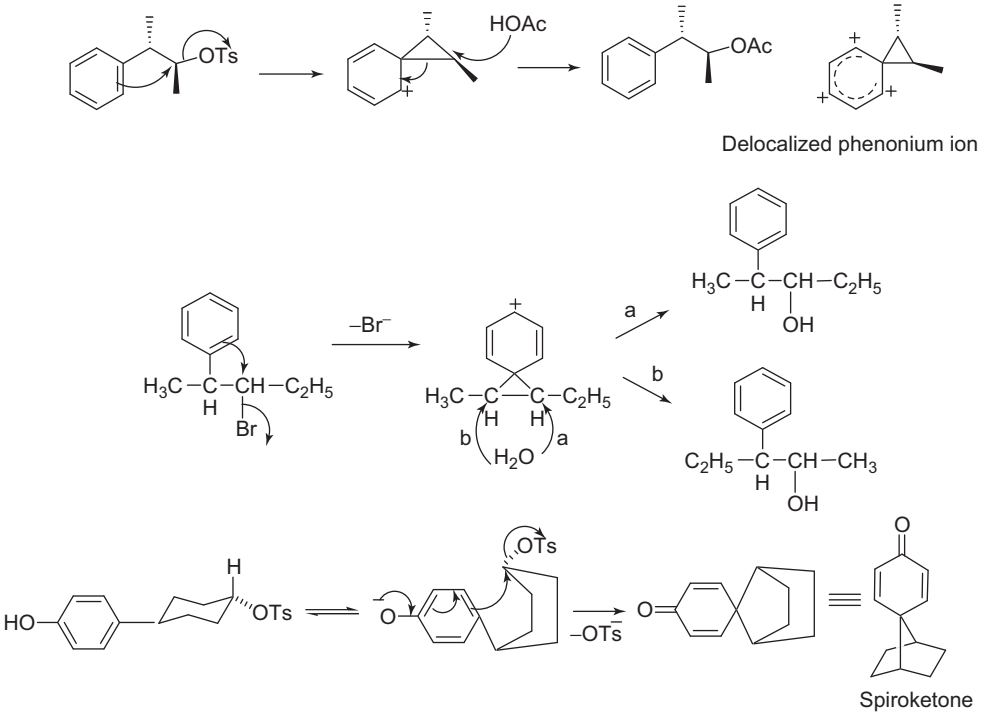
$PhC(CH_3)_2-CH_2Cl$ undergoes solvolytic rearrangement thousands of times faster than neopentyl chloride because the rate-determining step in the former case involves formation of a delocalized ("bridged") phenonium ion. The rate of the reaction is increased by the presence of electron-releasing groups in the aromatic ring and retarded by electron-withdrawing groups (Scheme 2.41).

Secondary alkyl chloride with good nucleophile (Et_2N) can participate in the formation of an aziridinium intermediate that is attacked by HO^- in S_N2 mode to give an amino-alcohol (Scheme 2.42). The CH_2 carbon has less steric crowing than the CHMe carbon. Intramolecular reactions, including participation, that give three-, five-, or six-membered rings are usually faster than intermolecular reactions.

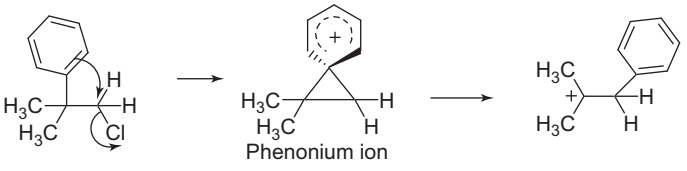
Tetramethylene chlorohydrin in H_2O is converted into THF about 10^3 times faster compared to ethylene chlorohydrin conversion into ethylene oxide (Scheme 2.43).

2.9 Radical Cations

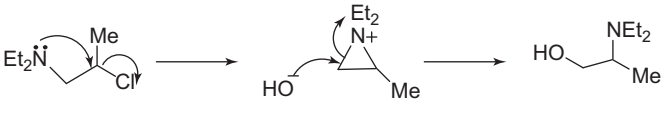
Radical ions possessing both an odd electron and charge are known. A radical ion possessing both an odd electron and a negative charge is known as a *radical anion*. Each of the carbocations discussed to this point has been a species in which all of the electrons were spin-paired. Another type of positively charged reactive intermediate is the radical cation – a species that has both an unpaired electron



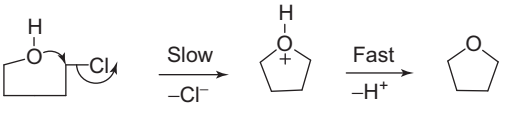
Scheme 2.40



Scheme 2.41



Scheme 2.42



Scheme 2.43

and a positive charge. Such species can be produced by the one-electron oxidation of a neutral species having no unpaired electrons. Radical cations play important roles in many radiochemical and photochemical reactions, and they may also be important in biological processes, including photosynthesis and the biosynthesis of natural products.

Organic radical cations can be generated from neutral organic compounds through:

1) chemical oxidation by a wide variety of oxidizing agents, including Brønsted acids, Lewis acids, metal ions and oxides, nitrosonium ions, other organic radical cations, semiconductor materials, and some zeolites;
2) electrochemical oxidation;
3) radiolysis with ionizing radiation (X-rays and γ-rays);
4) photoinduced electron transfer (PET) resulting from bimolecular reaction of a photoexcited molecule with a ground state molecule;
5) electron-impact ionization (commonly used for the production of radical cations in mass spectrometry).

Among the major analytical tools for detecting and studying radical cations are mass spectrometry, electron spin resonance spectroscopy, nuclear magnetic resonance spectrometry, and particular variations of these methods.

Organic radical cations can be classified according to the type of orbital from which an electron is removed from a neutral parent compound. Compounds with nonbonded electrons, such as amines, ethers, and ketones, can be oxidized to produce *n*-radical cations. For example, the one-electron oxidation of methanol is conveniently viewed as the removal of an electron from a nonbonding orbital associated with oxygen (Figure 2.19).

The formulation of the radical cation of methanol might suggest a species in which both the positive charge and the unpaired electron density are localized on oxygen. However, the HOMO of an alcohol is delocalized onto other atoms as well. The calculated methane radical geometry of the methanol radical cation indicates that one C–H bond is aligned with the p orbital on oxygen, this C–H distance is lengthened, and the O–C distance is shortened in comparison with neutral methanol. The implication of this geometry is that the delocalization results in shifting of electron density from C–H bonding to C–O bonding.

One-electron oxidation of alkenes, alkynes, and arenes produces species known as *π-radical cations*, formed by removal of an electron from a π molecular orbital (Figure 2.20).

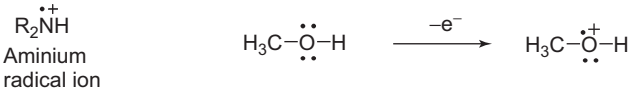


Figure 2.19 Examples of organic radical cations.

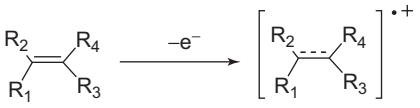
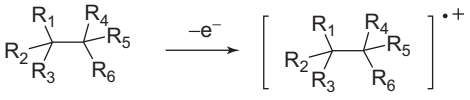


Figure 2.20 Formation of a π-radical cation.

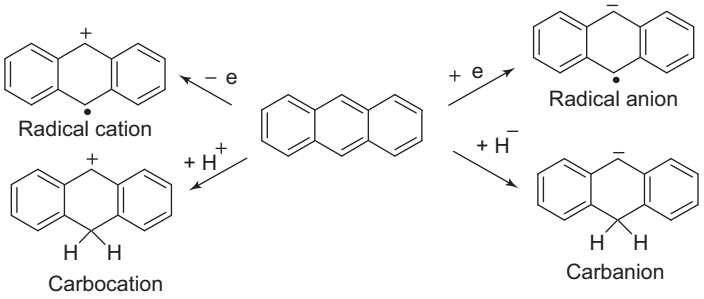
From an analysis of the photoelectron spectrum of ethene, the ethene radical cation was found to have a torsion angle of 25°. The C–C bond length is 1.405 Å, and the C–H bond length is 1.091 Å. The H–C–H bond angle is 117°51′. The geometry of the ethene radical cation has been explained on the basis of a compromise between some remaining π bonding in the singly occupied molecular orbital (SOMO) (optimized at a torsional angle of 0°) and hyperconjugative interaction of the p orbital on each carbon with the C–H bonding orbitals on the adjacent methylene group.

For larger alkenes, hyperconjugation with an alkyl group α to an olefinic carbon atom eliminates the need for rotation, so the radical cations of almost all alkenes other than ethene are planar. One-electron oxidation of alkanes leads to σ-radical cations. Such ionization removes an electron from an orbital associated with σ bonding among carbon atoms (Scheme 2.44).



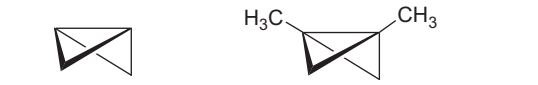
Scheme 2.44

The relation between the structure of carbocation, carbanion, radical cation, and radical anion can be best illustrated by considering the reaction of anthracene with different reagents (Scheme 2.45).



Scheme 2.45

Alkyl groups may also delocalize the unpaired electron and charge density in radical cations formed from strained alkanes. For example, radical cations of bicyclo[1.1.0]butane and 1,3-dimethylbicyclo[1.1.0]butane have been detected in a Freon matrix following γ-irradiation of the parent hydrocarbon (Figure 2.21).

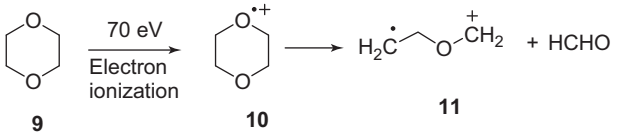


Bicyclo[1.1.0]butane 1,3-Dimethylbicyclo[1.1.0]butane

Figure 2.21 Examples of strained alkanes.

The data suggest that much of the unpaired electron density in the bicyclo[1.1.0] butane radical cation is associated with the two bridgehead carbon atoms, but that in the 1,3-dimethylbicyclo[1.1.0]butane radical cation about 15% of the unpaired electron density is associated with the methyl substituents at these positions.

In each of the radical cation structures discussed so far, the unpaired electron and the positive charge have been closely associated. However, there are also radical cations in which the radical center and the cation center are separate from each other. For example, electron ionization of 1,4-dioxane (**9**) in a mass spectrometer produces the radical cation (**10**), which eliminates formaldehyde to form a new species (**11**), which were termed *distonic* by Radom to emphasize the distance between the charge and radical sites; such species are lower in energy than the radical cation (Scheme 2.46).



9 **10** **11**

Scheme 2.46

Radical cations exhibit a wide variety of reactions, including unimolecular reactions such as rearrangement, fragmentation, and intramolecular bond formation as well as bimolecular reactions with ionic, radical, or ground state species. Notable processes include reaction with nucleophiles to produce radicals, reaction with radicals to produce cations, reaction with electron donors to produce biradicals, and reaction with ground state molecules to give addition products. Often the products of reactions of radical cations with neutral species are different from those observed by reaction of the corresponding carbocation with the same reactant.

Radical cations of weak acids may react either by heterolytic cleavage (loss of a proton to produce a radical) or homolytic cleavage (loss of a hydrogen atom to form a carbocation). In a polar solvent heterolytic cleavage is usually favored because of the favorable solvation energy of the proton, and radical cations are ordinarily much more acidic than the corresponding neutral compounds. For example, the pK_a value of toluene in DMSO is 43, while the pK_a^+ value for the radical cation of toluene is −20. Therefore, the difference in pK_a values of toluene and its radical cation is 63.

In the gas phase, heterolytic cleavage is favored because the positive charge can be stabilized by charge delocalization in a larger ion. Reaction of a radical cation

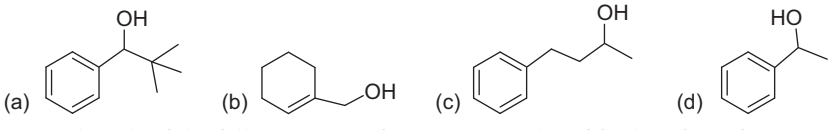
with a nucleophile can occur either by electron transfer to give a diradical or by attachment to give a radical.

2.10 Summary

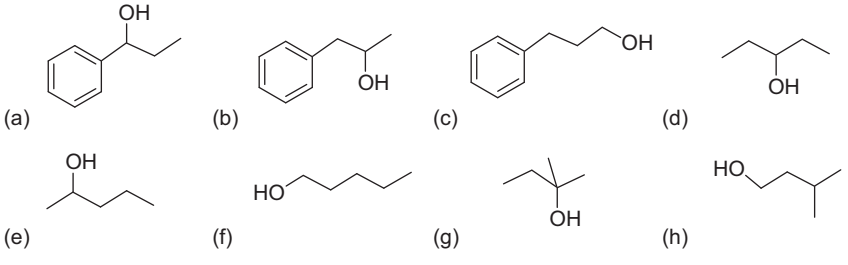
- Molecules with a positively charged carbon atom are called *carbocations*.
- Among simple alkyl carbocations, tertiary carbocations are the most stable and the primary carbocations the least stable.
- Carbocations are stabilized by resonance interactions and by adjacent lone pairs.
- Carbocations are most stable next to electron donating groups. Alkanes are slightly electron donating. This explains why S_N1 and E1 reactions need a secondary or tertiary α-carbon.
- Carbocations are formed by the loss of a leaving group from a carbon atom or by addition of an electrophile to a carbon–carbon double bond.
- A carbocation has no σ^* C–LG antibond. Instead, the carbocation loses its original shape to become planar. In this conformation electron density can be donated from *either* side of the carbocation.
- Carbocations may react by combination with a nucleophile, may undergo loss of a proton, or rearrangement.
- Polar, protic solvents favor S_N1 and E1 reactions. The polar and protic properties of the solvent stabilize the carbocation and solvate the leaving group.
- Increased stability of the rate-limiting transition state increases the rate of the reaction.

Problems

1. For each of the following alcohols, determine whether a primary, secondary, tertiary, allylic, or benzylic carbocation would be produced by protonation of oxygen followed by loss of water.



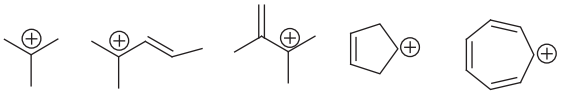
2. Rank each of the following sets of isomers in order of facility (from fastest to slowest) of acid-catalyzed dehydration.



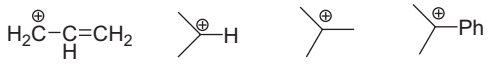
3. Rank the following sets of intermediates according to stability (most stable first).

(a) 

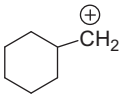
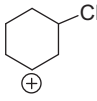
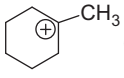
(b) $C_6H_5^{\bullet+}$ $p\text{-}NO_2.C_6H_5^{\bullet+}$ $p\text{-}CH_3.C_6H_5^{\bullet+}$ $p\text{-}Cl.C_6H_5^{\bullet+}$

(c) 

(d) $CH_3CH_2\overset{\oplus}{C}H_2$ $CH_3NH\overset{\oplus}{C}H_2$ $CH_3O\overset{\oplus}{C}H_2$ $FCH_2CH_2\overset{\oplus}{C}H_2$

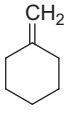
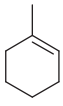
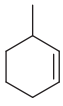
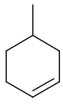
(e) 

4. Which of the following carbocations would you expect to rearrange?

(a)  (b)  (c)  (d)  (e)  (f) 

5. (a) How many carbon–hydrogen bond orbitals are available for overlap with the vacant p-orbital in the methyl cation?
(b) Which is more stable, a methyl cation or an ethyl cation?

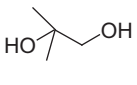
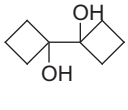
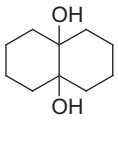
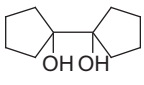
6. Give the major product obtained from the reaction of each of the following with HBr.

(a) $H_3C{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH{=}CH_2$ (b)  (c)  (d)  (e)  (f) $H_2C{=}CH{-}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}CH_3$

7. Arrange the following in decreasing order of their reactivity toward an electrophilic reagent (e.g., H^+).

(a) $H_2C{=}CH\overset{+}{N}Me_3$ (b) $H_2C{=}CH_2$ (c) $H_2C{=}CHMe$ (d) $H_2C{=}CHOMe$
(e) $H_2C{=}CHBr$ (*f*) $H_2C{=}CHNO_2$

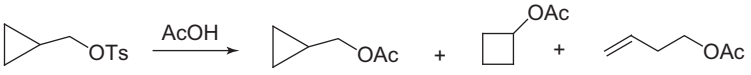
8. Suggest structures for the rearrangement products formed on treatment of the following substrates with acid.

(a)  (b)  (c)  (d) 

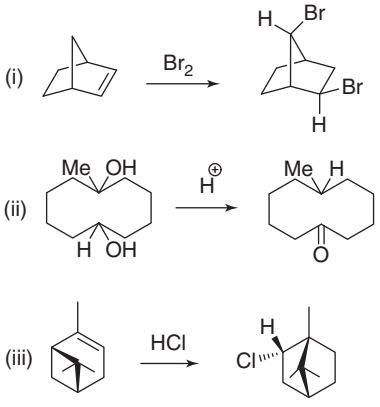
9. The triphenylmethyl cation is so stable that some of its salts can be stored for months. Explain why this cation is so stable.

10. Define and give an example for each of the following terms:
(a) classical carbenium ion;
(b) heterolytic cleavage;
(c) nonclassical carbenium ion;
(d) transition state;
(e) intermediate;
(f) rate-limiting step.

11. Give the mechanism for the following reaction.

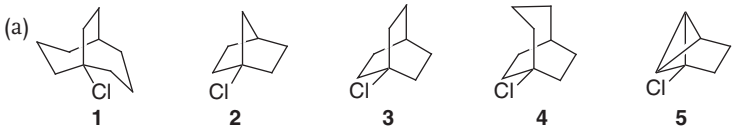


12. Explain each of the following reactions with a suitable mechanism.



13. The proton NMR spectrum of the 2-norbornyl cation in strong acid solution at 0 °C shows only one absorbance. Explain why.

14. Arrange the following compounds in order of solvolytic reactivity:

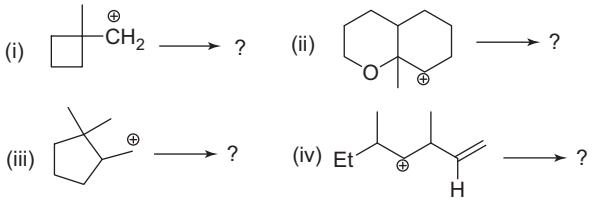


(b) $C_6H_5CH_2Br$, $(C_6H_5)_2CHBr$, and $(C_6H_5)_3CBr$.

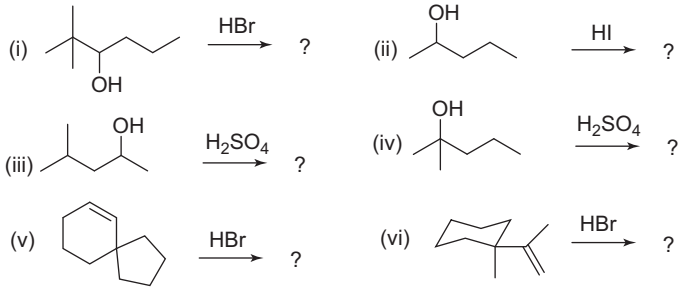
15. Can you think of a reason why the hydrogen atoms on carbons adjacent to a carbocation center are much more acidic than ordinary alkane hydrogen atoms?

16. When 1-methoxypropene is protonated, which atom acts as the H^+ acceptor, and why?

17. Draw the rearranged carbocations and discuss their comparative stability.

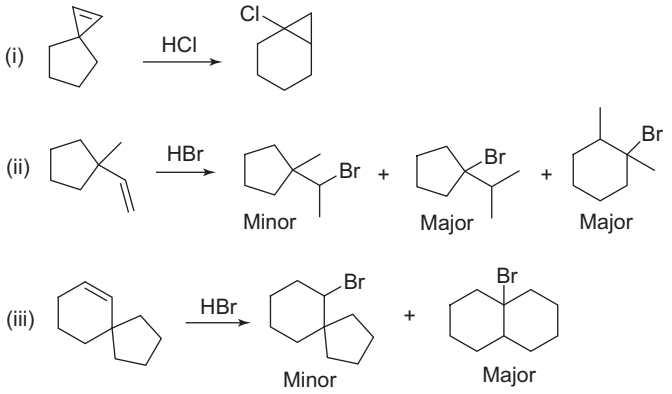


18. Predict both major and minor products for the following reactions.



19. Sketch the reaction coordinate versus energy diagram of the following unimolecular reaction. Reactant **1** is solvated to carbocation **2**. Then carbocation **2** rearranges to carbocation **3**. Finally, the solvent reacts with carbocation **3** to form product **4**.

20. Write the mechanisms that account for the following products.



21. For the following diols predict the major rearrangement product formed on treatment with cold dilute acid and propose a suitable mechanism:

(a) 2,3-diphenylbutan-2,3-diol;
(b) 1,1-diphenyl-2-methylpropan-1,2-diol;
(c) 2-methylpropane-1,2-diol;
(d) butan-2,3-diol.

Further Reading

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3
Carbanions

3.1
Structure and Geometry of Carbanions

Only intermediates that are formed before the rate-determining step can accumulate. Reactions where intermediates can be isolated in a normal work up are rather rare. More often, intermediates might be observable by spectroscopic techniques. The existence of short-lived intermediates or of intermediates occurring after the rate-determining step can still be demonstrated by trapping reactions or by special techniques such as matrix isolation. This chapter provides detailed explanations of reaction mechanisms involving carbanions, possible transition states, and the scope of the reactions. The selected experimental procedures can be implemented quickly and easily in the laboratory.

Carbanion is a unit that contains a negative charge on a carbon atom, and is therefore a base/nucleophile depending upon the reaction conditions. The negative charge gives good nucleophilic properties to the unit that can be used in the formation of new carbon–carbon bonds. Carbanions are powerful Brønsted bases because their conjugate acids are extremely weak acids. Formally, a carbanion is the conjugate base of a carbon acid and its valence shell is filled and bears a formal charge of 1. For the simplest methanide anion (CH_3^-), which exists only in the rarefied gas phase or under exotic conditions, we expect four pairs of electrons to be arranged around the central carbon atom with the nonbonded pair of electrons in an orbital that is approximately a sp^3 hybrid (Figure 3.1a). This expectation is in accordance with experimental evidence indicating that the methanide anion in the gas phase is tetrahedral (counting the nonbonded pair of electrons as a substituent). NMR studies of alkyl Grignard reagents in solution also show evidence of a tetrahedral carbanion that can undergo inversion of the lone pair similar to ammonia (Figure 3.1b).

Carbanions are trivalent species with sp^3 hybridization. The lone pair of electrons occupies one of the sp^3 orbitals, and the geometry is thus tetrahedral. The tetrahedron can undergo inversion or retain its stereochemistry depending upon the attached substituents. However, the geometry of a carbanion stabilized by conjugation with substituents is different. A methyl carbanion has a barrier to inversion of about 2 kcal mol^{-1}, whereas the trifluoromethyl carbanion has a

Reactive Intermediates in Organic Chemistry: Structure, Mechanism, and Reactions, First Edition.
Maya Shankar Singh.

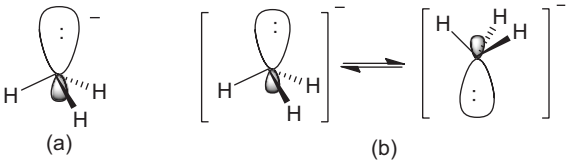
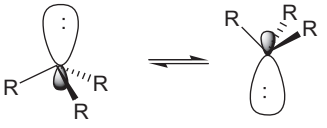
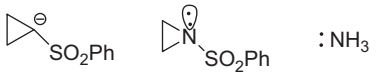


Figure 3.1 (a) sp^3-Hybridized methanide anion; (b) inversion of configuration.



R = H; barrier = 2 kcal/mol
R = F; barrier = 120 kcal/mol

Figure 3.2 A barrier to inversion of carbanions.



17 kcal 10 kcal 5.8 kcal

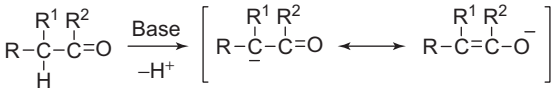
Figure 3.3 Comparison of rate of inversion.

barrier of 120 kcal mol^{-1} (Figure 3.2). A fluorine atom is thus more stabilizing than a hydrogen atom because of its high electronegativity.

The rate of inversion in hydrocarbon system is slowed by incorporation of the carbanion into a three-membered ring (Figure 3.3).

Valence shell electron pair repulsion (VSEPR) rules are a model in chemistry used to predict the shape of individual molecules based upon the extent of electron-pair electrostatic repulsion. According to VSEPR theory, the lone pair–lone pair (lp-lp) repulsion is considered to be stronger than the lone pair–bond pair (lp-bp) repulsion, which in turn is stronger than the bond pair–bond pair (bp-bp) repulsion. Hence, the weaker bp-bp repulsion is preferred over the lp-lp or lp-bp repulsions. Thus, the bond angles involving the carbon atom and any two of its three substituents may be less than 109.5°. Because there is not a preference for a planar geometry, we would expect bridgehead carbanions to form without difficulty and, except for steric inhibition, this is found to be true. Electron delocalization results in the formation of a double bond, which requires that all the atoms involved in it should be coplanar (Scheme 3.1). Loss of optical activity becomes understandable as the asymmetry of the negative carbon is destroyed with the formation of a carbon–carbon double bond (C=C). Coplanarity is an essential requirement for the formation of a carbanion stabilized by a neighboring group.

By similar arguments, we would predict that vinyl carbanions exhibit sp^2 hybridization and acetylenic carbanions show sp hybridization. Based on the idea that the greater the s character in an orbital the more easily it can accommodate



Scheme 3.1 Electron delocalization resulting in a coplanar structure.

a negative charge, we would expect carbanions in which the negative charge is associated with a pair of nonbonded electrons in an sp-hybrid orbital to be more easily formed than those in which the electrons are in sp^2 or sp^3 hybrid orbitals. Similarly, electron withdrawal by induction can stabilize a carbanion, as can conjugation/resonance interactions. A negatively charged carbon atom is only a convenient simplification of carbanion structure. In some cases the species we use as carbanions may have much less than a full negative charge. For example, ^{13}C and ^{7}Li NMR studies of *n*-butyllithium and *tert*-butyllithium in hydrocarbon solvent suggest a polar covalent C–Li bond with only a small negative charge on the carbon atom. Moreover, the species present appears to be an associated, not a monomeric species. *n*-Butyllithium is reported to be hexameric in hydrocarbon solutions but to exist as an equilibrium mixture of tetramers and dimers in THF (tetrahydrofuran) solution.

n-Butyllithium is an organolithium reagent. It is widely used as a polymerization initiator in the production of elastomers such as polybutadiene or styrene–butadiene–styrene (SBS). In addition, it is broadly employed as a strong base (superbase) in organic synthesis, both industrially and in the laboratory. Butyllithium is commercially available as solutions (15%, 25%, 2 M, 2.5 M, 10 M, etc.) in alkanes such as pentane, hexanes, and heptanes. Solutions in diethyl ether and THF can be prepared, but are not stable enough for storage. *n*-BuLi exists as a cluster both in the solid state and in a solution. The tendency to aggregate is common for organolithium compounds. The aggregates are held together by delocalized covalent bonds between lithium and the terminal carbon of the butyl chain. In the case of *n*-BuLi, the clusters are tetrameric (in ether) and hexameric (in cyclohexane) (Figure 3.4).

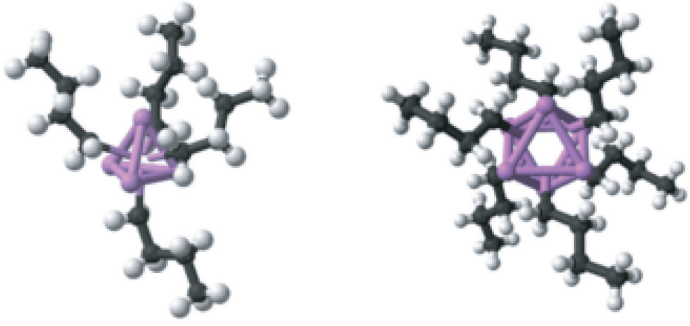


Figure 3.4 Polymeric structure of *n*-butyllithium in different solvents.

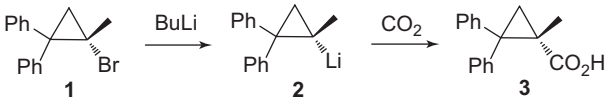
Carbanions in solution can be considered as resonance hybrids of two contributing structures, one purely covalent and one purely ionic (Eq. (3.1)):

$$\overset{\delta^-}{C}\ \overset{\delta^+}{M} = C\text{–}M \longleftrightarrow \overset{-}{C}: + M^+ \qquad (3.1)$$

The degree of ionic character depends on the nature of the metal, the medium, and the substituents on the carbanionic carbon atom. For simple alkyls (those in which resonance stabilization of the negative charge is not expected), the nature of the metal is especially important. The percent ionic character (alternatively, the percent contribution of the ionic resonance structure to the hybrid) increases with increasing difference in electronegativity of the two atoms.

The covalent character present in many carbanion carbon–metal bonds means that we must use caution in discussing the properties of carbanions based on reactions of organometallics. One way to study the structures of carbanions is to determine whether chiral carbanions undergo racemization. Studies of noncyclic carbanions indicate that the retention of configuration at a chiral carbanionic center depends on solvent and temperature, with solvents such as diethyl ether decreasing the covalent character of the carbon–metal interaction, and thus facilitating epimerization at the chiral center.

At bridgehead a carbon does not undergo reactions in which it must be converted into a carbocation. However, reactions that involve carbanions at such centers take place with ease, and stable bridgehead carbanions are known. The carbanionic carbon can in principle be a center of chirality, unlike the carbon center of carbocation or a radical, which have symmetry about the plane of the carbon atom. All reactions that involve the formation of a chiral carbanion should give retention of configuration. However, this never happens due to rapid inversion between two possible forms (i.e., an umbrella effect as in amines). Racemization at a chiral center can be retarded if the rate of inversion can be slowed. Although cyclopropyl radicals racemize, cyclopropyl carbanions retain their configuration. For example, lithiation of the optically active bromocyclopropane derivative **1** and subsequent addition of CO_2 was reported to produce the cyclopropanecarboxylic acid **3** with 100% retention of configuration, which suggests that the three-membered ring inhibits the inversion of carbanion **2** (Scheme 3.2).

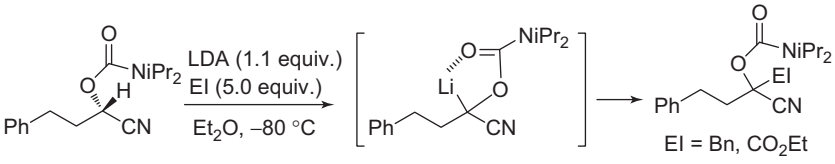


Scheme 3.2 Retention of configuration of the cyclopropyl carbanion.

In contrast, however, substituents that accept electron density by resonance can stabilize carbanionic centers and lessen the interaction with metal ions, leading to racemization. For example, the 1-lithio derivative of (–)-(*R*)-1-cyano-2,2-diphenylcyclopropane is alkylated with methyl iodide to yield racemic-1-methyl-1-cyano-2,2-diphenylcyclopropane, indicating racemization at the carbanionic center.

This result could be ascribed either to a planar carbanion with appreciable C=N=N$^-$ character or to a rapidly inverting tetrahedral carbanion. The X-ray crystal structure of 1-cyano-2,2-dimethylcyclopropyllithium indicated a tetrahedral carbanion carbon atom, supporting the latter explanation.

Although α-nitrile carbanions have been extensively used for carbon–carbon bond formation because of their powerful nucleophilic character due to the small steric demand, extension to an enantioselective version using enantiopure chiral carbanions next to a nitrile group has been considered to be challenging because the chirality is immediately lost by the formation of an sp^2-hybridized keteniminate. A α-chiral nitrile carbanion generated by deprotonation of enantioenriched O-carbamoyl cyanohydrin has been trapped *in situ* with ethyl cyanoformate to give the corresponding ester derivative in 92% yield and 90 : 10 ee, providing the first example of trapping of an α-chiral acyclic nitrile carbanion, which has been considered to be very configurationally labile (Scheme 3.3).



Scheme 3.3 Trapping of an α-chiral acyclic nitrile carbanion.

We know how stabilized carbanions such as enols and enolated enamines are key intermediates in biological isomerization reactions and in carbon–carbon bond-forming and bond-breaking events. In this chapter, we will look at two more important reaction types, called *Michael additions* and β-*eliminations*, which involve stabilized carbanion species as intermediates. In a Michael addition, a nucleophile and a proton are added to the two carbons of an alkene that is conjugated to a carbonyl group. The reverse of a Michael addition is called a β-*elimination*.

3.2
Generation of Carbanions

3.2.1
Reduction of C–X Bond with Metal

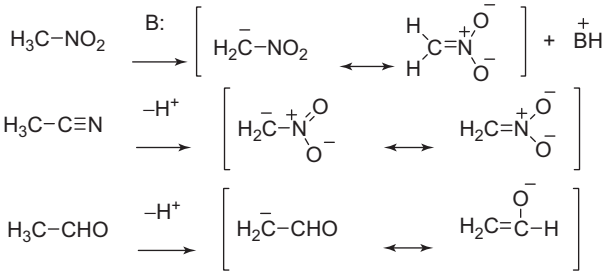
A common procedure for the synthesis of organometallic compounds is the reduction of a carbon–halogen bond with a metal (M), as illustrated in Eq. (3.2). This simple equation ignores the role of solvent molecules and aggregated species in some of these reactions:

$$R_3C{-}X \;+\; 2\,M \;\rightleftharpoons\; R_3C^{-}\,M^{+} \;+\; MX \qquad (3.2)$$

3.2.2
Deprotonation from a C–H Bond

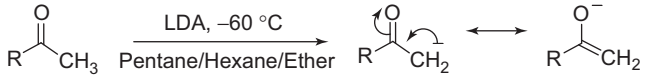
Certain methyl groups can be deprotonated. For example, the acidity of the methyl groups in acetone (Me_2CO) is about 10^{20} more acidic than methane. The resulting carbanions are key intermediates in many reactions in organic synthesis and biosynthesis. Reagents such as *n*-butyllithium, methyllithium, and phenyllithium are commercially available. Carbanions can also be formed by an acid–base reaction involving heterolytic dissociation of a carbon–hydrogen bond, as illustrated by the hypothetical example in Eq. (3.3) (Scheme 3.4):

(3.3)



Scheme 3.4 Generation of carbanion.

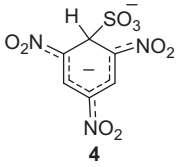
Because the polarity of carbon–hydrogen bond is very small and exhibits very low acidity, very strong bases are required for such reactions. However, C–H bonds adjacent to substituents such as carbonyl or cyano groups are stabilized by resonance/induction and are more acidic. Nitrogen bases have been used effectively in these reactions to minimize the nucleophilic addition that can compete with proton removal when an organometallic compound such as *n*-butyllithium is used as the base. For example, methyl ketones react with lithium diisopropylamide (LDA) to form the enolate ion (Eq. (3.4)), and even more sterically hindered amides have been used. The enolate anion is a strong base and a good nucleophile:



(3.4)

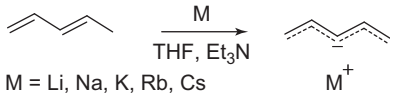
3.2.3
Reaction of a Metal with an Alkene

In some cases metals will react directly with alkenes (Eq. (3.5)), and alkenes sometimes form carbanions by addition of nucleophiles (Eq. (3.6)):

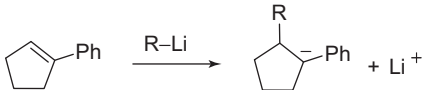


4

Figure 3.5 Jackson–Meisenheimer complex.



(3.5)

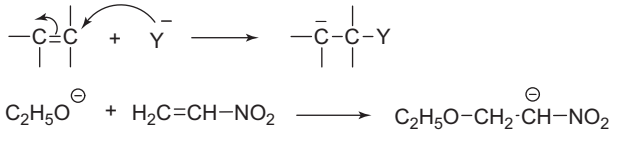


(3.6)

Addition of nucleophiles to aromatic compounds with several nitro or cyano groups leads to the formation of a resonance-stabilized carbanion known as a *Jackson–Meisenheimer complex*. For example, addition of sulfite ion to 1,3,5-trinitrobenzene leads to the complex **4** (Figure 3.5).

3.2.4
A Negative Ion Adds to a Carbon–Carbon Double or Triple Bond

The addition of a negative ion to a carbon–carbon double or triple bonds leads to a carbanion. The addition of a negative ion to a carbon–oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen. Carbanions are also formed when a nucleophile adds to an α,β-unsaturated compounds (Eq. (3.7)):

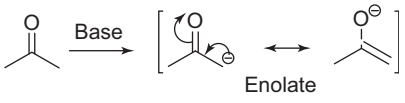


(3.7)

The formation of carbanions can occur in several solvent systems. Very strong bases cannot be formed in protic solvents because they abstract a hydrogen atom from the solvent to form a hydrocarbon. Commonly used solvents are: diethyl ether, THF, hexane (covalent aprotic); water, alcohols (polar protic); and DMSO (dimethyl sulfoxide), DMF (dimethylformamide), and HMPA (hexamethylphosphoramide) (polar, aprotic). The strongest bases are obtained from the reaction of metal with organohalogen compounds to give reagents known as *Grignard reagents* or commercially available organolithium reagents such as *n*-BuLi, PhLi, and MeLi. Potassium *tert*-butoxide, which is commercially available, and LDA, which is easily prepared in the laboratory, are frequently used for reaction with the α-hydrogen of carbonyl compounds to produce enolates.

3.3 Stability of Carbanions

The negative charge on a carbanion is stabilized by neighboring electron withdrawing groups (EWGs) such as carbonyl, nitro, cyano, and sulfone. Carbonyl functions are very effective in stabilizing an adjacent negative charge and when two carbonyl groups are present (as in diethyl malonate or acetylacetone) a very useful carbanionic intermediate is produced. The intermediate is called an *enolate* (Scheme 3.5). The dithiane system can stabilize the carbanion by dispersal of the charge into the d orbitals of the sulfur atoms.



Scheme 3.5 Stabilization of carbanion through formation of enolate.

We frequently measure anion stability in terms of the acidity of the corresponding protonated species. Thus, the acidity of carbon acids, in which the acidic proton is removed from a carbon atom, provides one measure of carbanion stability. The stability of a carbanion is directly related to the strength of the conjugate acid. The weaker the acid the greater the base strength, and lower the stability of the carbanion. There has been a rapid change in our models of carbanion stability in recent years. Carbanions vary widely in stability, depending on the hybridization of the carbon atom and the ability of substituents groups to stabilize negative charge. In the absence of substituents that are effective at stabilizing the charge, proton removal from the C–H bond is difficult.

A carbanion works as a nucleophile when attacks any electron-deficient center except a proton. The stability and reactivity of a carbanion is determined by several factors. These include:

- The inductive effect: electronegative atoms adjacent to the charge will stabilize the charge.
- Hybridization of the charge-bearing atom: the greater the s-character of the charge-bearing atom the more stable the anion.
- The extent of conjugation of the anion: Resonance effects can stabilize the anion. This is especially true when the anion is stabilized as a result of aromaticity.

The alkyl substitution at the carbanionic site results in an intensification of the carbanionic character because of the electron-donating character of the alkyl groups. The order of stability in carbanions is the reverse of that of carbocations, that is:

vinyl > phenyl > cyclopropyl > primary > secondary > tertiary

This order is well documented in metal alkyls. We can interpret this stability order solely as a consequence of field effect since resonance is absent. For example, methyllithium is stable in diethyl ether while *tert*-butyllithium decomposes to give

ethylene. The carbanions can be stabilized by electron-withdrawing substituents, unlike the carbocations, which are stabilized by electron-donating substituents.

The order of effectiveness of various groups for stabilizing the carbanion is:

$$-NO_2 > -COR > -SO_2R > -CO_2R > -CN > Hal > H > R$$

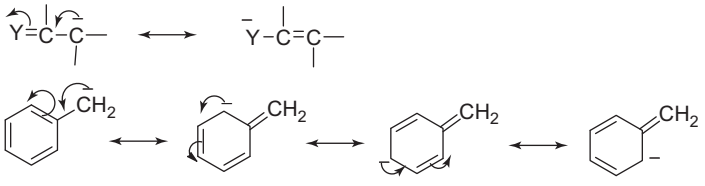
Major new insights into the electronic effects of substituents have resulted from measurements conducted in the gas phase, where the effects of solvent are eliminated. DePuy and coworkers determined that the order of acidity in the gas phase is:

ethane < propane (2°hydrogen atoms) < methane < isobutane (3°hydrogen atom)

This rather surprising result, that methane is more acidic than ethane, has some support in theoretical calculations. Therefore, the effect of alkyl substitution on a carbanion in solution may be better described as a result of the interference of solvation by bulky substituents.

Many carbanions are more stable than the simple kind mentioned above due to certain structural features:

1) Conjugation of the unshared pair with an unsaturated bond:
Allylic and benzylic anions are about 59 kJ mol^{-1} (14 kcal mol^{-1}) more stable than their non-allylic and nonbenzylic counterparts. There are two reasons for the stabilities of these anions. The first is *resonance stabilization* and second is the *polar effect* of the double bond (Scheme 3.6).



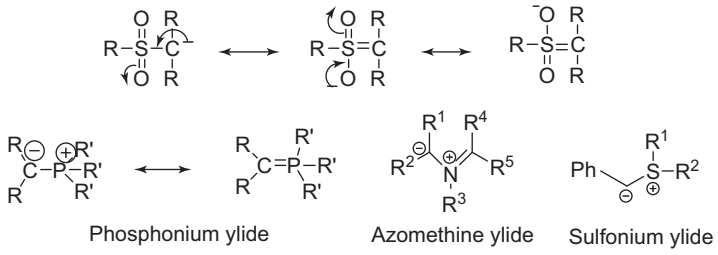
Scheme 3.6 Resonance stabilization of carbanions.

The order of decreasing acidity $Ph_3CH > Ph_2CH_2 > PhCH_3$ reflects the ability of each successive phenyl group to delocalize the negative charge on carbon and thereby stabilize the carbanion.

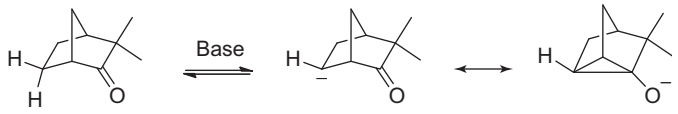
2) Carbanions increase in stability with an increase in the amount of s character at the carbanionic carbon. Thus the order of stability is:

$$RC \equiv C^- > R_2C = CH^- \approx Ar^- > R_3C - CH_2^-$$

3) Stabilization by sulfur or phosphorus:
The second row elements, particularly phosphorus and sulfur, stabilize the adjacent carbanion. The cause of stability is due to delocalization of negative charge of carbanion by a vacant d-orbital (pπ–dπ bonding) of phosphorus and sulfur, for example, sulfur and phosphorus ylides. Ylides are more stable than the corresponding simple carbanions (Scheme 3.7).



Scheme 3.7 Stabilization of carbanion by adjacent heteroatoms.



Scheme 3.8 Stabilization of carbanion by a nonadjacent π bond.

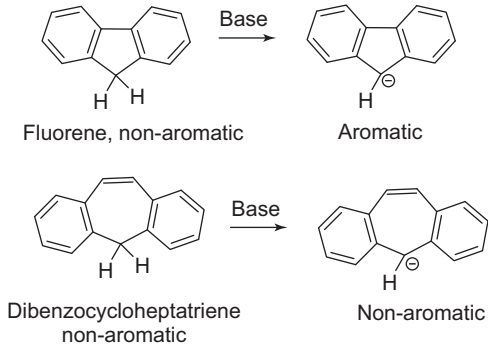
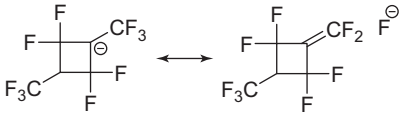


Figure 3.6 Stabilization through aromatization.

4) Stabilization by a nonadjacent π bond (Scheme 3.8):
5) Stabilization through aromatization:
   The much greater acidity of fluorine relative to dibenzocycloheptatriene reflects the aromatic stabilization of the cyclopentadienide ring in the fluorene anion (Figure 3.6).

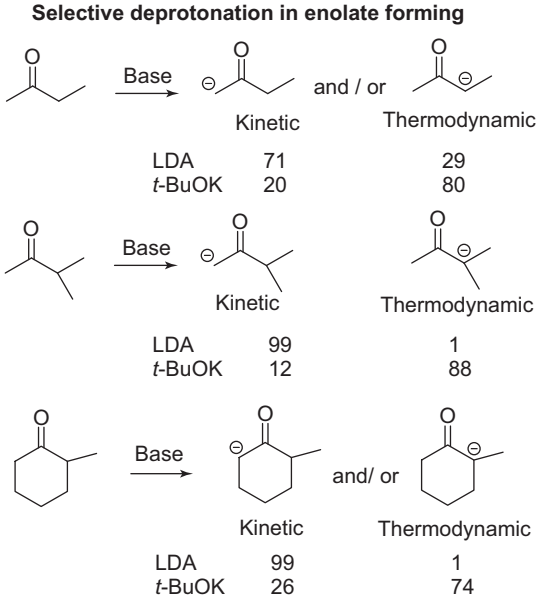
Carbanions containing β-fluorine atoms are strongly stabilized. The electronegativity of the fluorine atom is the main reason but some consideration must be given to "**negative hyperconjugation**," as has been found from the crystal structure of the compound (Scheme 3.9). Negative hyperconjugation is possible because fluorine atoms have a very low energy sigma star (σ*) orbital to accept the electron. In the structures shown the fluorine atom position is identical in each structure.

When carbanions are formed in unsymmetrical ketones, two types of carbanions are possible. One, the more substituted carbanion and more stable, is called the *thermodynamic anion*, while the least substituted and first formed anion is called



Scheme 3.9 Negative hyperconjugation.

the *kinetic anion*. LDA is a base of choice for the formation of kinetic products while hydroxide and alkoxides give the thermodynamic anion. In ketones with α-hydrogens on both sides of the carbonyl carbon, selectivity of deprotonation may be achieved to generate two different enolate structures. At low temperatures (−78 °C, i.e., dry ice bath) in aprotic solvents and with bulky non-equilibrating bases (e.g., LDA) the "kinetic" proton may be removed. The "kinetic" proton is the one that is sterically most accessible. Under thermodynamic conditions (higher temperatures, weak base, and protic solvent) equilibrium is established between the ketone and the two possible enolates, and the enolate favored is termed the "*thermodynamic*" enolate, which is favored because of its lower energy level than the other possible enolate. Thus, by choosing the optimal conditions to generate an enolate, one can increase the yield of the desired product while minimizing formation of undesired products (Scheme 3.10).

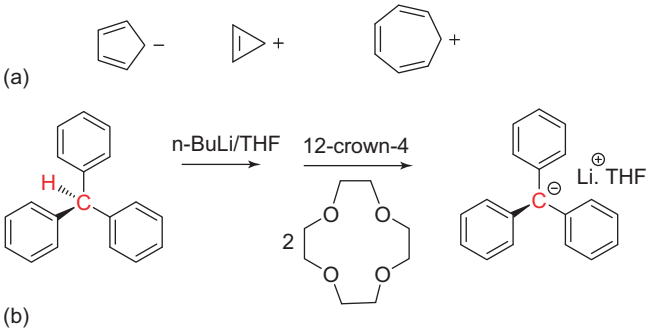


Scheme 3.10 Formation of kinetic and thermodynamic carbanions.

Fluorine atoms alpha to a carbonyl group oppose the normal polarization of the carbonyl, which contains a positive charge on the carbon and a negative charge

on the oxygen. Thus, fluorinated aldehydes and ketones show higher enol content than the hydrogen counterparts.

Both the carbanion and carbocations are stable provided they contain $(4n+2)$ π electrons. For example, cyclopentadienyl anion, cyclopropenium cation, and tropylium cation exhibit unusual stability. Stable carbanions do, however, exist. In 1984 Olmstead presented the lithium crown ether salt of the diphenylmethyl carbanion from diphenylmethane, butyllithium, and 12-crown-4 at low temperatures. Addition of *n*-butyllithium to triphenylmethane in THF at low temperatures followed by 12-crown-4 resulted in a red solution and the salt complex precipitated at −20 °C. The central C–C bond lengths are 145 pm with the phenyl ring propelled at an average angle of 31.2° (Scheme 3.11).



Scheme 3.11 (a) cyclopentadienyl anion and cyclopropenium and tropylium cations; (b) formation of the triphenylmethane carbanion.

Two important (and uncommon) examples of stable carbanions are the *cyanide anion* (NC^-) and the *metallocenes*. Metallocenes, an extremely important class of catalysts for modern polymer synthesis, are made from the reaction of two cyclopentadienylide anions (obtained by deprotonation of cyclopentadiene by an organometallic reagent such as a Grignard reagent) with a metal. The result is the metallocene salt, where the cationic metal is located between the two cyclopentadienylide rings in what is commonly called a *"sandwich"* arrangement. One tool for the detection of carbanions in solution is proton NMR. A spectrum of cyclopentadiene in DMSO shows four vinylic protons at 6.5 ppm and two methylene proton at 3.0 ppm whereas the cyclopentadienyl anion has a single absorption at 5.50 ppm.

Carbanions bear many substituents that can affect their structure and reactivity and can influence the acidity of a parent C–H precursor. Halogens stabilize carbanions in the order Br > Cl > F. A prominent I–π repulsion between the F and carbanionic center causes some destabilization in α-fluorinated carbanions. The magnitude of the destabilization depends on the carbanion structure. The destabilization is maximized as the carbanion structure approaches a planar configuration. Thus, fluorinated carbanions possess pyramidal structures with high barriers to inversion.

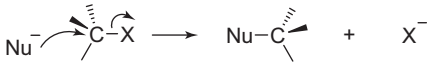
3.4 Reactions of Carbanions

A carbanion may act as base or nucleophile depending on the reaction conditions. Action as a base involves electron pair donation to H^+, whereas nucleophilic reactions involve electron pair donation to other atoms such as carbon. Can we relate base strength to nucleophilic reactivity? Here are some comparisons:

base strength: $C_2H_5O^- > OH^- > CN^- > Cl^-$;
nucleophilic reactivity: $CN^- > C_2H_5O^- > OH^- > Cl^-$.

The concepts are linked but are not the same. Nucleophilic reactivity is measured by the rate of reaction, whereas base strength is measured by the equilibrium constant, K_b. Here, we can use the acidity of the acid HX to get an idea of the ability of X^- as a leaving group in nucleophilic substitution, since both Eqs. (3.8) and (3.9) have X^- on the right-hand side:

(3.8)



(3.9)

Although the second is a kinetically controlled reaction whereas the first is a thermodynamically controlled equilibrium, one can provide a guide to the other. The best leaving groups are often the conjugate bases of strong acids. Thus, Br^- and Cl^- leave readily, CH_3COO^- less readily and OH^- the base corresponding to the very weak acid H_2O, much less readily. This neatly explains the idea of protonating alcohols with strong acid to make them more open to nucleophilic attack. As a leaving group, H_2O, the base corresponding to the strong acid H_3O^+, is a much than OH^-.

Carbanions are very useful intermediates for the formation of new carbon–carbon bonds. Thus carbanions participate in (i) S_N2 alkylation reactions, (ii) α-halogenation of ketones, (iii) 1,2 additions to carbonyl functions, and (iv) 1,4-additions such as Michael reactions. Fluorinated carbanions are very common useful intermediates for the synthesis of new fluorinated materials. As already noted, the fluorine atom will act in a stabilizing manner to withdraw electrons from the carbanion when the carbanion has a pyramidal shape. Fluorine back-bonding would be just the opposite in donating electrons to the carbanion center, and thus be destabilizing. The overall result is that fluorinated carbanions are pyramidal and therefore stabilized by the fluorine. There appears to be little difference between fluorinated and non-fluorinated carbanions in synthetic procedures. Carbanions have three pairs of bonding electrons and a pair of nonbonding electrons around the central carbon atom. Because of the localization of electron density and negative charge, carbanions act as both bases (coordination with proton only) and nucleophiles (reaction with any electron-deficient center except proton). Carbanions can take part in most of the main reaction types, for example,

addition, elimination, displacement, rearrangement, and so on. As a base, a carbanion can abstract a proton from any substance with a pK_a smaller than that of the protonated carbanion.

3.5 Enolate Reactions with Carbonyl Groups

Carbanions frequently add to the carbonyl double bond. The aldol reaction, Claisen reaction, Dieckmann reaction, Michael reaction, and Knoevenagel condensation are familiar examples of carbanions (as enolates) undergoing nucleophilic addition to carbon–oxygen double bonds.

3.5.1 Aldol Condensation

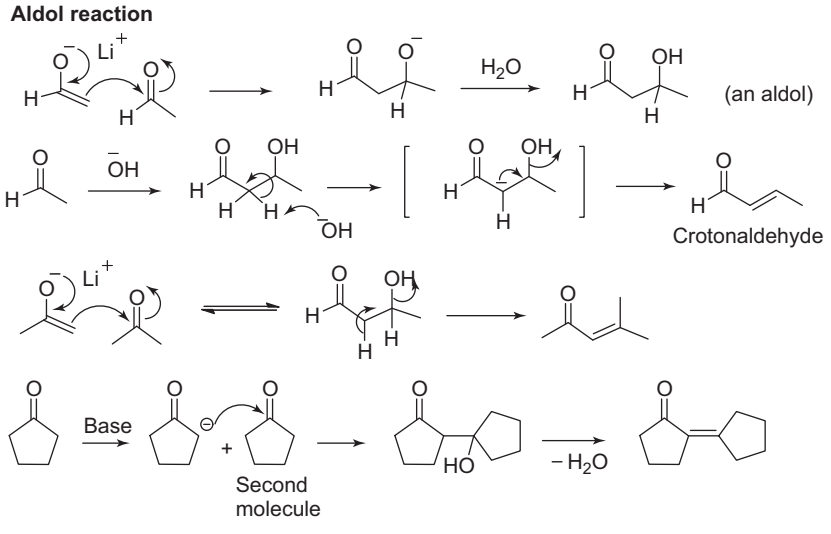
An aldehyde or ketone that has a hydrogen next to the carbonyl group can form an enolate in basic solution, and the enolate can react by nucleophilic addition at the carbonyl group of another molecule. This process is a very important synthetic procedure and is known as the *aldol condensation*. The final product from aliphatic aldehydes or ketones contains both a carbonyl and an alcohol group. The product is called an *aldol* (Scheme 3.12).

Aromatic ketones bearing α-hydrogens give aldol reaction products readily, but in this case the aldol product spontaneously loses water to form the unsaturated ketone. When benzaldehyde is used in the crossed-aldol condensation the final product is the unsaturated aldehyde or ketone. Conjugation of the double bond with the aromatic ring is the reason for the spontaneous dehydration (Scheme 3.13).

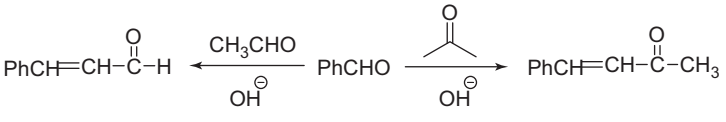
Fluoroacetonitrile condenses with carbon disulfide in an interesting aldol-type reaction (Scheme 3.14). The carbanion for ethyl fluoroacetate reacts readily with benzaldehyde in a cross-aldol reaction to give the fluorinated alcohol. α-Fluorinated carbonyl compounds are often very toxic materials because biologically they are converted into fluoroacetate, which is toxic to the Krebs cycle. Thus, extreme care is needed during the use of these compounds.

Esters, like aldehydes and ketones, give an aldol-type reaction. The α-hydrogen of the ester is removed by base to give the enolate. The enolate reacts with another molecule of the ester in an addition–elimination reaction characteristic of esters, which appears as displacement of the alkoxide. The resulting product is a β-ketoester. The reaction is known as the *Claisen condensation* (Scheme 3.15). The α-hydrogens in the product β-ketoester are more acidic than the α-hydrogens in the starting ester. Thus, a new enolate is formed that is more stable than the first enolate, thus helping the reaction go to completion.

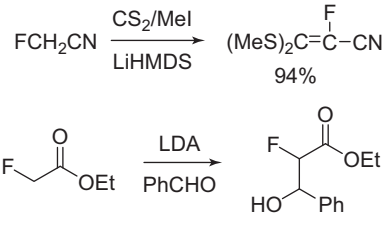
There are several useful esters that cannot enolize and, thereby, cannot act as enol partner. The four shown below are the most important, of which first three are more electrophilic than most esters, so they should acylate an ester enolate faster than the ester being enolized:



Scheme 3.12 Aldol reactions.

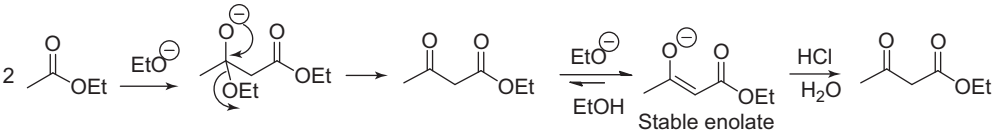


Scheme 3.13 Aldol condensation.

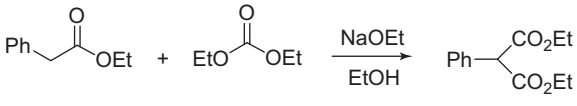


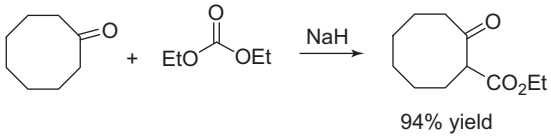
Scheme 3.14 Cross-aldol reaction.

Claisen ester condensation

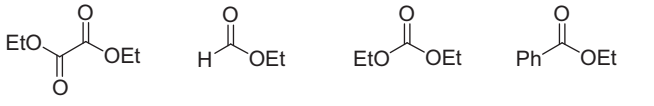


Crossed Claisen ester condensation



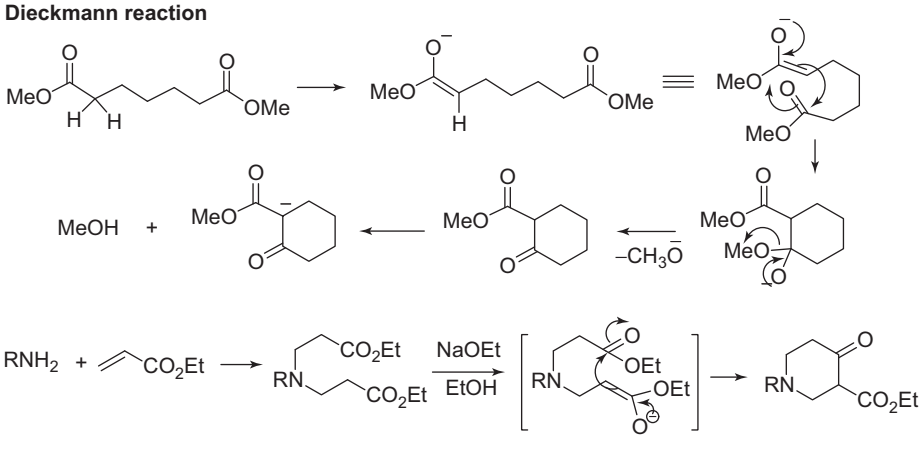


Scheme 3.15 Claisen condensation.



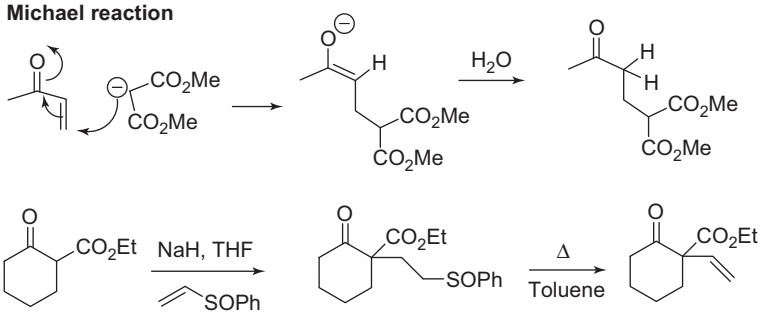
Intramolecular Claisen condensations go by the name of Dieckmann condensations and are useful for the preparation of five- and six-membered rings (Scheme 3.16).

Dieckmann reaction



Scheme 3.16 Dieckmann reaction.

Enolates may also be alkylated with α,β-unsaturated carbonyl substrates. The enolate adds in 1,4-fashion to give a unit extended by three carbon atoms in a process known as the *Michael reaction*. Many α,β-unsaturated carbonyl systems may be prepared by the dehydration of aldol products. Examples of the Michael reaction using methyl vinyl ketone and (vinylsulfinyl)benzene, two common units in the reaction, are shown in Scheme 3.17.



Scheme 3.17 Michael reaction.

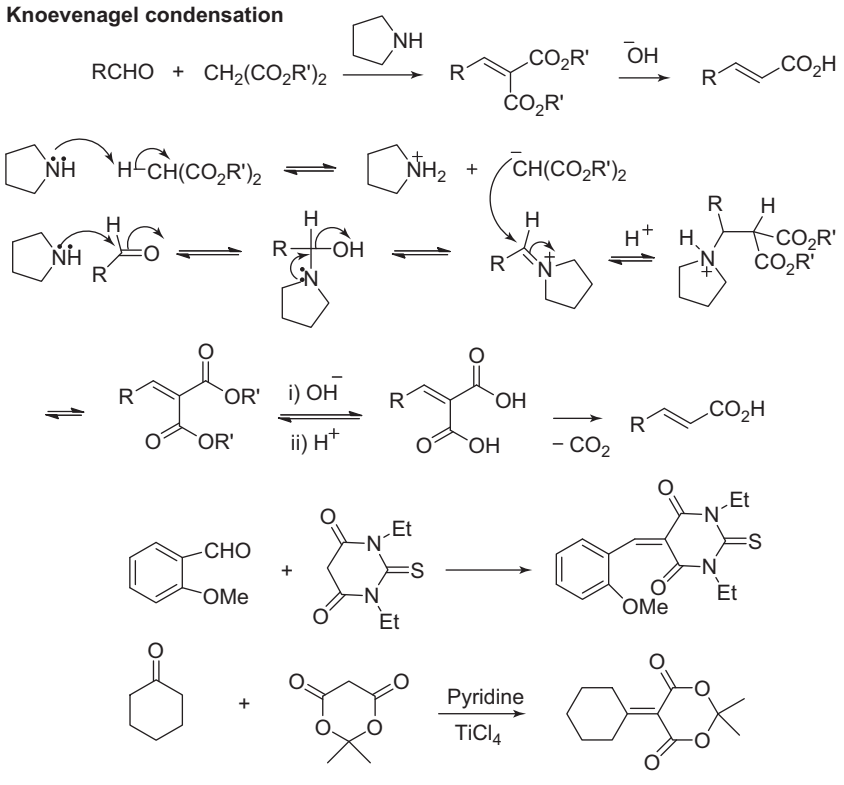
The **Knoevenagel condensation** reaction is a reaction of an enolate with an aldehyde or ketone named after Emil Knoevenagel. It is a modification of the aldol condensation. A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by dehydration (Scheme 3.18). The reaction conditions are generally mild and typically employ an amine such as pyridine, sometimes in the presence of the Lewis acid $TiCl_4$. When the two carbonyl (or other electron-withdrawing) groups in the active methylene compound are different, then condensation with an aldehyde (or unsymmetrical ketone) can give rise to two geometrical isomers. In such cases, the thermodynamically more stable product is normally formed.

3.5.2
Enamine Additions

Enamines, the products of the acid-catalyzed addition of secondary amines to aldehydes or ketones, can be viewed as weakly nucleophilic enolate anions. Enamines react with α,β-unsaturated carbonyl systems in a Michael-type reaction, introducing new carbon–carbon bonds adjacent to the carbonyl group. Endocyclic enamines, such as pyrrolines and tetrahydropyridines, are useful for the synthesis of complex heterocyclic compounds, as found in many alkaloids (Scheme 3.19).

3.5.3
Robinson Ring-Forming Reaction

A unique reaction that produces a new ring containing an α,β-unsaturated ketone is the Robinson reaction. When an enolate derived from a ketone reacts with methyl



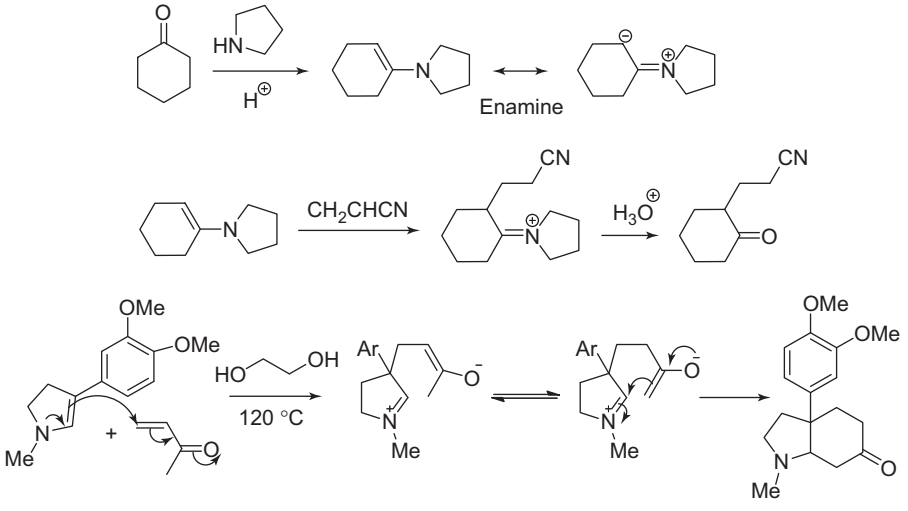
Scheme 3.18 Knoevenagel reaction.

vinyl ketone, the enolate adds in the Michael reaction, then a second enolate in the ketone product is formed that cyclizes in an aldol condensation to give the final product (Scheme 3.20).

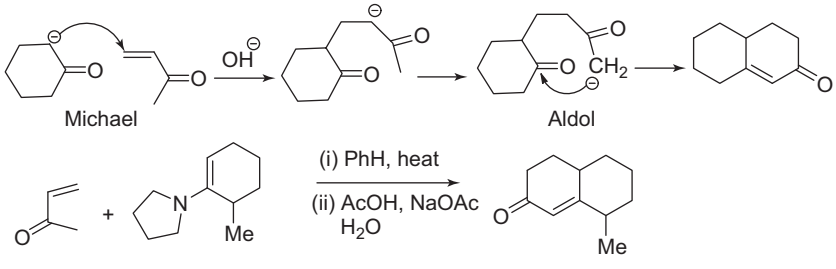
The use of isotopically labeled proton donors affords a useful synthesis of labeled compounds. For example, abstraction of a proton from the methyl group of *exo*-3-acetyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]octane (**5**) gave an enolate ion that could abstract a deuterium ion from solvent to produce the monodeuterated compound. Repeated exchange of the methyl protons led to a nearly quantitative yield of trideutero product **6** (Scheme 3.21).

Typically, decarboxylation of a carboxylic acid takes place through the carboxylate anion, from which the group R departs along with its bonding electron pair. Once formed, the carbanions react with a proton source to give a new carbon–hydrogen bond. Any factor that increases the stability of the carbanion should promote decarboxylation (Scheme 3.22).

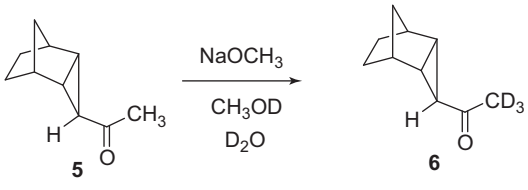
As a nucleophile, a carbanion can react readily with a carbon atom bearing a good leaving group, which is a useful method for forming new carbon–carbon bonds (Scheme 3.23).



Scheme 3.19 Michael-type reaction.



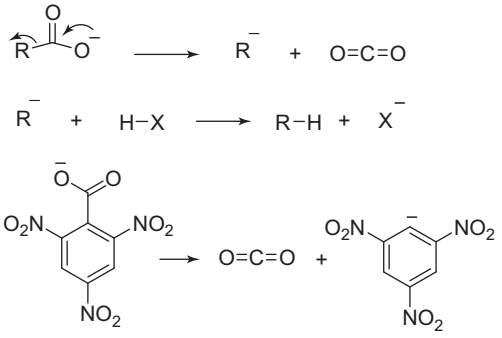
Scheme 3.20 Robinson ring-forming reaction.



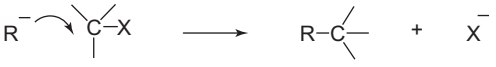
Scheme 3.21 Synthesis of trideutero-ketone.

Carbanions may also act as nucleophiles in S_N2 reactions. For example, the synthesis of 2,3-diphenylpropionic acids takes advantage of the reaction of a carbanion with benzyl chloride (Scheme 3.24).

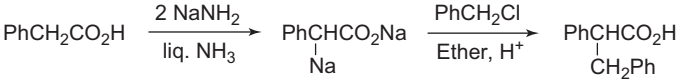
A further interesting and synthetically useful reaction of carbanions and of organometallic compounds acting as sources of negative carbon is addition to the very weak electrophile CO_2, to form the corresponding carboxylate anion in what



Scheme 3.22 Decarboxylation of carboxylic acid.

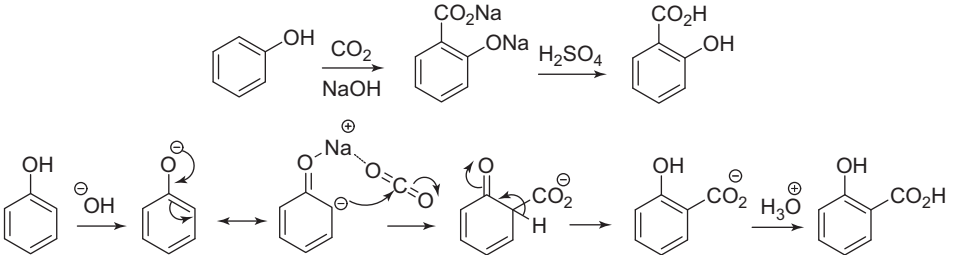


Scheme 3.23 Carbanion acting as nucleophile.



Scheme 3.24 Carbanion as nucleophile in S_N2 reaction.

is known as *carbonation*. It occurs with alkyls, aryls, or acetylides of metals more electropositive than magnesium. The Kolbe–Schmidt reaction is another example of carbanion carbonation. It proceeds via the nucleophile addition of a phenolate to CO_2 to give the salicylate. The final step is reaction of the salicylate with acid to form the desired salicylic acid (Scheme 3.25).



Scheme 3.25 Kolbe–Schmidt reaction.

Oxidation of carbanions by molecular oxygen is also an important reaction. Equation (3.10) shows the oxidation of the anion of triphenylmethane by molecular oxygen in a solution composed of 80% DMF and 20% *t*-butyl alcohol. Addition of water to the reaction mixture allowed isolation of triphenylmethyl hydroperoxide in high yields (e.g., 87%). When the reaction was carried out in 80% DMSO–20%

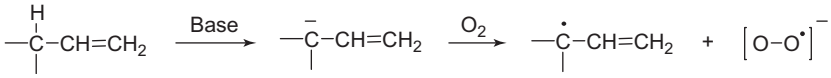
t-butyl alcohol mixtures, the product isolated was the triphenylmethanol, apparently due to reaction of the hydroperoxide with the solvent:

$$Ph_3CH \xrightarrow{Na} Ph_3\overset{-}{C}\overset{+}{Na} \xrightarrow{O_2} Ph_3C\cdot \qquad (3.10)$$

The triphenylmethyl carbanion is oxidized slowly by air to give the triphenylmethyl free radical (Eq. (3.11)):

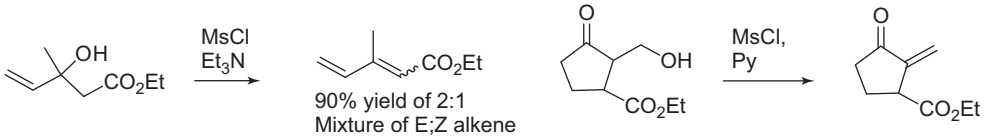
$$Ph_3CH \xrightarrow{Na} Ph_3CNa \xrightarrow{O_2} Ph_3C\cdot \qquad (3.11)$$

Carbanions react with O_2 in alkaline medium to give a radical (Scheme 3.26).



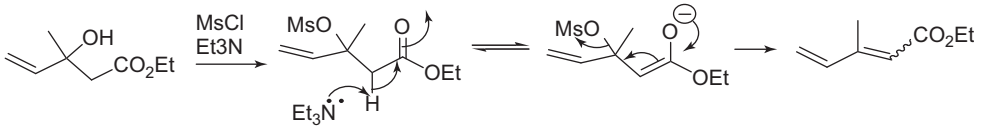
Scheme 3.26 Oxidation of a carbanion.

The reversible nature of the initial proton abstraction is proved by carrying out the reaction in a deuteriated solvent. Notably, while HO^- is never a leaving group in E2 reactions it can be a leaving group in E1cB reactions. The establishment of conjugation also assists loss of HO^-. As Scheme 3.27 implies, other leaving groups are possible too. Here are two examples with methanesulfonate leaving groups.



Scheme 3.27 E1cB reactions.

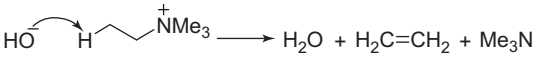
The first looks like E1 (stabilized cation) and the second like E2, but in fact both are E1cB reactions. The most reliable way to spot a likely E1cB elimination is to see whether the product is a conjugated carbonyl group. If it is, the mechanism is probably E1cB (Scheme 3.28).



Scheme 3.28 E1cB reaction mechanism.

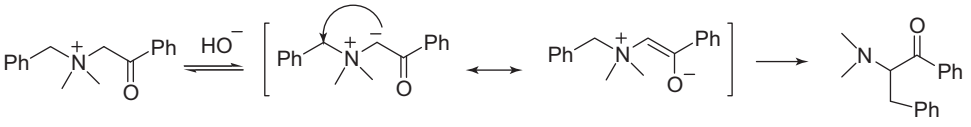
β-Halocarbonyl compounds can be rather unstable: the combination of a good leaving group and an acidic proton means that E1cB elimination is extremely easy. The rate of the reaction depends on the stability of the carbanion. The presence of

electron-withdrawing groups on the β-carbon and any group that is able to undergo π–p (filled) conjugation will increase the rate of the reaction. Quaternary ammonium ions that contains β-hydrogen atoms undergo E2 (Hofmann) elimination with base (Scheme 3.29).



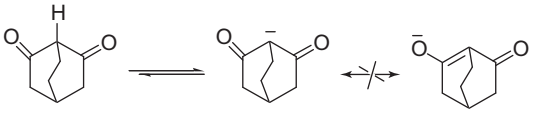
Scheme 3.29 Hofmann elimination.

If, however, none of the alkyl groups possess a β-hydrogen atom but one has a β-carbonyl group, an α-hydrogen is removed by base to give an ylide (Scheme 3.30).



Scheme 3.30 Formation of ylide.

Loss of optical activity becomes clear as the chirality of the negative carbon is destroyed with the formation of a carbon–carbon double bond. Coplanarity is an essential requirement for the formation of carbanions stabilized by a neighboring group. For example, bicyclo[2.2.2]octan-2,6-dione has negligible acidity, although it has a bridgehead hydrogen flanked by two carbonyl groups. The bridgehead prevents the coplanarity of the atoms that would be involved in the charge delocalization of the potential carbanions (Scheme 3.31).



Scheme 3.31 Acidity of bicyclo[2.2.2]octan-2,6-dione.

3.6 Rearrangements of Carbanions

3.6.1 Homoallylic Rearrangements

Figure 3.7 shows representative allylic, homoallylic, and homobenzylic structures. The prefix "homo" means that there is one additional carbon atom. Some interesting rearrangements occur with the homoallylic systems.

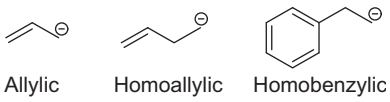
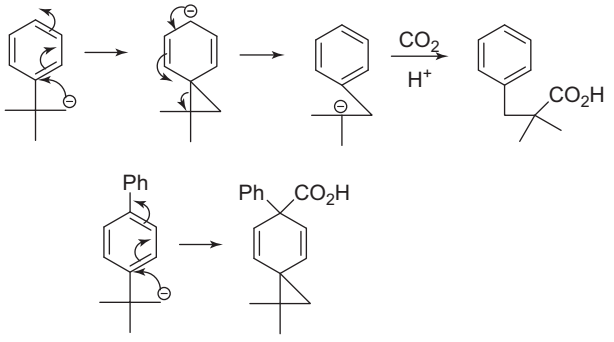


Figure 3.7 Structures of allylic, homoallylic, and homobenzylic carbanions.

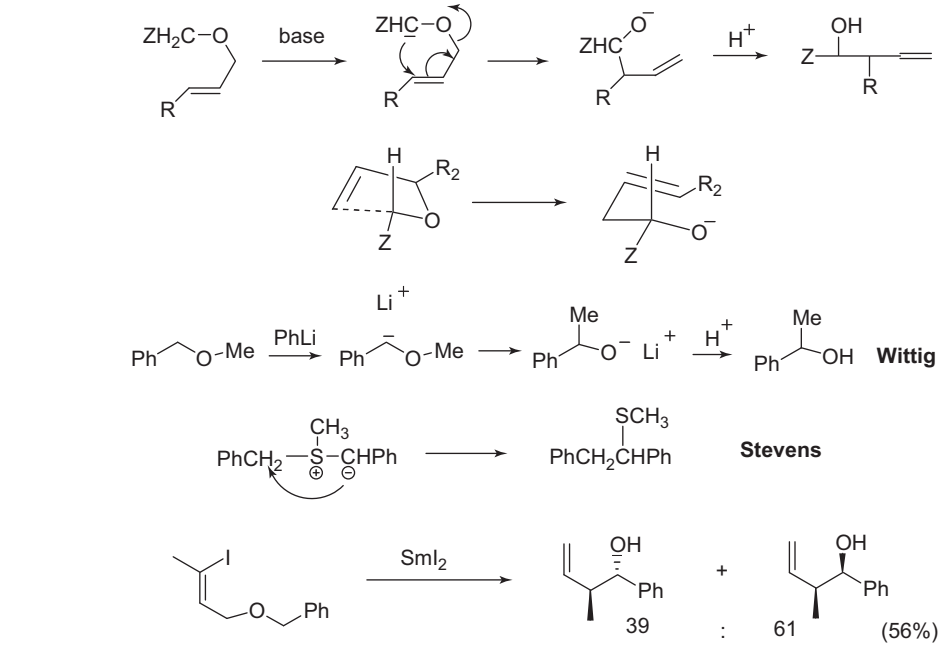
Scheme 3.32 shows a homobenzylic rearrangement where the carbanion interacts with the aromatic ring. The carbanion appears to insert between the ring and the carbon containing the two methyl groups. The mechanism of the rearrangement is proven by isolation of the cyclopropane structure when a *para* phenyl group is present.



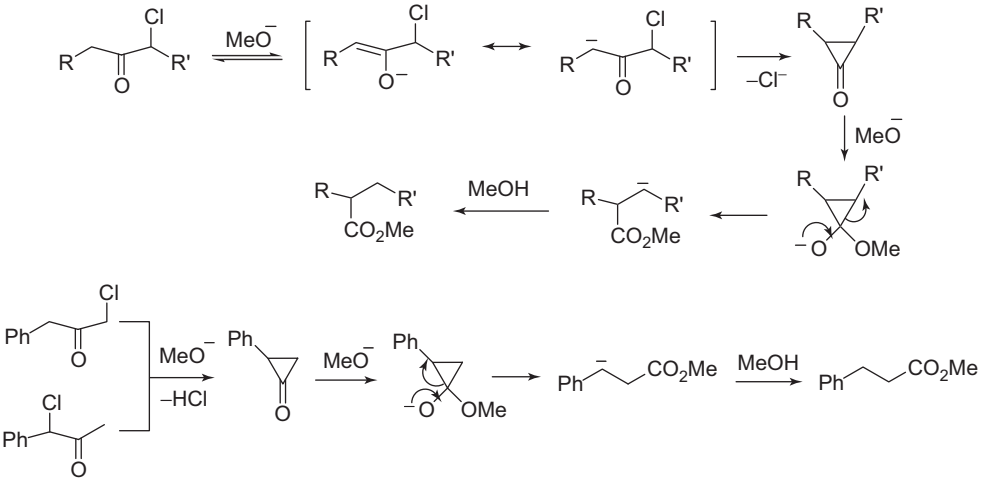
Scheme 3.32 Homobenzylic rearrangement.

The Wittig rearrangement is directly analogous to the Stevens rearrangement in mechanism and outcome (Scheme 3.33). It is an example of [2,3] sigmatropic rearrangement in which benzyl and allyl ethers undergo a base-catalyzed rearrangement to α-allyl alkoxides, analogous to the Stevens rearrangement. A benzylic or allylic carbanion is generated by the action of a powerful base such as amide ion or phenyllithium and migration of carbon then leads to the more stable oxyanion. The stereochemistry of the Wittig rearrangement can be predicted in terms of a cyclic five-membered transition state in which the α substituent prefers an equatorial orientation. Migratory aptitudes are in the order allyl ~ benzyl > alkyl > methyl > aryl, with electron-withdrawing substituents increasing the aryl group migratory aptitude.

α-Haloketones react with base to give enolates, which rearrange to esters via cyclopropanones. The direction of ring opening of the cyclopropanone is determined by the more stable of the two possible carbanions that can be formed. Alkyl groups destabilize carbanions, whereas aryl groups stabilize them by delocalization of the negative charge. For example, $PhCH_2–COCH_2Cl$ and PhCHCl–COMe give the same product. Chloroketones are normally preferable to bromoketones as reactants in the Favorskii rearrangement. The reaction can be classified as an intramolecular rearrangement from carbon to carbon involving a migrating group moving without its electron from the migrating origin to an electron-rich terminus (Scheme 3.34).

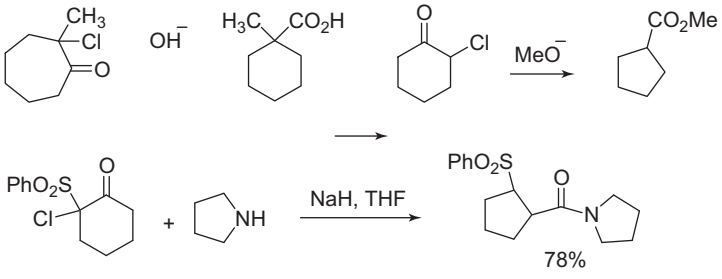


Scheme 3.33 Wittig and Stevens rearrangements.



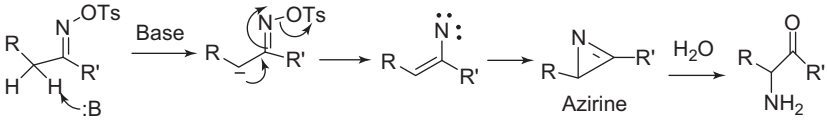
Scheme 3.34 Favorskii rearrangement.

The rearrangement can be employed to bring about ring contraction in cyclic systems, for example, 2-chlorocyclohexanone and methoxide ion give methyl cyclopentanecarboxylate in 60% yield (Scheme 3.35).



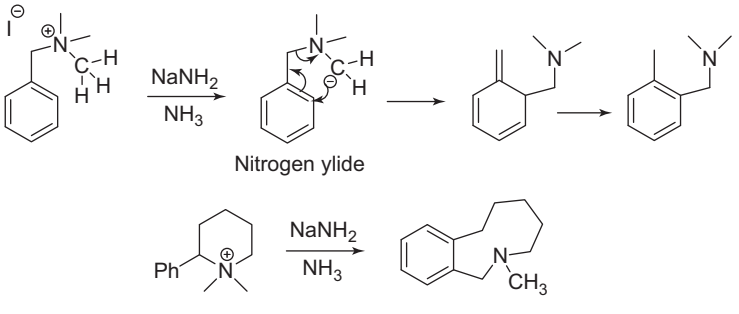
Scheme 3.35 Contraction of rings.

Ketoxime toluenesulfonate may also be rearranged in the presence of base to yield α-aminoketones (**Neber rearrangement**, Scheme 3.36); aldoximes, though, do not undergo this reaction.



Scheme 3.36 Neber rearrangement.

The **Sommelet–Hauser rearrangement** (named after M. Sommelet and Charles R. Hauser) is a rearrangement reaction of certain benzyl quaternary ammonium salts. The reagent is sodium amide or another alkali metal amide and the reaction product is an N-dialkyl benzyl amine with a new alkyl group in the aromatic *ortho*-position. The benzylic methylene proton is acidic and deprotonation takes place to give the nitrogen ylide. The second step is a 2,3-sigmatropic rearrangement (Scheme 3.37). The Stevens rearrangement is a competing reaction.

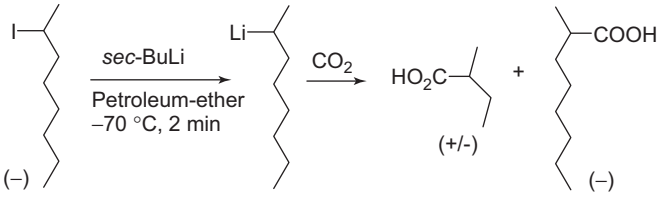


Scheme 3.37 Sommelet–Hauser rearrangement.

3.7 Chiral Carbanions

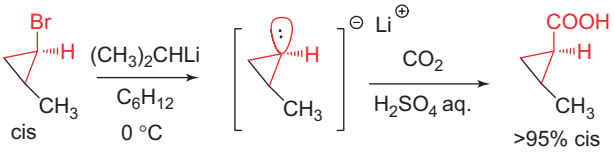
With the molecular geometry for a carbanion described as a trigonal pyramid the question is whether or not carbanions can display chirality. After all, when the activation barrier for inversion of this geometry is too low any attempt at introducing chirality will end in racemization. However, solid evidence exists that carbanions can indeed be chiral, for example, in research carried out with certain organolithium compounds.

The first evidence for the existence of chiral organolithium compounds was obtained in 1950. Reaction of chiral 2-iodooctane with *sec*-butyllithium in light petroleum at −70 °C followed by reaction with dry ice yielded mostly racemic 2-methylbutyric acid with small amount of optically active 2-methyloctanoic acid (Scheme 3.38).



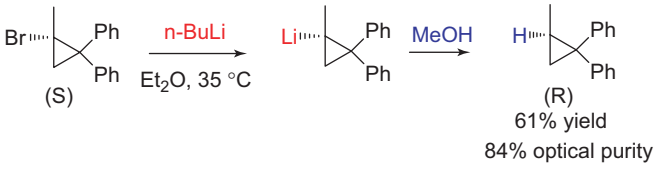
Scheme 3.38 Chiral carbanion.

On heating the reaction to 0 °C the optical activity is lost. More evidence followed in the 1960s. Reaction of the *cis*-isomer of 2-methylcyclopropyl bromide with *sec*-butyllithium, again followed by carboxylation with dry ice, yielded *cis*-2-methylcyclopropylcarboxylic acid. The formation of the *trans*-isomer would have indicated that the intermediate carbanion was unstable (Scheme 3.39).

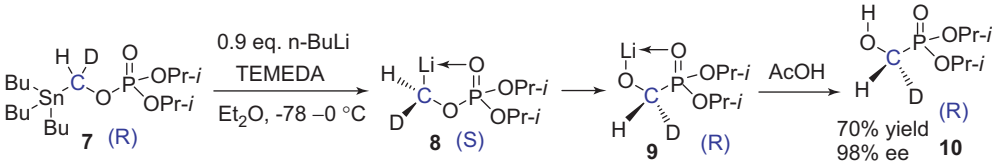


Scheme 3.39 Retention of stereochemistry.

In the same manner the reaction of (+)-(*S*)-l-bromo-l-methyl-2,2-diphenylcyclopropane with *n*-butyllithium followed by quench with methanol resulted in product with retention of configuration (Scheme 3.40). Recently, chiral methyllithium compounds have been obtained. The phosphate **7** contains a chiral group with a hydrogen and a deuterium substituent. The stannyl group is replaced by lithium to give intermediate **8**, which undergoes a phosphate-phosphorane rearrangement to phosphorane **9**, which on reaction with acetic acid gives alcohol **10**. Once again, in the range −78 to 0 °C, the chirality is preserved in this reaction sequence (Scheme 3.41).



Scheme 3.40 Retention of configuration.



Scheme 3.41 Retention of chirality.

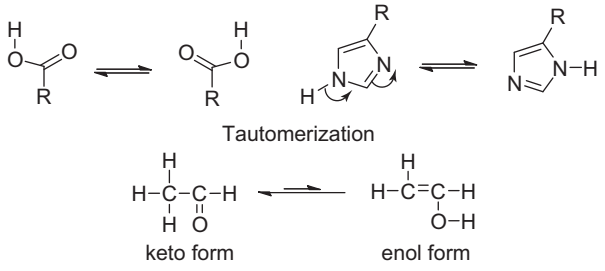
Biological synthesis of fatty acids is analogous to the malonate synthesis of carboxylic acids. The enolate carbanion from malonate acts as a nucleophile in a nucleophilic substitution on the acetyl-CE followed by decarboxylation. Each series puts the three-carbon malonate on the ACP and then decarboxylates the substitution product, resulting in lengthening of the carbon chain by two carbons at a time. Naturally occurring fatty acids are even numbered carboxylic acids.

3.8
Carbanions and Tautomerism

A ketone and an enol differ only in the location of a double bond and in the location of hydrogen. Such isomers are called *tautomers*. Tautomers are isomers differing only in the positions of hydrogen atoms and electrons, with the carbon skeleton remaining the same. The conversion of one tautomer into the other tautomer is called *tautomerization*. If an aldehyde or ketone possesses at least one hydrogen atom on the carbon atom adjacent to the carbonyl group, called the *alpha* (α) *carbon*, this hydrogen can migrate to the oxygen atom. As a result, a carbonyl compound with a α-hydrogen can exist in two isomeric forms, called *tautomers*. In the keto-form the hydrogen is attached to the alpha carbon, while in the enol-form it is attached to the carbonyl oxygen with migration of the double bond. *Keto-enol interconversion* is also called *keto-enol tautomerization* or *enolization*. Scheme 3.42 shows the tautomers of acetaldehyde.

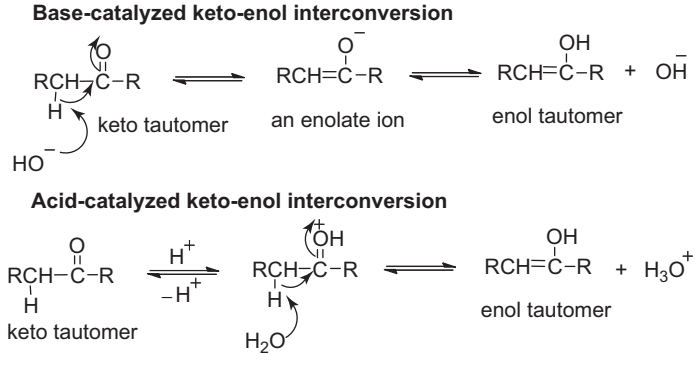
3.8.1
Mechanism of Keto-Enol Interconversion

Any reaction that simply involves the intramolecular transfer of a proton is called a *tautomerism*. Keto-enol interconversion may happen in basic as well as acidic solution. The steps are reversed in the base-catalyzed and acid-catalyzed reactions. In the base-catalyzed reaction, the first step is removal of an α-proton and the



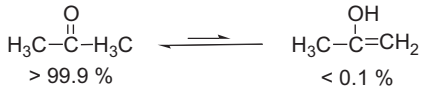
Scheme 3.42 Tautomerization.

second step is protonation of oxygen. In the acid-catalyzed reaction, the first step is protonation of the oxygen and the second step is removal of an α-proton (Scheme 3.43).



Scheme 3.43 Mechanism of keto-enol interconversion.

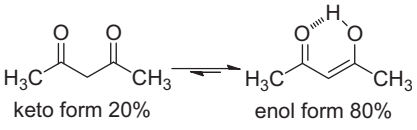
Acetone exists in equilibrium almost wholly in its *keto*-form, as the *enol*-form is not stabilized through either resonance or intramolecular hydrogen bonding (Scheme 3.44).



Scheme 3.44 Keto-enol equilibrium in acetone.

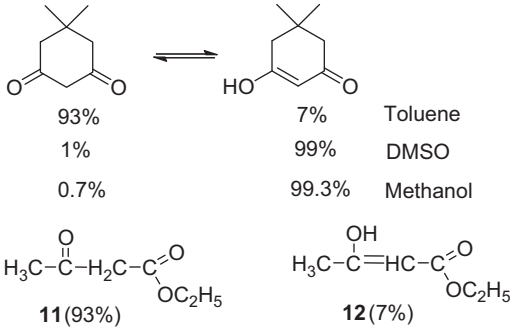
The enol form is so-called because it is a combination of **ene** for the double bond and **ol** for the -OH (hydroxyl) group. The two isomers exist in equilibrium, and in any such case both tautomers are present, but in simple cases the keto form is much more stable than the enol form. For example, in acetaldehyde about six molecules out of every 10 million molecules are in the enol form at any given time. Nevertheless, the equilibrium always exists, and every molecule of acetaldehyde (as well as any other aldehyde or ketone with an alpha hydrogen) is converted into the enol form (and back again) several times per second. This is an important

characteristic because several reactions of carbonyl compounds take place only through the enol forms. The fraction of enol tautomer is considerably greater for a β-diketone because its enol tautomer is stabilized by internal hydrogen bonding and by conjugation of carbon–carbon double bond with the second carbonyl group. For example, in the case of pentane-2,4-dione, 80 of every 100 molecules are in the enol-form (Scheme 3.45).



Scheme 3.45 Keto-enol equilibrium in pent-2,4-dione.

Ethyl acetoacetate ($CH_3COCH_2COOC_2H_5$) gives the reactions of a carbonyl (C=O) group, such as formation of cyanohydrin with HCN, bisulfate addition compound with sodium bisulfate, and phenyl hydrazone derivative with phenyl hydrazine. In addition to these, it behaves as an unsaturated alcohol (enol) as it evolves hydrogen on treatment with sodium, shows reddish–violet coloration with ferric chloride, and decolorizes bromine water and adds diazomethane. These chemical properties of ethyl acetoacetate suggest that it exists in two forms: a saturated ketone **11** (keto-form) and an unsaturated alcohol **12** (enol-form) that is an example of *prototropy* (Scheme 3.46).



Scheme 3.46 Keto and enol forms of 1,3-diketones.

The hybridization of carbon flanked by carbonyl and ester groups changes from sp^3 in **11** to sp^2 in **12.** These two forms exist together so that the properties of both keto and enol are observed in the reactions of ethyl acetoacetate. Structures **11** and **12** are isomeric and differ in the relative position of hydrogen atom and the position of double bond. Since a 1,3-proton shift takes place in the above example from carbon atom to oxygen atom, this form of tautomerism is known as *prototropy*. The enol form is favored in relatively nonpolar solvents like alkanes and carbon disulfide and also by dilution. In hydroxylic solvents like water, methanol, ethanol, acetic acid, and so on, the keto form is favored due to the formation of hydrogen bonds between the oxygen atom of the carbonyl group and a hydrogen atom of the solvent molecule (ZH) (Figure 3.8).

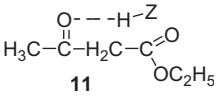


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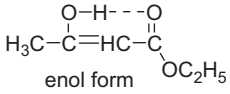
Figure 3.8 Intermolecular hydrogen bonding favors the keto-form.

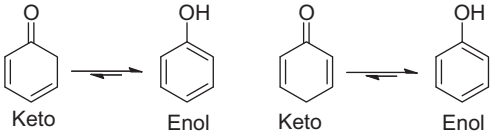
On dilution, the intermolecular hydrogen bonds (between two different types of molecules like A and ZH are broken and, therefore, the percentage of enol form in the mixture increases. Two factors usually stabilize the enol form:

1) **Intramolecular hydrogen bonding**: hydrogen bond formation within the same molecule as shown below in the enol form of 1,3-diketones:



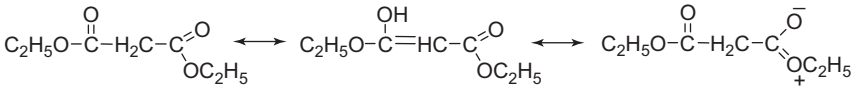
enol form

2) **Resonance**: The enol form (phenol) of either 2,4-cyclohexadienone or 2,5-cyclohexadienone (keto forms) is stabilized by resonance to a greater extent than a similar stabilization of the keto forms, which require charge separation. Phenol is unusual in that its enol tautomer is more stable than its keto tautomer, because the enol tautomer is aromatic but the keto tautomer is not (Scheme 3.47).



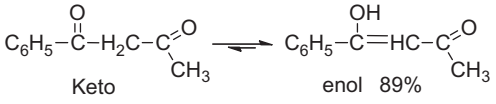
Scheme 3.47 Keto-enol equilibria.

Sometimes, the keto form is stabilized more due to resonance than the stabilization in the enol form due to intramolecular hydrogen bonding. This explains the larger percentage of the keto form as compared to the enol form of ethyl acetoacetate. The resonance effect is more pronounced in diethyl malonate, where the keto form is stabilized and hence only traces of enol are present (Scheme 3.48).



Scheme 3.48 Resonance in diethyl malonate.

In liquid state, the percentage of enol forms in acetylacetone and benzoyl acetone is 80% and 89%, respectively. The enol form of benzoyl acetone gets further stabilization, besides the intramolecular hydrogen bonding shown above for acetyl acetone, due to conjugation of the carbon–carbon double bond with the phenyl group (Scheme 3.49).



Scheme 3.49 Keto-enol equilibrium in benzoyl acetone.

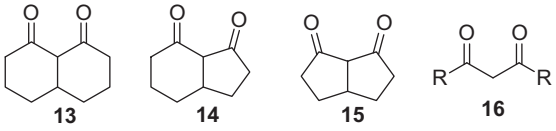


Figure 3.9 Some bicyclic and alkyl diketones.

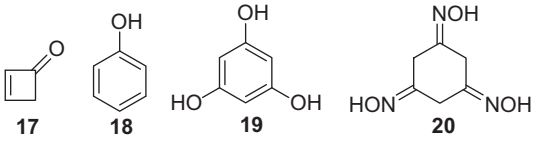
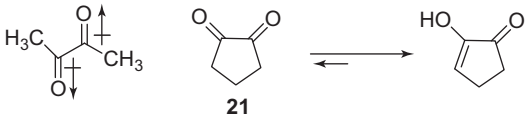


Figure 3.10 Keto/enol forms of various compounds.

In the series of *cis*-fixed bicyclic diketones **13–15** the percentage enol varies from 100 to 80 to 1.4, respectively; in this series the hydrogen bond becomes obviously longer and weaker. For disubstituted 1,3-diketones (**16**) the enol content increases rapidly as the size of the alkyl substituent is increased, when R is *tert*-butyl the keto-form is undetectable (Figure 3.9).

The keto-enol equilibrium has often been used as a measure of the resonance stabilization; for example, no enolization occurs in 3-cyclobutenones (**17**) and no ketone can be detected in phenol (**18**). Fluoroglucinol (**19**) behaves chemically more like a triketone than a triol; thus, it readily forms the trioxime (**20**) with hydroxylamine (Figure 3.10).

Sometimes conformation plays a dominant role in deciding the extent of enolization in certain α-diketones. Biacetyl, for example, has very little enol content in contrast to 1,2-cyclopentanedione, which exists mostly in the enolic form. The carbonyl groups of the biacetyl are oriented in opposite directions so as to reduce dipole–dipole repulsion whereas cyclopentane-1,2-dione (**21**) being a cyclic compound has no such choice and has to resort to enolization to avoid this repulsion (Scheme 3.50).



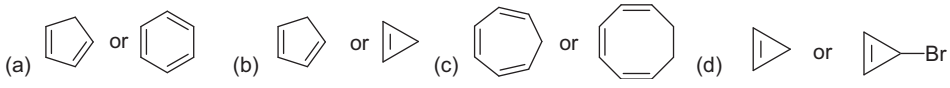
Scheme 3.50 Keto-enol equilibrium in cyclopentane-1,2-dione.

3.9 Summary

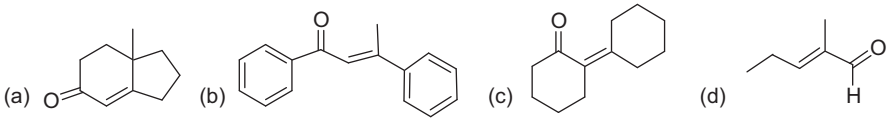
- Molecules with a negatively charged carbon atom are called *carbanions*.
- Carbanions are stabilized by the same factors that stabilize the conjugate base of any acids.
- One of the most important ways of stabilizing carbanions is by delocalization of the negative charge, particularly onto atoms such as oxygen, nitrogen, and sulfur.
- The most common way of forming carbanions is by removal of a proton from a carbon atom.
- Carbanions can also be formed from alkyl halides with metals or organometallic compounds.
- Grignard reagents are a common type of carbanion-like molecule.
- Most carbanions are strong bases, and so must be handled with strict exclusion of proton sources such as water.
- Carbanions are nucleophilic and undergo many of the typical reactions of nucleophiles such as reacting with carbonyl groups and other electrophilic centers.
- Grignard reagents react with esters to produce tertiary alcohols, but do not react with alkyl halides.
- Carbanions may give elimination reactions if a leaving group is present.
- The product that forms faster is called the *kinetic product* and the product that is more stable is called the *thermodynamic product*.
- Similarly, conditions that give rise to the kinetic product afford so-called *kinetic control* and conditions that give rise to the thermodynamic product afford so-called *thermodynamic control*.

Problems

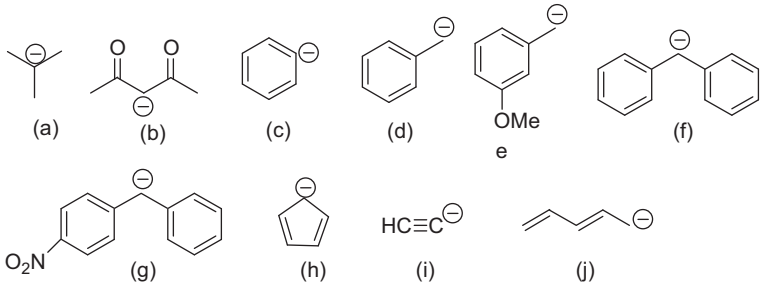
1. Which member of each of the following pair of compounds is more readily deprotonated and why?



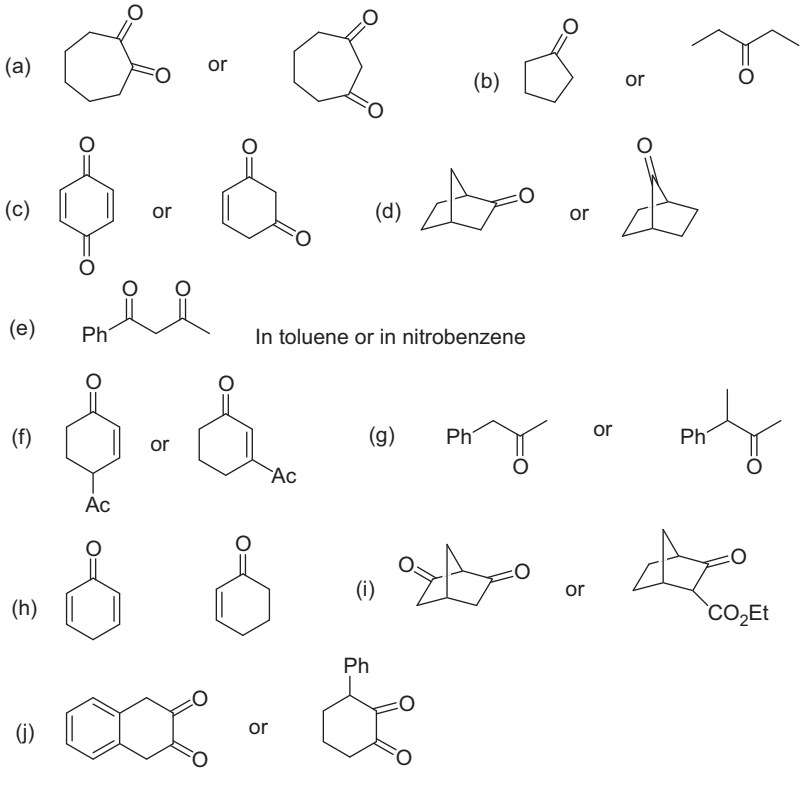
2. Write the structure of the starting material that would lead to each of the following enones via an aldol condensation upon treatment with base.



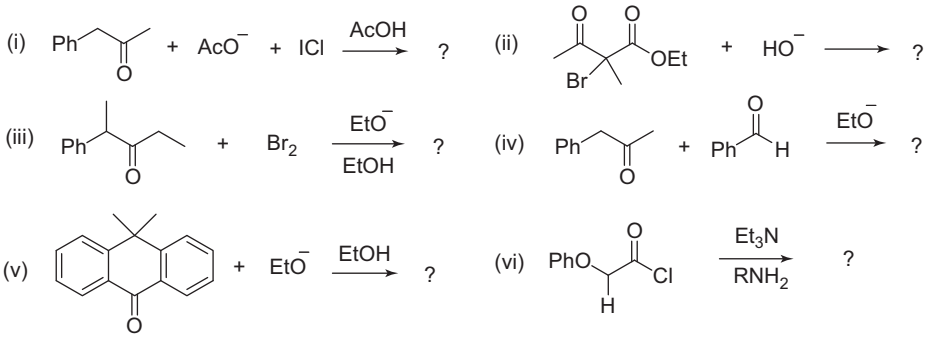
3. Arrange the following carbanions in order of stability.



4. Predict which member in each of the following pairs is the more extensively enolized. Justify your choice in each case.



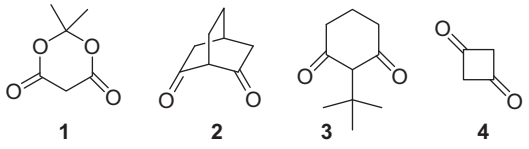
5. Predict the products for each of the following reactions, justifying your choice in each case.



6. Draw all the possible enol forms of the following compounds:

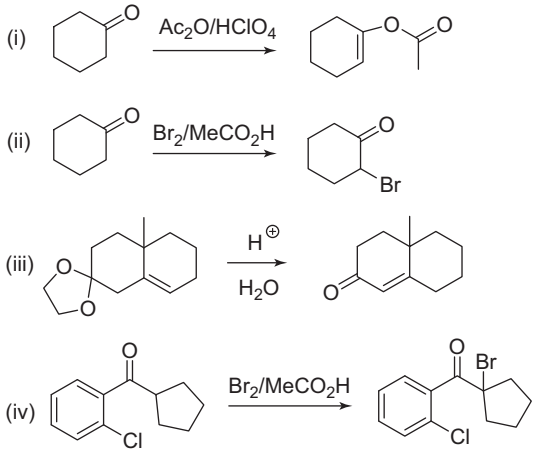
a. 2-pentanone,
b. 3-pentanone,
c. cyclohexanone,
d. dimedone,
e. 2,4-pentanedione,
f. cyclobutane-1,3-dione.

7. Explain why **1** is 100% enol but **2–4** are 100% ketone.

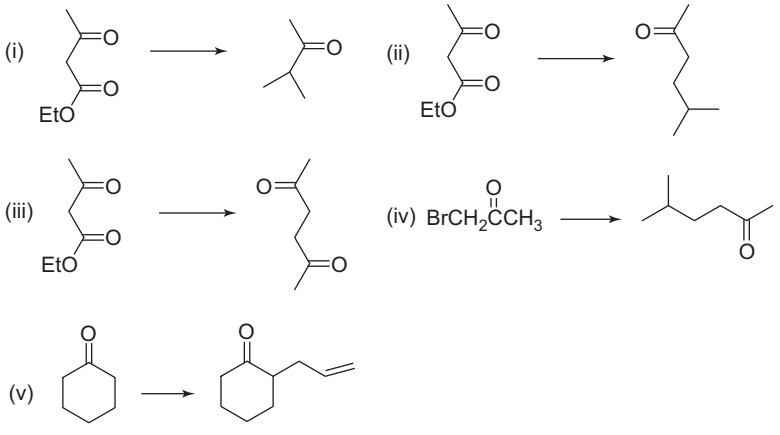


1 **2** **3** **4**

8. Suggest mechanisms for the following reactions and explain why these products are formed.

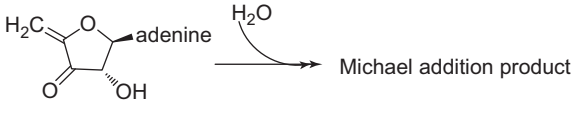


9. Complete each of the following reactions with a suitable mechanism.

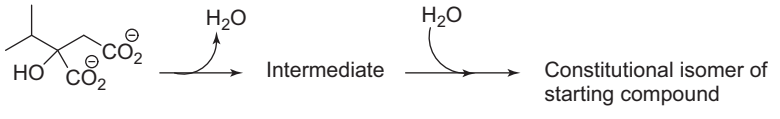


10. In general, carbonyl compounds cannot be alkylated directly. Explain why this is so with suitable reasons.

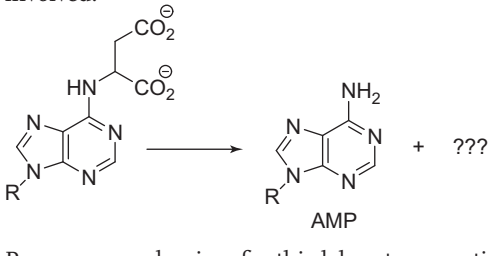
11. Show the product and provide a mechanism for the following Michael addition reaction.



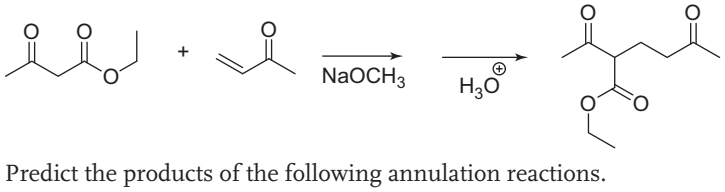
12. The following substrate undergoes an E1cb dehydration followed by rehydration to form a different constitutional isomer. Predict the structure of the isomer, and also the structure of the intermediate.



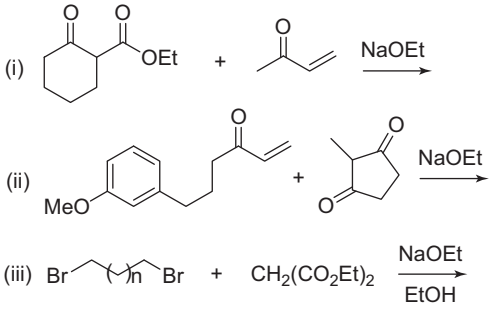
13. Predict the second product for this reaction. What type of mechanism is involved?



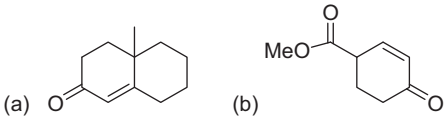
14. Propose a mechanism for this laboratory reaction.



15. Predict the products of the following annulation reactions.



16. Show the starting materials that you could use to synthesize the following compounds by Robinson annulation.



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4
Radicals

4.1
Introduction

Mechanistic organic chemistry is a vibrant area and active ground for new experimental, theoretical, and computational developments that contribute to the increasing relevance of chemistry, leading to important connections with medicine to material science. A reactive intermediate corresponds to a shallow dip in a diagram of free energy versus reaction coordinate. Generally, the rate of conversion of this intermediate into the reaction product is fast compared with the rate of its formation (otherwise, the intermediate would be an isolable compound or a species in rapid equilibrium with the reactants). Radicals are neutral species with an unpaired electron (the single electron is represented by the dot in displayed formulae). A carbon-centered radical is a structure having only seven valence electrons on a carbon atom and a formal charge of zero. Thus, a radical is an atom or a group of atoms with an unpaired electron. (This definition includes certain stable inorganic molecules and atoms such as NO, NO_2, alkali-metal atoms, and transition metal ions.)

Carbon atoms are the most frequently found radical centers with their electron septet occupying an intermediate position between the carbenium ions and the carbanions. Radicals are often called *free radicals*, a term that arose from early nomenclature systems in which a ''radical'' was a substituent group that was preserved as a unit through a chemical transformation. Thus, the CH_3 group as a substituent was known as the *methyl radical*, so a neutral CH_3 group became a free radical. The terms *radical* and *free radical* are now used interchangeably. Some common examples of radicals include the methyl radical (**1**), vinyl radical (**2**), phenyl radical (**3**), triphenylmethyl radical (**4**), allyl radical (**5**), and benzyl radical (**6**) (Figure 4.1).

Nitrogen-centered or oxygen-centered radicals are less stable than carbon-centered radicals. They are higher in energy because of the higher electronegativity of these elements relative to carbon. The chemistry of free radicals dates from 1900, since Gomberg's attempt to prepare hexaphenylethane from the reaction of triphenylmethyl chloride with zinc dust, which gives a colored solution. The results were interpreted in terms of equilibrium between hexaphenylethane (**7**) and triphenylmethyl radicals (**4**) (Scheme 4.1).

Reactive Intermediates in Organic Chemistry: Structure, Mechanism, and Reactions, First Edition.
Maya Shankar Singh.

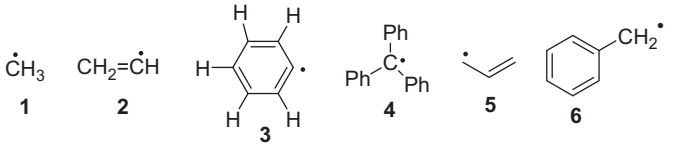
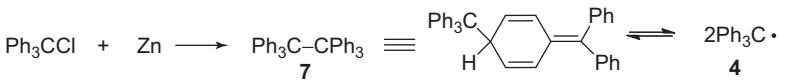
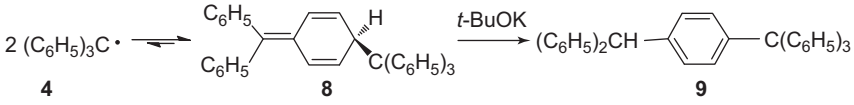


Figure 4.1 Some common free radicals.



Scheme 4.1 Equilibrium between hexaphenylethane and triphenylmethyl radical.

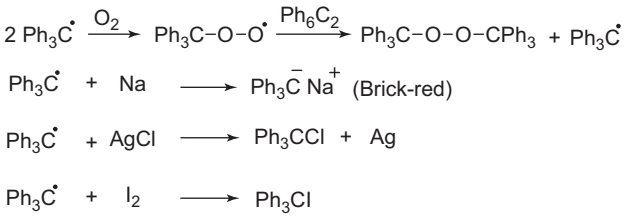
Hexaphenylethane was accepted as the structure for the dimer of triphenylmethyl for over 60 years. However, studies of dimers of diarylalkylmethyl radicals led Lankamp, Nautu, and MacLean to examine the PMR (proton magnetic resonance) spectrum of the supposed ''hexaphenylethane,'' which suggested that the dimer is most likely **8**. The finding of Guthrie and Weisman that treating the dimer with *t*-BuOK produces 1-diphenylmethyl-4-triphenylmethylbenzene (**9**) strengthened the structural assignment. Even though the proposal of **4** as the structure of the dimer was in error, the demonstration of the existence of radicals as transient species led to a great effort to study other radicals (Scheme 4.2).



Scheme 4.2 Structure of triphenylmethyl radical.

Triphenylmethyl radicals react immediately with several reagents to form triphenylmethyl derivatives, for example, with oxygen it forms colorless peroxide, and combines with sodium to form triphenylmethyl sodium, a brick-red solid. In addition, it can act as a powerful reducing agent, and will reduce the salts of silver, gold, and mercury to the metals (Scheme 4.3).

Nernst (1918) suggested that free radicals take part in chemical reactions and postulated a radical chain mechanism for the combination of H_2 and Cl_2. Paneth and coworkers (1929) first demonstrated the existence of alkyl free radicals by decomposition of metal alkyls. Norrish (1931) suggested that free radicals could occur as intermediates in the photolysis of carbonyl compounds. Rice and Herzfield (1934) produced radicals from the dissociation of hydrocarbons. Up until relatively recently, radicals were regarded as highly reactive species, whose reactions were unselective and difficult to control (remember the radical chlorination of methane). The last 20 years have seen the field developed to such an extent that it is now recognized that radicals can take part in highly useful and selective reactions,



Scheme 4.3 Reactions of triphenylmethyl radical.

and their chemistry offers a viable alternative to traditional ionic methods. The advantages of reactions involving radicals are:

1) Radicals are neutral and so are far less solvated than carbocations or carbanions. Therefore, they are smaller and can operate in polar, hindered environments, where ionic chemistry fails.
2) Unlike carbocations, radicals on the whole are less prone to rearrangements.
3) Unlike carbanions, alkoxy and sulfonyloxy groups β-to a radical center do not undergo elimination. However, halogen, sulfur, and selenium groups β-to radicals are eliminated. Thus, radical elimination chemistry can be complementary to that of anions.
4) Protection of -OH and -NH_2 groups is unnecessary in radical reactions (unlike carbanions, radicals are not basic). In many situations, cumbersome and yield-lowering protection-deprotection steps become unnecessary.

The utility of these features for organic transformations will emerge in the sections below, where actual examples are presented and discussed. One of the major disadvantages of radical chemistry is that they readily react with oxygen, which means that their reactions must be carried out under an inert atmosphere (there are others that will be discussed later).

4.2 Detection and Characterization of Radicals

The distinguishing characteristic of a free radical is the presence of an unpaired electron. Species with an unpaired electron are said to be paramagnetic. The relative stability of the triphenylmethyl radical allows it to be studied by magnetic susceptibility measurement, which involves weighing it both inside and outside a magnetic field. The unpaired electron makes the radical paramagnetic, so the sample is drawn into the magnetic field. By this technique the dissociation of hexaphenylethane to the triphenylmethyl radical was determined to occur to the extent of 2% in a 0.1 M sample.

A technique that has been of more value to organic chemists is that of *electron paramagnetic resonance* (EPR), which is also known as *electron spin resonance* (ESR) spectroscopy. This is a very sensitive method of detecting radicals, even at concentrations of 10^{-7} M. ESR not only confirms that radicals exist, but it can also

tell us quite a lot about their structure. The principle of ESR is similar to that of NMR, except that electron spin is involved rather than nuclear spin. The electrons are associated with the electron spin quantum number, m_s, which may have the value $+1/2$ or $-1/2$. If electrons are paired in an orbital, then one has $m_s = +1/2$ and the other has $m_s = -1/2$, so there is no net spin magnetic moment. If an electron is unpaired, however, there will be a net magnetic moment of 9.284×10^{-19} erg G^{-1}. The direction of the magnetic moment depends on the spin quantum number, so there will be two spin states. The two states are equal in energy in the absence of an external magnetic field. In the presence of an external magnetic field (with strength H_0) the two spin states have different energies, with the electron having $m_s = -1/2$ being lower in energy. The energy difference between the two states, ΔE, is:

$$\Delta E = h\nu = g\beta_e H_0$$

In this equation, g is the spectroscopic splitting factor, which is the ratio of the magnetic moment (μ) to the angular momentum of the electron. This value is 2.002 319 for a free electron, and does not vary greatly for unpaired electrons in organic radicals. The term β_e is the Bohr magneton, a constant with the value of 9.2732×10^{-21} erg G^{-1}. Thus, at a field of 3400 G the energy difference is $\Delta E = (2.0023) \times (9.2732 \times 10^{-21}$ erg $G^{-1}) \times (3400\ G) = 0.63 \times 10^{-16}$ erg, which corresponds to 0.91 cal mol^{-1} and to a frequency of 9500 MHz.

There are some similarities between PMR and EPR spectroscopy. In both, the sample is placed in a magnetic field and is irradiated with electromagnetic energy of an appropriate frequency. An EPR spectrophotometer records the absorption of energy when an electron is excited from lower to the higher state. The energy separation is very small on an absolute scale and corresponds to the energy of microwaves. The magnetic field is swept or varied linearly, and absorption of energy by the sample is recorded as a decrease in intensity of the radio frequency energy received by a detector. Thus, we can observe an absorption or *resonance* when the changing magnetic field strength makes the energy of the electromagnetic signal exactly equal to the energy difference between the two spin states (Figure 4.2a). For experimental reasons, however, the EPR signal is more often recorded as the first derivative of absorption, Figure 4.2b, or as the second derivative, Figure 4.2c. The g value in above equation has been compared to the chemical shift (δ) in PMR spectroscopy. However, the very slight variation in g values from radical to radical means that g values seldom give chemically useful information for most organic compounds.

A second type of structural information can be deduced from the hyperfine splitting in EPR spectra. The splitting of the EPR signal is due to interaction of the electron spin with the spins of nearby magnetic nuclei (e.g., ^1H, ^{13}C, ^{19}F, ^{31}P). This effect has been explained by McConnell *et al.* in terms of spin polarization involving the unpaired electron on carbon with the electrons in the C–H bond (Figure 4.3).

The number of lines is given by the equation $2nI + 1$, where I is the nuclear spin quantum number and n is the number of equivalent interacting nuclei. Thus, the EPR signal due to the methyl radical (shown as a second-derivative spectrum

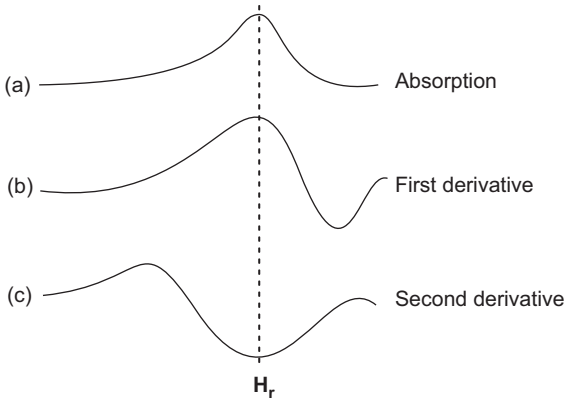


Figure 4.2 Representation of EPR spectra: (a) resonance signal, (b) first derivative, and (c) second derivative.

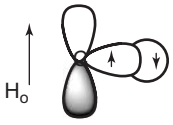


Figure 4.3 Mechanism of spin polarization for planar methyl radical.

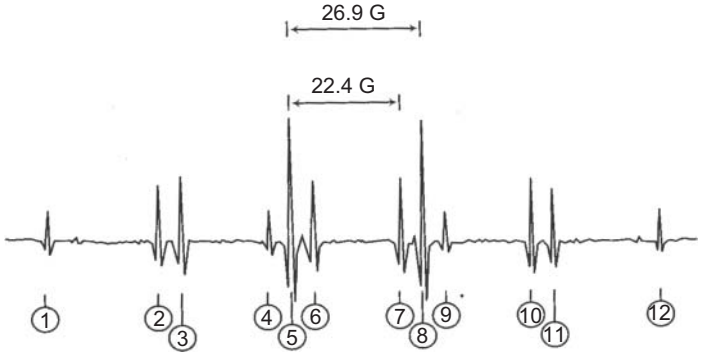


Figure 4.4 EPR spectrum for methyl radical.

in Figure 4.4) is split into a four-line pattern with relative intensities of 1 : 3 : 3 : 1 because of coupling with the three methyl protons. Similarly, the unpaired electron in the benzene radical anion is split by six equiv. protons, so the signal is septet intensities 1 : 6 : 15 : 20 : 15 : 6 : 1.

In the EPR spectrum of the ethyl radical (also as a second derivative), splitting of the signal by the two protons on the α carbon atom ($a_\alpha = 22.4$ G) gives rise to a three-line pattern, but each of those three lines is further split into four lines by the β protons ($a_\beta = 26.9$ G). The combination of the two sets of splitting results in a 12-line pattern. Note that EPR spectra, unlike NMR and IR spectra, are displayed

as the derivatives of absorption rather than as absorption. Also of interest here are the magnitudes of the two α values. The magnitude of the hyperfine coupling depends on the density of the unpaired electron in an orbital with s character about a magnetic nucleus. Therefore, it might seem surprising that the values of a_α and a_β for the ethyl radical are approximately equal, because such a result is not consistent with a simple model for the ethyl radical (Figure 4.5) in which all of the unpaired electron density is on the α-carbon atom. Nevertheless, it is common for values of a_α and a_β to be similar. However, values of a_γ (e.g., the hyperfine coupling constant for splitting of the signal of 1-propyl radical by the terminal methyl group) are much smaller, typically less than 1 G.

The valence bond explanation for the similarity of a_α and a_β values is based on the concept of hyperconjugation, which holds that a C–H or C–C sigma (σ) bond can be conjugated with an adjacent radical or cation center. Now the unpaired electron density is localized on one of the hydrogen atoms of the methyl group, and by rotation about the C–C bond all three hydrogen atoms can participate equally in the hyperconjugation (Figure 4.6).

Figure 4.7 shows the perturbational molecular orbital (PMO) description of radical stabilization. The singly occupied p orbital is the SOMO (singly occupied molecular orbital), which is higher in energy than a π-like orbital on the methyl fragment. The HOMO (highest occupied molecular orbital) is a C–H bonding orbital localized on the methyl group and parallel with the p orbital. The interaction of the SOMO and the HOMO produces two new orbitals, one lower in energy than the HOMO and one higher in energy than the SOMO. However, since two electrons go into the lower energy orbital while only one goes into the higher energy orbital, the overall effect is stabilizing. Additional insight into the structure of the ethyl radical comes from an extended Hückel calculation.

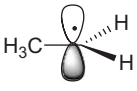


Figure 4.5 Localized model for ethyl radical.

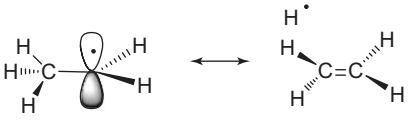


Figure 4.6 Hyperconjugation model for ethyl radical.

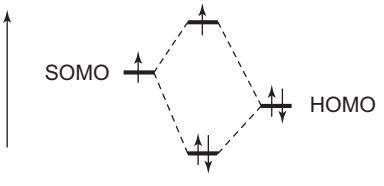
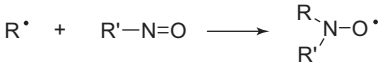


Figure 4.7 PMO description of radical stabilization; interaction of SOMO with donor HOMO.

A technique called *spin trapping* can also be used to study radicals. A diamagnetic molecule that has the property of reacting rapidly with radicals to give a stable paramagnetic species is introduced into the reaction system being studied. As radical intermediates are generated, they are trapped by the reactive molecule to give more stable, detectable radicals. The most useful spin traps are nitroso compounds (Scheme 4.4). They rapidly react with radicals to give stable nitro oxides. Analysis of the EPR spectrum of the nitro oxide can provide information about the structure of the original radical.



Scheme 4.4 Trapping of radicals by nitroso compounds.

Another technique for radical detection is *chemically induced dynamic nuclear polarization* (CIDNP). The instrumentation required for such studies is a normal NMR spectrometer. CIDNP is observed as a strong perturbation of the intensity of the NMR signals in products formed in certain types of free radical reactions. One aspect of both EPR and CIDNP studies is that either is capable of detecting very small amounts of radical intermediates. CIDNP, often pronounced like "kidnap," is a non-Boltzmann nuclear spin state distribution produced in thermal or photochemical reactions, usually from colligation and diffusion, or disproportionation of radical pairs, and detected by NMR spectroscopy as enhanced absorption or emission signals. CIDNP was discovered in 1967 by Bargon and Fischer, and independently by Ward and Lawler. Early theories were based on dynamic nuclear polarization (DNP) (hence the name). However, subsequent experiments have found that in many cases DNP fails to explain the CIDNP polarization phase. In 1969 an alternative explanation was proposed by Closs, and independently by Kaptein and Oosterhoff, which relied on the ability of nuclear spin interactions to alter the recombination probability in reactions that proceed through radical pairs. This mechanism, known as the *radical pair mechanism*, is currently accepted as the most common cause of CIDNP. However, there are exceptions, and the DNP mechanism was found to be operational, for example, in many fluorine-containing radicals. Detected as enhanced absorptive or emissive signals in the NMR spectra of the reaction products, CIDNP has been exploited for the last 30 years to characterize transient free radicals and their reaction mechanisms.

4.3 Structure and Bonding of Radicals

There are two possible structures for simple alkyl radicals, planar with the odd electron in a p orbital or pyramidal with the odd electron in a sp^3 orbital. ESR spectra of the methyl radical ($^{\bullet}CH_3$) and other simple alkyl radicals indicate that these radicals have planar structures (Figure 4.8). As shown in Figure 4.7, the odd

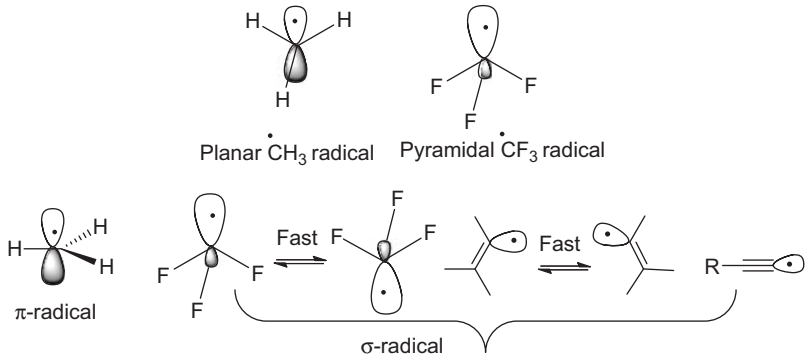
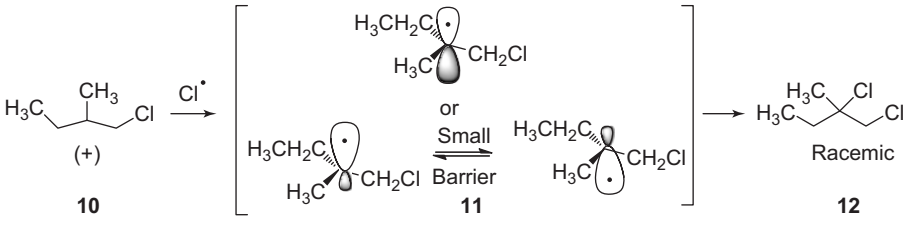


Figure 4.8 Planar and pyramidal structures of radicals.

electron in a radical can occupy an essentially pure p-orbital (a π radical) or an orbital containing some s-character as sp^3, sp^2, or sp (a σ-radical). The methyl radical and most simple aliphatic and alicyclic radicals belong to π-type (except cyclopropyl and bridgehead radicals), whereas those substituted with electronegative elements tend to acquire partial s-character. Vinylic and aromatic radicals are usually σ-radicals. Because of their partial s-character, σ-radicals tend to be more electrophilic in general than π-radicals.

In an s-orbital, the electron has a nonzero probability of being found near the positively charged nucleus, hence the greater coupling constant with a ^{13}C nucleus and a greater electrophilic character. π-Radicals are flat; σ-radicals invert very rapidly so that any stereochemical information contained in the precursor is lost at the radical stage. The stereochemical information can be restored, however, if other fixed centers in the molecule can force the radical to react preferentially from one side of the molecule. In the case of cyclic radicals memory effects may be observed, that is, radicals are captured before a change of conformation (through ring flipping). The orbital that holds the single electron is referred to as the *singly occupied molecular orbital*. Its interaction with both an empty or filled orbital is stabilizing: in the former case it is one-electron interaction, and the electron is stabilized, in the latter case it is a three-electron interaction, so two electrons are stabilized and one is destabilized, resulting generally in an overall stabilization of the system (Figure 4.7). Radicals are therefore **ambiphilic species** that are stabilized by both electron-withdrawing and electron-releasing substituents. Those that are flanked by one substituent of each type are called *captodative radicals* and seem to enjoy a special stabilization.

There is experimental evidence that alkyl radicals are planar, or pyramidal, structures that can become planar through inversion (like ammonia). For example, chlorination of (+)-1-chloro-2-methylbutane (**10**) produced racemic (±)-1,2-dichloro-2-methylbutane (**12**). The results are most consistent with an intermediate radical **11**, which is planar or which has only a small barrier to inversion so that the reaction of **11** can occur equally well from either face of the radical center. The loss of optical activity shows that radical is probably planar (Scheme 4.5).



Scheme 4.5 Experimental evidence for planar and pyramidal structures.

Spectroscopic data can be used to distinguish between planar and nonplanar rapidly inverting radical centers. The hyperfine coupling constant a_α in the methyl radical is 23.0 G, which is a typical value for the splitting of an EPR signal by protons attached to a radical center. Theoretical analysis of the spectrum suggested that the methyl radical is probably flat, although a deviation from planarity of 10–15° could not be ruled out. There is also spectroscopic evidence that the methyl radical in the gas phase is essentially planar. Thus, the methyl radical is conveniently described by sp^2 hybridization with the unpaired electron located primarily in the p orbital.

Estimates of the geometry of substituted radicals can be obtained from analysis of species labeled with ^{13}C. Fessenden and Schuler determined that the angle F–C–F in the trifluoromethyl radical is 111.1° (very nearly sp^3 hybridization) and that increasing fluorine substitution causes the radicals to go from planar, sp^2 hybridization for $^{\bullet}CH_3$ to nearly tetrahedral, sp^3 hybridization for $^{\bullet}CF_3$. This conclusion is consistent with results of INDO (intermediate neglect of differential overlap) calculations; Figure 4.9 shows the geometries of fluoromethyl radicals calculated by this method.

Pauling earlier gave a qualitative explanation of the geometry of fluoro-substituted radicals. Because of the electronegativity of fluorine, the C–F bonds are constructed with carbon orbitals having a greater degree of p character than would be the case for C–H bonds (sp^2 hybridization). The greater p character causes the bond angles about the central carbon atom to decrease and the unpaired electron to be in an orbital with greater s character. Of course, this explanation is based on the concept of a straight (internuclear) C–F bond and does not consider the possibility of curved bonds, which have since been advanced to explain the geometry of fluorocarbons.

Not only are fluoro-substituted radicals nonplanar, but alkyl substituted radicals are also found to be nonplanar. An explanation for the nonplanar nature of hydrocarbon radicals was provided by Paddon-Row and Houk, who ascribed the pyramidalization of the radical center to two effects: (i) increased staggering of

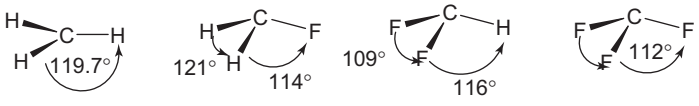


Figure 4.9 Calculated geometry of fluoro-substituted methyl radicals.

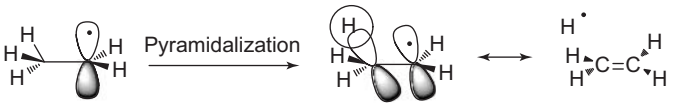
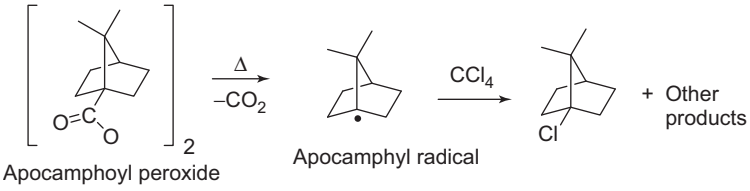


Figure 4.10 Stabilization of ethyl radical through pyramidalization.

bonds to the radical center with bonds on adjacent atoms and (ii) increased hyperconjugation of the p orbital with one of the adjacent σ bonds (Figure 4.10).

As shown in Figure 4.10, pyramidalization of the ethyl radical makes the C–H bonds on the CH_2 more nearly staggered with respect to two of the C–H bonds on the CH_3 group. At the same time, the p orbital on the CH_2 becomes more parallel with the orbitals comprising the third C–H bond, thus, stabilizing the unfilled orbital system of the radical. An especially interesting case is the *tert*-butyl radical. We might at first expect the radical to be planar because that geometry would minimize the steric repulsion of methyl groups. However, the a_c value was found experimentally to be 46.2 G, which was interpreted in terms of a C–C–C bond angle of 117.3°, suggesting that the electronic stabilization resulting from pyramidalization outweighs the increase in energy due to steric effects. In contrast to the situation with carbenium ions, free radicals have often been generated at bridgeheads (Scheme 4.6).



Scheme 4.6 Example of a bridgehead radical.

Rates of radical reactions at bridgehead carbon atoms do not indicate significant strain due to pyramidalization, at least not in comparison with the strain due to bridgehead carbenium carbon atoms (Figure 4.11). Radicals such as 1-adamantyl and 7-norbornyl can be formed, although their stabilities and rates of formation decrease with increasing deviation from the geometry observed for acyclic analogs (Figure 4.12). The general view that emerges from these studies is that only the methyl radical prefers to be planar, and even it has a low barrier to deformation.

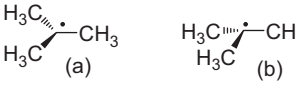


Figure 4.11 (a) Planar and (b) nonplanar geometries of *tert*-butyl radical.

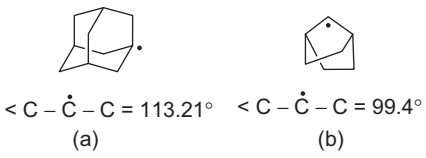
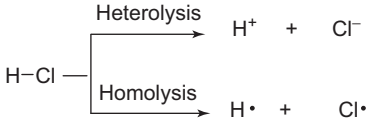


Figure 4.12 (a)1-Adamantyl and (b) 7-norbornyl radical.

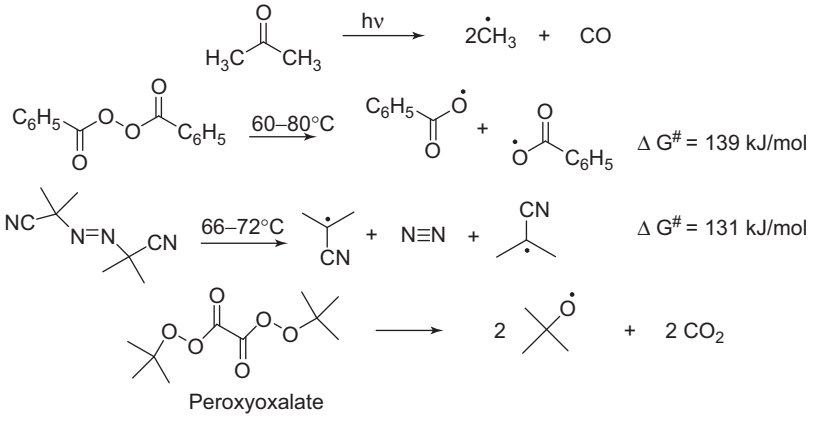
4.4 Generation of Free Radicals

When bonds break and one atom obtains both bonding electrons the process is called *heterolysis* and the products are **ions**. When bonds break and the atoms get one bonding electron each, the process is called *homolysis* and the products are **radicals**, which may be atoms or molecules, and contain an unpaired electron (Eq. (4.1)):



(4.1)

Several methods are used to generate free radicals. The three most general methods are outlined here. Radicals may be generated directly by (i) thermal, (ii) photochemical, or (iii) redox processes that accomplish homolytic dissociation of a two-electron bond. Organic peroxides and azo compounds (AIBN, azobisisobutyronitrile) have weak bonds that undergo dissociation to radicals (Scheme 4.7). An advantage of the generation of radicals from peroxides is that reactions generally occur at relatively low temperature.

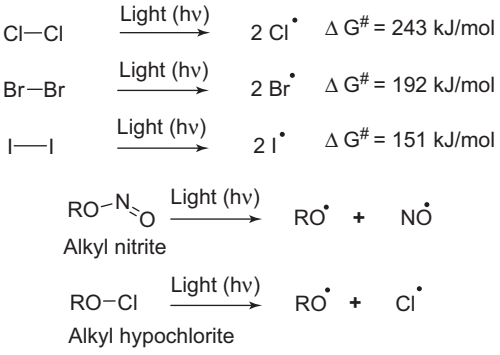


Scheme 4.7 Formation of free radicals.

The halogens are quite readily homolyzed by light. The 58 kcal mol^{-1} required to break the Cl–Cl bond is furnished by light, which is absorbed. The energy of a quantum of light depends on the wavelength and can be derived from a simple formula (Eq. (4.2)):

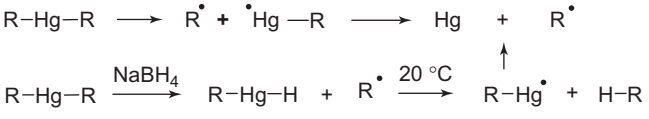
$$E(\text{kcal mol}^{-1}) = \frac{28\,635}{\lambda(\text{nm})} \tag{4.2}$$

Thus, blue light at 400 nm has energy of 71.6 kcal mol^{-1}, while UV light at 200 nm can furnish 143.2 kcal mol^{-1}. This energy is enough to break any covalent bond, if it is absorbed. Free radical bromination is even easier than chlorination (Scheme 4.8).



Scheme 4.8 Photolytic generation of free radicals.

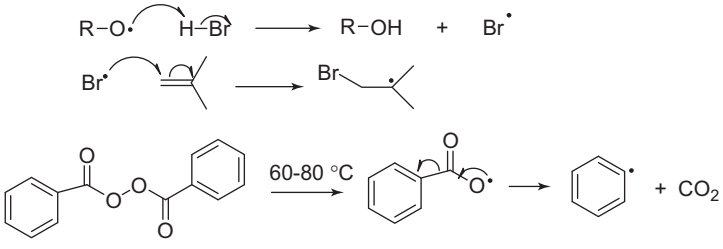
Some organometallic compounds, for example, organomercury or organocobalt compounds, have very weak carbon–metal bonds, and are easily homolyzed to give carbon-centered radicals. Alkyl mercury hydrides are formed by reducing alkyl mercury halides, but they are unstable at room temperature because the Hg–H bond is very weak. Bonds to hydrogen never break to give radicals spontaneously because H$^{\bullet}$ is too unstable to exist, but interaction with almost any radical removes the H atom and breaks the Hg–H bond (Scheme 4.9).



Scheme 4.9 Homolysis of organometallic compounds.

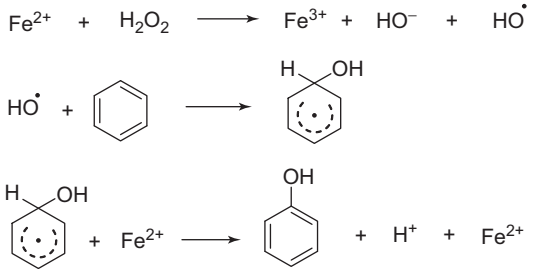
Radicals may also result from chemical or electrochemical oxidation or reduction of stable molecules. Single-electron transfer processes initially generate radical cations (for oxidation) or radical anions (for reduction), which may then fragment to radicals and ions. For example, Sargent and coworkers determined that in 1,2-dimethoxyethane solutions the radical anion of naphthalene (sodium naphthalenide, Na^+ Ar^-) transferred an electron to propyl iodide. Subsequent loss of

iodide ion from the propyl iodide radical anion produced the propyl radical. Radicals may be generated from other radicals by substitution (abstraction), addition, or elimination. The peroxy radical RO• abstracts H• from the HBr to give ROH, leaving behind a new radical Br•, which adds to the alkene to give a new carbon-centered radical (Scheme 4.10).



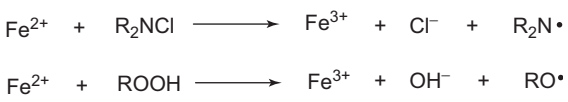
Scheme 4.10 Formation of radicals from radicals.

Fenton's reagent is a solution of hydrogen peroxide and an iron catalyst that is used to oxidize contaminants or wastewaters. Fenton's reagent can be used to destroy organic compounds such as trichloroethylene (TCE) and tetrachloroethylene (or perchloroethylene, PCE). It was developed in the 1890s by Henry John Horstman Fenton as an analytical reagent. Ferrous (Fe^{2+}) is oxidized by hydrogen peroxide to ferric (Fe^{3+}), a hydroxyl radical and a hydroxyl anion. Iron(III) is then reduced back to iron(II), a peroxide radical, and a proton by the same hydrogen peroxide (disproportionation). The hydroxyl free radical generated by Fenton's reagent is a powerful, non-selective oxidant. Oxidation of an organic compound by Fenton's reagent is rapid and exothermic (heat-producing) and results in the oxidation of contaminants to, primarily, carbon dioxide and water (Scheme 4.11).



Scheme 4.11 Oxidation of benzene by Fenton's reagent.

Ferrous ions are similarly employed in the production of radicals from N-chloroamines and hydroperoxides. The transfer of one electron to or from a species containing only paired electrons results in the formation of free radicals. Electron transfer can occur both from charged and neutral molecules (Scheme 4.12).



Scheme 4.12 Formation of radicals through ferrous ions.

Low-energy SOMOs are more willing to accept an electron than to give up one; radicals adjacent to electron-withdrawing groups are therefore *electrophilic*. High-energy SOMOs are more willing to give up an electron than to accept an electron; radicals adjacent to electron-donating groups are therefore *nucleophilic*.

4.5 Stability of Radicals

Stability in chemistry is not an absolute but a relative concept. It always refers to a stability difference with respect to a reference compound. Radicals reported in the literature range from extremely unstable, short-lived species to relatively stable one that could be isolated as pure substances.

Not all radicals show the same reactivity, broadly speaking the character of radicals is affected by (i) the nature of the atom that is the radical center and (ii) the electronic properties of the groups attached to the radical. The importance of the atom bearing the unpaired electron is nicely illustrated by the different reactivities of group 6 radicals, and is rationalized by the hard/soft nature of the radical center. Thus, alkoxy radicals ($RO^{\bullet}$) are small and hard; they typically undergo H-atom abstraction and β-scission reactions. However, they rarely add to C=C. Thiyl ($RS^{\bullet}$) and selenyl ($RSe^{\bullet}$) radicals, however, are larger and softer. They do not usually abstract H, but they do readily add to C=C. This is useful for (*Z*/*E*) isomerization of alkenes.

Within radicals centered on the same element, the groups attached can also influence reactivity. For example, consider carbon-centered radicals ($R_3C^{\bullet}$). These species do undergo addition to C=C bonds (in fact this is an extremely useful C–C bond-forming reaction, as we shall see later). Simple alkyl radicals ($R_3C^{\bullet}$) are generally considered to be nucleophilic radicals: they react fastest with electron-poor alkenes (e.g., α,β-unsaturated carbonyl compounds, cyanoalkenes, etc.). However, when R is an electron-withdrawing group, the radicals are electrophilic and react fastest with electron-rich alkenes (e.g., enol ethers, enamines). This leads to the concept of **radical umpolung** (reverse polarity): for example, malonates are traditionally used as carbon nucleophiles; however, the malonyl radical is electrophilic. Similarly, α-halo ethers are regarded as electrophiles in ionic chemistry, but the derived radicals are nucleophilic.

Carbon–hydrogen bonds decrease in strength in R–H when R goes from primary to secondary to tertiary. Tertiary alkyl radicals are therefore the most stable and methyl radicals are the least stable. As C–H bonds next to conjugating groups such as allyl or benzyl are particularly weak, allyl and benzyl radicals are more stable.

In contrast, C–H bonds next to alkynyl, alkenyl, or aryl groups are strong. Figure 4.13 shows the order of stability of some radicals.

Adjacent functional groups appear to weaken C–H bonds; radicals next to carbonyl, nitrile, or either functional groups, or centered on a carbonyl carbon atom, are more stable than even tertiary alkyl radicals. Both electron-withdrawing and electrons-donating functional groups seem to stabilize radicals (Figure 4.14).

Thus, anything that would stabilize an anion or a cation will stabilize a radical. Steric hindrance makes radicals less stable. For example, Koelsch reported that the α,γ-bisdiphenylene-β-phenylallyl radical **13** is indefinitely stable as a solid and could be recovered in part after being subjected to molecular oxygen in boiling benzene for 6 h. A well-known example of a nitrogen-centered radical is 2,2-diphenyl-1-picrylhydrazyl **14**, which is stable chiefly because of extensive delocalization of the odd electron; it is commercially available as violet crystals and can be kept for years. Tetramethylpiperidine *N*-oxide free radical **15** is so stable that reactions can be performed on it without affecting the unpaired electron. The 2,4,6-tri-*tert*-butylphenoxy radical **16** is formed by oxidation of the corresponding phenol, which is black, stable solid, to give a blue solution. Radicals that have long lifetimes and are resistant to dimerization or other routes for bimolecular self-annihilation are called *stable free radicals*. Radical **17** is stable in solution for days, even in the presence of air. It is stable indefinitely in solid state and thermally stable up to 300 °C. Such a free radical is said to be an *inert free radical* (Figure 4.15).

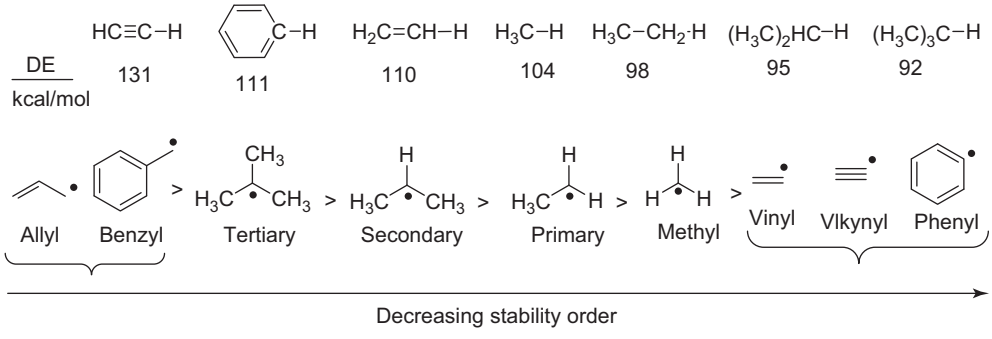


Figure 4.13 Stability of free radicals.

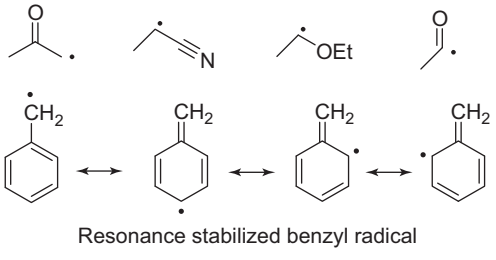
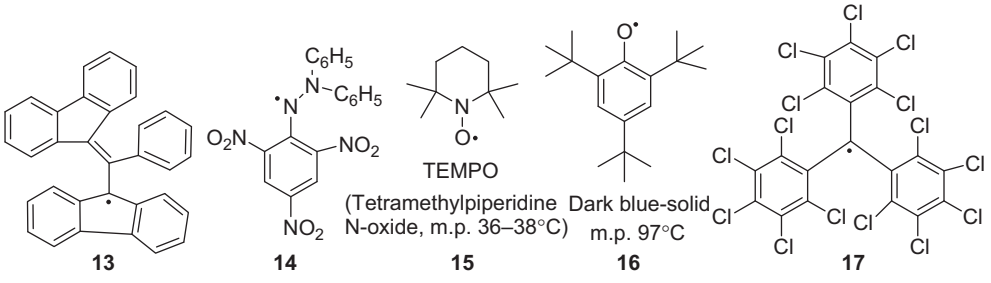


Figure 4.14 Relatively stable free radicals.



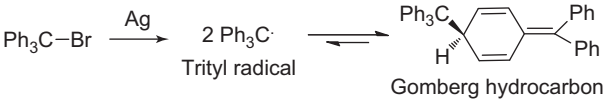
13 14 15 16 17

Figure 4.15 Persistent free radicals.

There are two reasons why some radicals are more persistent than others:

1) steric hindrance;
2) electronic stabilization.

Persistent radical compounds are those whose longevity is due to steric crowding around the radical center, which makes it physically difficult for the radical to react with another molecule. Just as several alkyl groups increasingly stabilize a radical center, phenyl substituents also stabilize a radical center via resonance stabilization. The stability of the triphenylmethyl radical, generated from bromotriphenylmethane by reduction with silver, is accounted for in part by the delocalization of the unpaired electron and in part by the steric forces inhibiting its reactions. For the trityl radical, dimerization leads to the Gomberg hydrocarbon in which an aromatic sextet is lost. The trityl radical cannot dimerize, to give hexaphenylethane, because the van der Waals repulsions between the substituents would be too severe (Scheme 4.13).



Scheme 4.13 Formation of Gomberg hydrocarbon.

4.6 Reactions of Free Radicals

Organic chemists are interested in the reactions of compounds, which yield products that may be isolated and purified easily. Free radical intermediates are generally involved in reactions carried out at high temperatures, under the influence of light, or in the presence of free-radical generators. Even at room temperature many reactions proceed by a free-radical mechanism, particularly in nonpolar solvents in the presence of a radical producer. A radical has a choice, it can find another radical and combine to form a spin-paired molecule or it can react with a spin-paired molecule to form a new radical; both are possible. A third alternative is

to decompose in a unimolecular reaction giving rise to a new radical and a spin-paired molecule. A fourth class of reaction is rearrangement, which is relatively rare. Most common radicals are extremely reactive and are difficult to isolate. Such radicals are referred to as *short-lived radicals*, in contrast to *stable radicals* that are not so reactive and exist in equilibrium with the normal compounds.

Till now, we have seen that radicals can be considered to be either nucleophilic (reacting fastest with electron-poor alkenes) or electrophilic (reacting fastest with electron-rich alkenes). These tendencies can be nicely rationalized in terms of frontier molecular orbital (FMO) theory. Recall the key ideas of this theory:

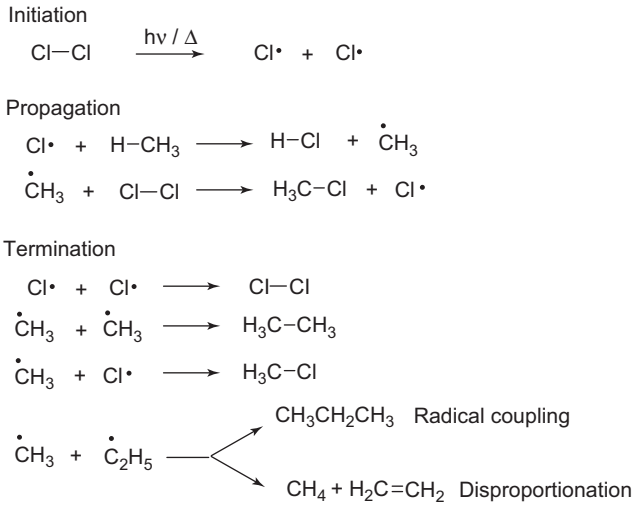
- Best overlap (and maximum stabilization) results from interaction of a filled orbital (the HOMO of one reactant) and an unoccupied orbital (LUMO, lowest unoccupied molecular orbital, of the other reactant) that are close together in energy. For radicals, we need to consider the interactions with a SOMO.
- Electron-withdrawing groups lower orbital energies; electron-donating groups raise them.
- Electrophilic radicals have low energy SOMOs, and the dominant interaction is with the HOMO of an electron-rich alkene.
- Nucleophilic radicals have high energy SOMOs and the dominant interaction is with the LUMO of an electron-poor alkene.

In general, nucleophilic radicals are more discriminating in their reactions since ΔE_1 is inherently larger than ΔE_2. Most synthetically useful radical reactions involve chain reactions. The main features of a chain reaction can be illustrated by considering the reduction of haloalkanes by tributyltin hydride. The key steps are initiation, propagation (molecule + radical to give another molecule and another radical), and termination (Scheme 4.14). The chain process can be terminated by combination of two radicals, a process that has a very high rate constant (often approaching diffusion control). However, the concentration of radicals is very low in the chain process, leading to low actual rates of radical combination. To summarize, the key steps of a chain reaction are:

- an initiation step (e.g., one of the generation reactions discussed in the previous section);
- a series of propagation steps;
- one or more termination steps that stop the chain reaction.

Some characteristics of free-radical reactions are:

1) The reactions are similar whether they take place in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.
2) Acids, bases, and polar solvents have almost no effect on radical reactions.
3) Free-radical initiators are necessary. The most frequently used radical initiators are AIBN and dibenzoyl peroxide.
4) The rates of free-radical reactions are decreased or suppressed by inhibitors, for example, NO, O_2, benzoquinone, and so on.



Scheme 4.14 Reactions of free radicals.

Each propagation step in a radical chain involves the reaction of a species with one unpaired electron to produce another species having an unpaired electron. Moreover, the reactant in one step is a product in a subsequent step. One example of a propagation step in a radical chain reaction is the abstraction of a hydrogen atom by a halogen in free-radical halogenations. Methane and chlorine do not react in the dark at room temperature, but under the influence of UV light or at 250–400 °C they react vigorously to yield HCl and a mixture of CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4.

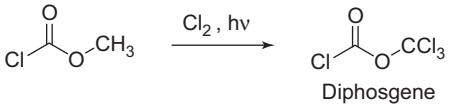
The order of reactivity of the halogens for methane can be explained by energy considerations. Scheme 4.15 gives the ΔH values for the two principal propagation steps.

	kcal/mol			
	F_2	Cl_2	Br_2	I_2
$CH_4 + X^{\bullet} \longrightarrow {}^{\bullet}CH_3 + HX$	–31	+1	+17	+33
$CH_3 + X_2 \longrightarrow CH_3X + X^{\bullet}$	–71	–26	–24	–19

Scheme 4.15 Order of reactivity of the halogens.

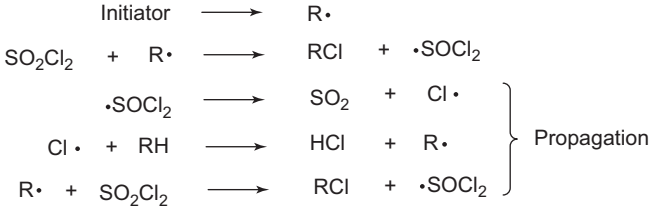
The corresponding reaction with iodine atoms is so strongly endothermic that the reaction is ineffective; indeed, HI can reduce alkyl iodides to alkanes and iodine. For fluorine, both propagating steps are strongly exothermic; reaction is violent and is accompanied by the fragmentation of alkyl groups. Another valuable multiple chlorination is the photochemical perchlorination of methyl chloroformate, which leads to diphosgene (Scheme 4.16). Diphosgene is a colorless liquid and a valuable

reagent in the synthesis of organic compounds. It is related to phosgene but is more conveniently handled because it is a liquid, whereas phosgene is a gas.



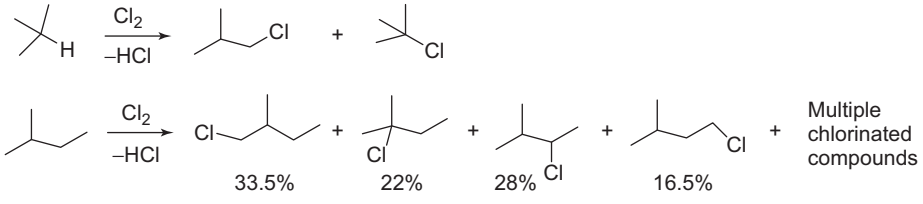
Scheme 4.16 Photochemical perchlorination of methyl chloroformate.

Radical-catalyzed chlorination and bromination occur readily on alkanes and substituted alkanes, both in the gas phase and in solution. Both thermal and photochemical generation of the halogen atoms are employed; for chlorinations, sulfuryl chloride in the presence of an initiator such as dibenzoyl peroxide is also used (Scheme 4.17).



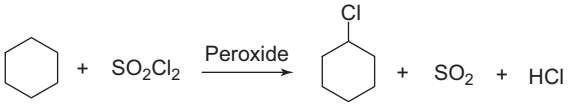
Scheme 4.17 Radical-catalyzed chlorination.

For example, the chlorination of *iso*-butane in the gas phase at 100 °C gives comparable quantities of *iso*-butyl chloride and *tert*-butyl chloride, and at 300 °C 2-methylbutane gives a mixture of products (Scheme 4.18).



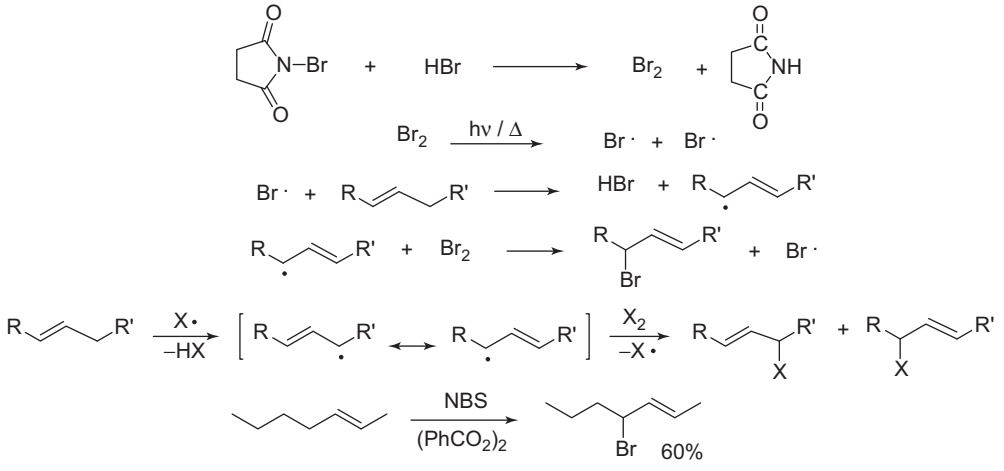
Scheme 4.18 Chlorination of *iso*-butane and 2-methylbutane.

Cyclohexyl chloride can be isolated in 89% yield by treating cyclohexane with sulfuryl chloride in the presence of dibenzoyl peroxide (Scheme 4.19).



Scheme 4.19 Chlorination of cyclohexane.

N-Bromosuccinimide (NBS) is a very specific reagent for allylic and benzylic bromination. NBS acts as a bromine reservoir maintaining a low concentration of molecular bromine by reacting with HBr. The bromine molecule dissociates into bromine atoms in the presence of light or radical initiators. H-abstraction by bromine atom generates an allylic radical, which then reacts with Br_2 to yield the product. Allylic compounds of the type RCH=CH–CH_2R′ give mixtures of two monohalogenated products because the allylic radical can react at each of the two carbon atoms (Scheme 4.20). Bromination is favored to occur at the more highly substituted position, because the corresponding intermediate radicals are better stabilized. CCl_4 is the solvent of choice, because NBS is poorly soluble and the resulting succinimide is insoluble and floats at the surface. This keeps the concentration of reagents low and is a signal that the reaction is finished. However, environmental concerns have all but eliminated the use of CCl_4, and its replacement, CH_2Cl_2, is being restricted as well. Many other solvents are reactive toward NBS, and are thus unsuitable, but acetonitrile can be used to good effect. The **Wohl–Ziegler reaction** is a chemical reaction that involves the allylic or benzylic bromination of hydrocarbons using an *N*-bromoimide and a radical initiator.

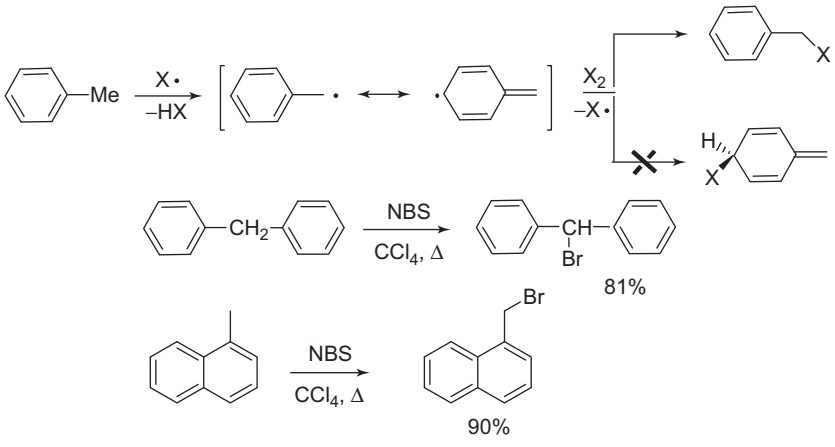


Scheme 4.20 Allylic bromination.

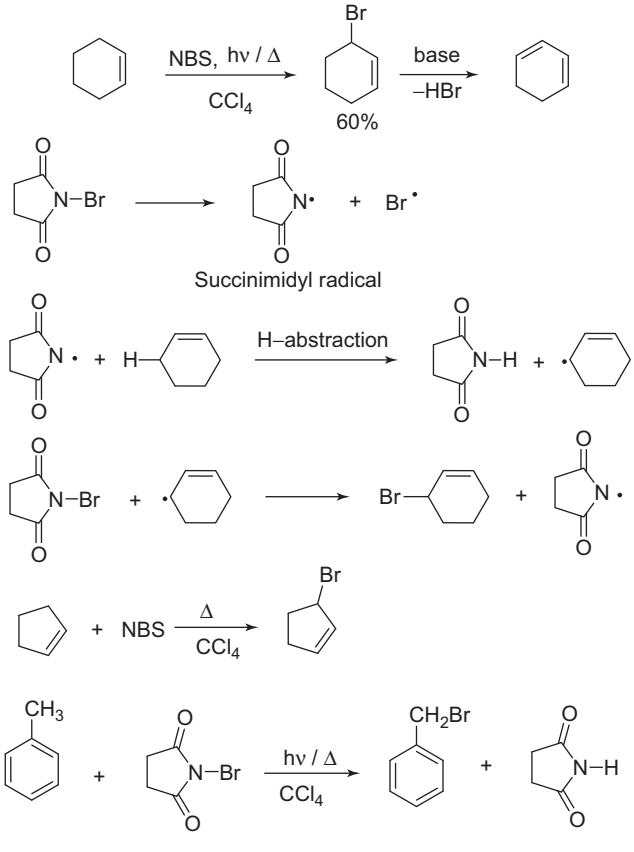
Benzylic compounds, on the other hand, give only one product because the possible isomers, being non-aromatic, are of much higher energy content (Scheme 4.21).

The bromination of allylic compounds (Wohl–Ziegler reaction) is generally used in the conversion of alkenes into conjugated dienes, which are obtained from the allylic bromides by base-catalyzed elimination (Scheme 4.22).

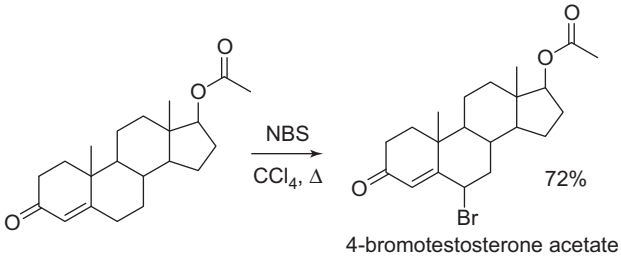
The reaction has also been used to make changes in steroid structures. Testosterone acetate is converted into 6-bromo derivatives by NBS (Scheme 4.23).



Scheme 4.21 Benzylic bromination.

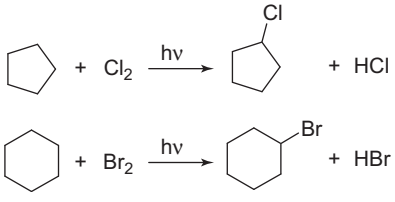


Scheme 4.22 Wohl–Ziegler reaction.



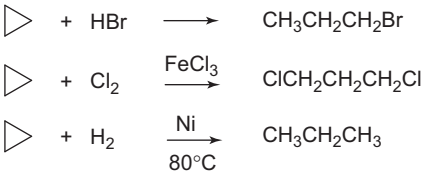
Scheme 4.23 Allylic bromination of testosterone.

Cyclic compounds undergo the same reactions as noncyclic compounds. For example, cyclic alkanes and cyclic alkenes undergo radical substitution reactions with chlorine or bromine (Scheme 4.24).



Scheme 4.24 Radical substitution in cycloalkanes.

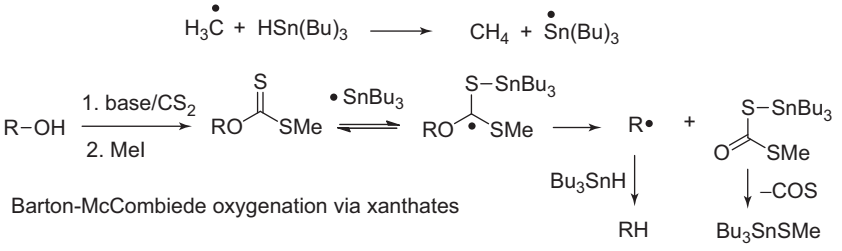
Cyclopropane is one notable exception, as it undergoes electrophilic addition reactions. Cyclopropane is more reactive than propene toward addition of acids such as HBr and HCl but is less reactive towards addition of Cl_2 and Br_2, so a Lewis acid, $FeCl_3$, is needed to catalyze halogen addition (Scheme 4.25).



Scheme 4.25 Ring-opening reactions of cyclopropane.

A carbon-centered radical can also abstract an atom from another molecule (or from another atom in the same molecule) to fill its outer shell if the process is radical trapping, in which a radical abstracts a hydrogen atom from a facile hydrogen atom donor such as tri-*n*-butyltin hydride (Bu_3SnH). This reaction can serve as a means of detecting radical intermediates, because the appearance of the species R–H upon addition of Bu_3SnH to a reaction suggests the intermediacy of $R^{\bullet}$ in the reaction. Alcohols cannot normally be deoxygenated by direct reaction with an organotin hydride. A more general method, devised by Barton and McCombie,

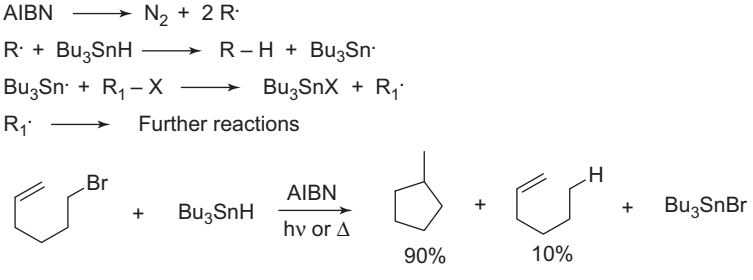
involves the use of a thiocarbonyl derivative of the alcohol such as a xanthate (Scheme 4.26).



Scheme 4.26 Trapping of methyl radical by Bu_3SnH.

It has long been known that the carboxyl radical readily loses CO_2 to give an alkyl radical. However, an efficient way of making the carboxyl radicals was not known until the late 1970s when Barton developed the chemistry of O-acyl thiohydroxamates. These compounds are readily prepared from acid chlorides and undergo reaction with Bu_3SnH/AIBN to give carboxyl radicals, which lose CO_2 to give alkyl radicals, which are then trapped by Bu_3SnH to give the alkane.

Trialkyltin hydrides are effective hydrogen atom transfer agents, and trialkyltin radicals will abstract chlorine, bromine, or iodine atoms from alkyl halides. Together with a radical initiator, such as AIBN and trialkyltin hydrides, alkyl halides can give reduction or other radical-derived products (Scheme 4.27).

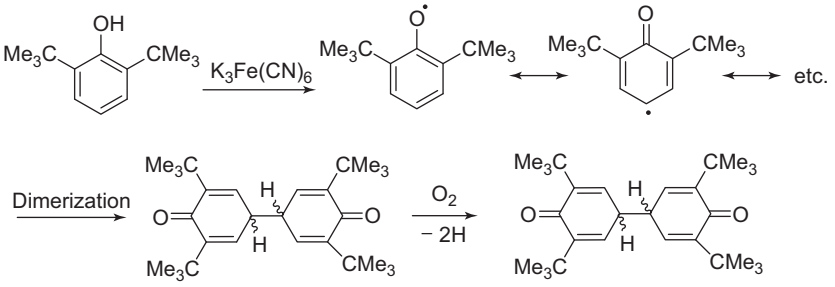


Scheme 4.27 Reaction of trialkyltin hydride with halide in the presence of AIBN.

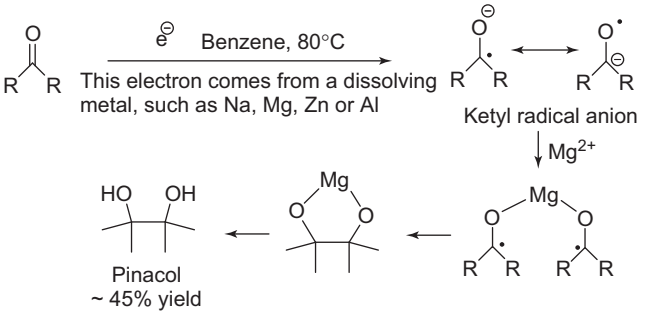
In some cases the acceptor is usually a transition metal ion in a high-valence state, such as a hexacyanoferrate(III) ion in the oxidation of certain phenols (Scheme 4.28).

The pinacol reaction is an example of radical dimerization (Scheme 4.29).

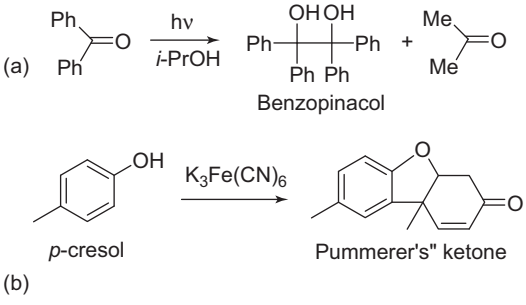
Stabilized free radicals have sufficiently long lifetimes to permit coupling outside solvent cage confinement. Scheme 4.30 shows two such coupling reactions. The first is the photochemical reduction of benzophenone to benzopinacol (Scheme 4.30a). The second is an example of the oxidative coupling of phenols, a transformation that is an important step in the biosynthesis of alkaloids (Scheme 4.30b).



Scheme 4.28 Oxidation of 2,6-di-*tert*-butylphenol.



Scheme 4.29 Pinacol reaction.

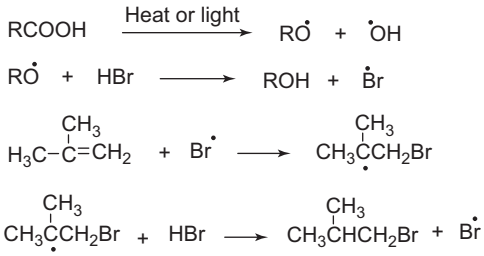


Scheme 4.30 Coupling reaction of (a) benzophenone and (b) *p*-cresol.

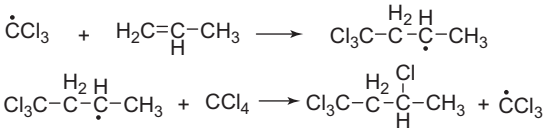
Another common propagation step is addition of a radical to a double or triple bond as in the anti-Markovnikov addition of HBr to an alkene (Scheme 4.31). Carbon tetrachloride can be added to propylene in 80% yield (Scheme 4.32).

The relative rates of alkyl radical formation by a chlorine radical is tertiary (5.0) > secondary (3.8) > primary (1.0) (Scheme 4.33), while the relative rates by a bromine radical is tertiary (1600) > secondary (82) > primary (1).

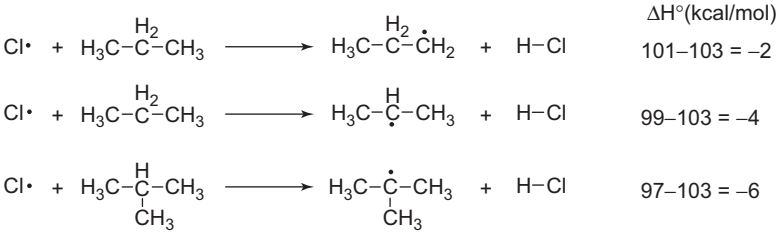
When bromine radical is the hydrogen-abstracting agent, the differences in reactivity are very great. To find out why this is the case, we must look at the ΔH^0 values for formation of primary, secondary, and tertiary radicals as a result of



Scheme 4.31 anti-Markovnikov addition of HBr to an alkene.

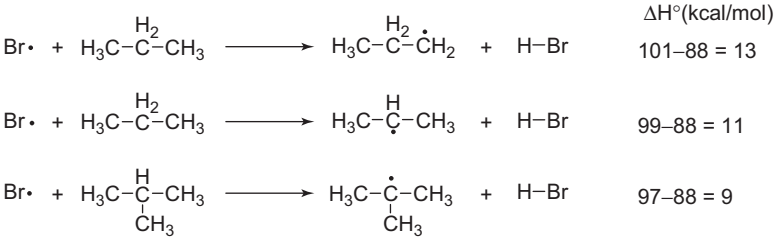


Scheme 4.32 Addition of CCl_4 to propylene.



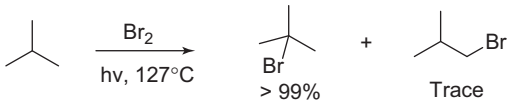
Scheme 4.33 Relative rates of alkyl radical formation.

reaction with chlorine radical and as a result of reaction with bromine radical. These ΔH^0 values can be calculated using the bond dissociation energies (Scheme 4.34).



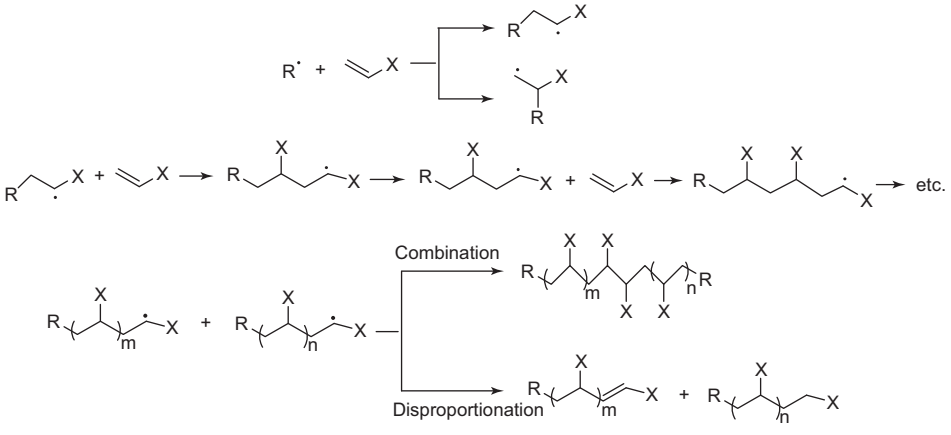
Scheme 4.34 ΔH^0 values of primary, secondary, and tertiary radicals.

Bromination reactions are much more selective than chlorination reactions. For example, when 2-methylpropane is treated with bromine in the presence of light at 127 °C the product is almost exclusively 2-bromo-2-methylpropane (Scheme 4.35).



Scheme 4.35 Regioselective bromination of 2-methylpropane.

Radical addition to a multiple bond is the key step in radical polymerization. For example, in the polymerization of styrene, the initiation step is homolysis of an initiator, which produces a radical that adds to a styrene molecule to begin the polymer chain. Two carbon–carbon single bonds are more stable than one carbon–carbon double bond by about 20 kcal mol^{-1}, and so the difference in the strengths of carbon–carbon single and double bonds provides the driving force for the reaction. Increasingly, radical addition reactions are finding application in organic synthesis. Because charged species are not involved in the reaction, subtle effects due to orbital interactions and steric interactions can provide opportunities for stereoselective syntheses (Scheme 4.36).

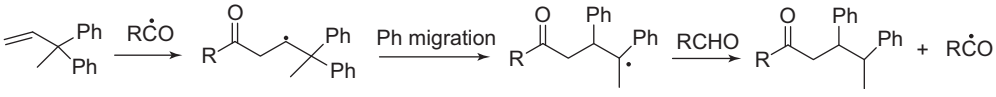


Scheme 4.36 Radical polymerization of alkene.

Another useful chain reaction involves the PTOC (pyridine-2-thione-*N*-oxycarbonyl) esters developed by Barton. Reaction of a carboxylic acid chloride (RCOCl) with the sodium salt on *N*-hydroxypyridine-2-thione produces an ester designated as R-PTOC. Addition of radical $Y^{\bullet}$ (formed by an earlier initiation step) to the R-PTOC leads to the carboxy radical $RCO_2^{\bullet}$. The carboxy radical then decarboxylates to produce the radical $R^{\bullet}$, which can continue the chain reaction or can undergo other reactions.

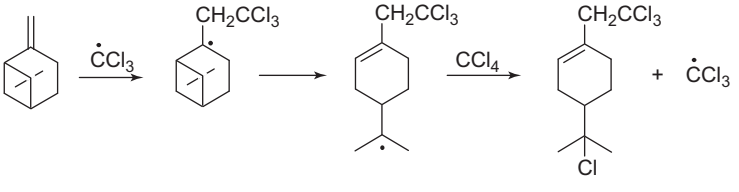
Another reaction of radicals is rearrangement. Radicals are generally less susceptible to rearrangement than are carbocations, and the 1,2 hydrogen or carbon shifts seen with carbocations are not observed with radicals. However, apparent phenyl migration has been observed (Scheme 4.37). Treatment of neophyl chloride with phenylmagnesium bromide and cobaltous chloride produced isobutylbenzene

(15%), 2-methyl-3-phenyl-1-propene (9%), and β,β-dimethylphenylethene (25%). The 1,1-dimethylspiro[2.5]octadienyl radical has been proposed as an intermediate or transition structure in the rearrangement.



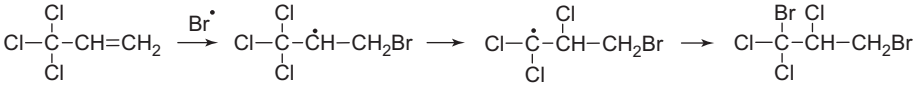
Scheme 4.37 Radical rearrangement reaction.

Rearrangements can also occur when they result in the relief of strain in a cyclic system, as in the radical-catalyzed addition of carbon tetrachloride to β-pinene (Scheme 4.38).



Scheme 4.38 Radical-catalyzed addition of CCl_4 to β-pinene.

Migrations have also been observed for chloro groups. Migration of a halogen could occur via a transition state in which the odd electron is accommodated in a vacant d-orbital of the halogen (Scheme 4.39).



Scheme 4.39 Migration of chloro group.

The characteristic of radical termination steps is that two radical centers react to produce a product that has an even number of electrons. The two most important processes are dimerization (Scheme 4.40) and disproportionation (Scheme 4.41). Dimerization is the reverse of the thermal dissociation of a σ bond to produce two radicals. This process is usually quite exothermic and has small or negligible activation energy. However, significant steric hindrance can lower the dissociation energy and introduced a barrier to recombination. For example, the dissociation energy of 1-(2,6-dimethylphenyl)-2-(2,6-dimethylphenyl)ethane is only 22 kcal mol^{-1}.

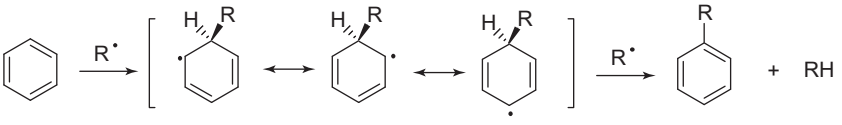
Scheme 4.40 Radical dimerization.

Scheme 4.41 Radical disproportionation.

Disproportionation can be considered to be hydrogen abstraction from another radical. The overall result is the destruction of two radicals, one radical center being converted into a carbon–hydrogen bond, the other being converted into a double bond. Both dimerization and disproportionation represent bimolecular processes of radicals. Dimerization is more exothermic than is disproportionation, but the ΔS for dimerization is much more negative than is ΔS for disproportionation. Therefore, the reaction of two radicals depends strongly on the temperature, with higher temperatures favoring disproportionation and lower temperatures favoring dimerization.

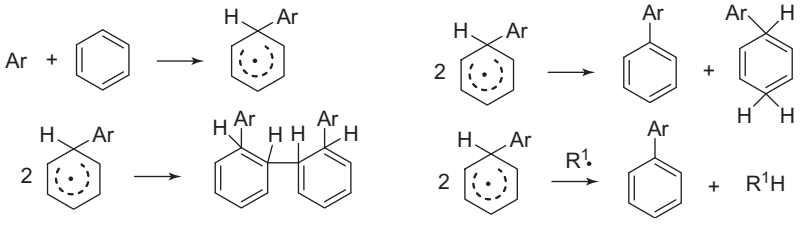
There is one important exception to the statement that radical termination steps produce products with an even number of electrons. A radical addition step may produce a radical product that is much less reactive than the reacting precursor, such that further addition may be precluded. This process, known as *spin trapping*, is primarily useful as a means of studying radicals that cannot be studied directly by EPR. Adding a nitroso compound or a nitrone to a reaction mixture involving short-lived radicals can produce a spin adduct, a longer-lived species that can be studied directly by EPR spectrometry. The spectrum of the product is often diagnostic of its radical precursor.

Both alkyl and aryl radicals substitute in aromatic nuclei by an addition–elimination sequence. Substituents in the *ortho*- and *para*-positions are able to increase the delocalization of the intermediate radical and consequently activate these positions to substitution (Scheme 4.42).



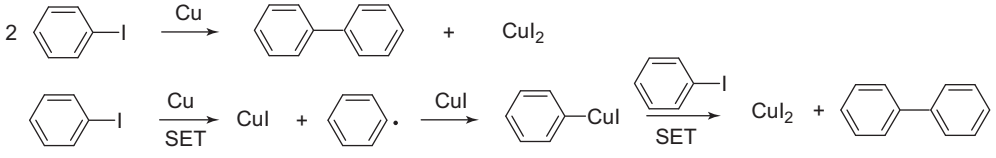
Scheme 4.42 Radical addition–elimination reaction.

The coupling of two aromatic rings cannot be explained on the basis of simple abstraction. The products can be explained, though, by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring; the intermediate formed is stable due to resonance. The reaction may terminate in three ways: by simple coupling, by disproportionation, or simply by hydrogen abstraction (Scheme 4.43). All substituents (electron-donating and electron-withdrawing) increase reactivity at the *ortho*- and *para*-positions over that of benzene and that of *meta*-substituents (which usually show similar reactivity to that of benzene).



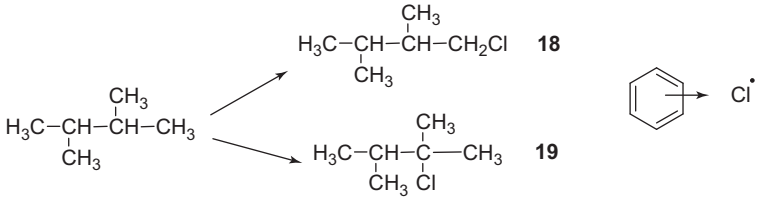
Scheme 4.43 Radical reactions of aromatic rings.

Homocoupling of aryl iodide in the presence of Cu (**Ullmann reaction**) proceeds via a radical mechanism (Scheme 4.44).



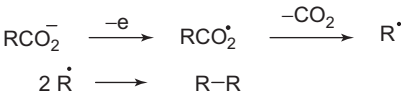
Scheme 4.44 Ullmann reaction.

The solvent usually has little effect on free-radical substitutions; however, in certain cases it can make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% **18** and 40% **19**, while in aromatic solvents the ratio became about 10 : 90. This result is attributed to complex formation between the aromatic solvent and the chlorine atom, which makes the chlorine less reactive and more selective (Scheme 4.45).



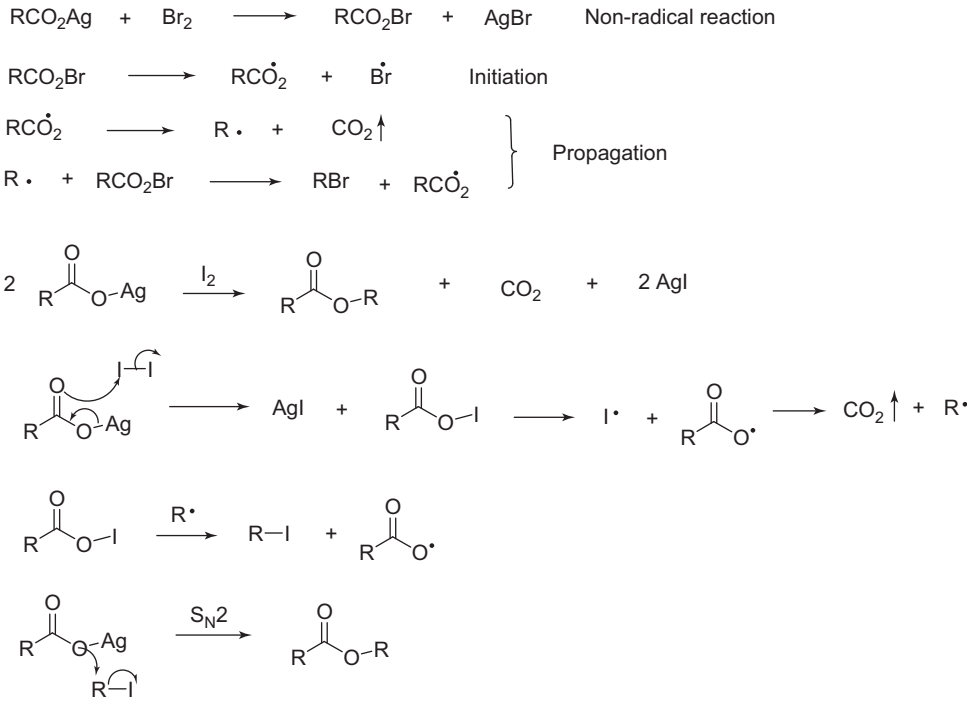
Scheme 4.45 Solvent dependent chlorination of 2,3-dimethylbutane.

Free-radical reactions may be divided into two classes. In the first, the product results from the combination of two radicals, as in the Kolbe synthesis. Electrolysis of the alkali metal salts of aliphatic carboxylic acids results in the liberation of alkyl radicals at the anode and their subsequent dimerization (Scheme 4.46). In the second class, the product results from the reaction of a radical with a molecule, as in the case of photochemical chlorination of methane. The fundamental difference between the two types of reaction is that the latter class involves a chain reaction.



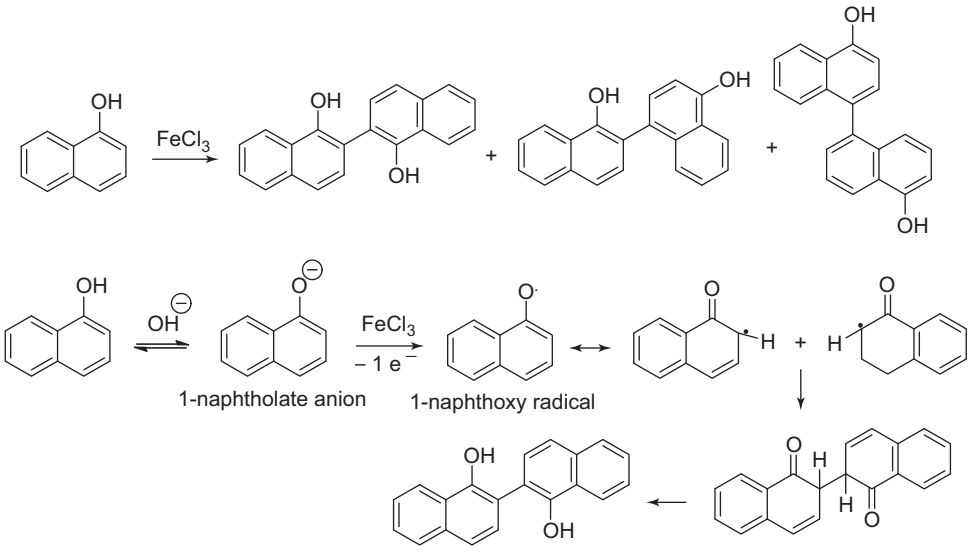
Scheme 4.46 Kolbe synthesis.

One particular radical decarboxylation reaction, which is used in the synthesis of alkyl or aryl bromide (**Hunsdiecker reaction**), involves reaction of the silver salt of a carboxylic acid with bromine, and results overall in loss of CO_2 to form the corresponding alkyl or aryl bromide (Scheme 4.47). When silver carboxylate is treated with I_2 ester formation occurs (**Simonini reaction**).



Scheme 4.47 Hunsdiecker reaction.

Phenols that have only one hydroxyl group are oxidized by a wide variety of oxidizing agents to give compounds in which carbon–carbon bonds have been formed between aromatic rings; such reactions are called *oxidative coupling reactions*. For example, 1-naphthol gives three products when oxidized with ferric chloride. The new carbon–carbon bond between aromatic rings is formed *ortho* or *para* to the hydroxyl groups (Scheme 4.48).



Scheme 4.48 Oxidative coupling of 1-naphthol.

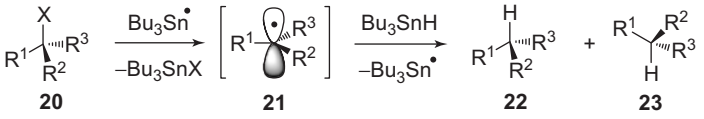
4.7
Stereochemistry of Radical Reactions

For many years, the stereoselective synthesis of important target molecules involving free-radical reactions was overlooked due to a lack of selectivity. Now the situation is gradually changing and several new and milder methods of radical generation have been developed, which have helped researchers to gain a better understanding of the key factors that influence selectivity in radical transformations. As a consequence, the use of radicals in stereoselective synthesis is increasing and there are several important intra- and intermolecular additions, where high levels of stereoselectivity have been achieved in the formation of carbon–carbon bonds.

To understand stereoselectivity in radical reactions it is first necessary to have a general understanding of the principles of radical reactions such as understanding of the importance of bond dissociation energies, steric effects, stereoelectronic effects, and radical polarity in radical reactions. Radicals are now valued synthetic intermediates because they can be used for transformations that are often difficult to accomplish by other methods. The kinds of protection schemes that are often essential for synthetic sequences of ionic reactions are rarely required for radical reactions.

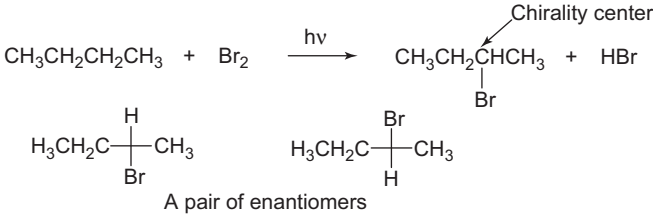
An important problem that needs to be faced when using radical reactions to stereoselectively form asymmetric centers is that most carbon-centered radicals are planar or nearly so. Once a carbon radical has been created it usually adopts a trigonal planar shape, or nearly so, and both faces of the radical are identical. For example, following abstraction of a halogen atom (by the $Bu_3Sn^{\bullet}$ radical) from the

organohalide enantiomer **20**, the planar carbon-centered radical **21** is formed. This can equally well abstract a hydrogen atom from the top or bottom face to give a racemic (1 : 1) mixture of alkanes **22** and **23** (Scheme 4.49). If a radical substitution reaction creates a chirality center in the product, both the (*R*)- and (*S*)-enantiomers will be formed (Scheme 4.50). The carbon bearing the unpaired electron is sp^2 hybridized, that is, the three groups to which it is bonded lie in a plane. The incoming halogen has equal access to both sides of the plane. As a result, both the (*R*)- and (*S*)-enantiomers are formed in equal amounts.



20 **21** **22** **23**

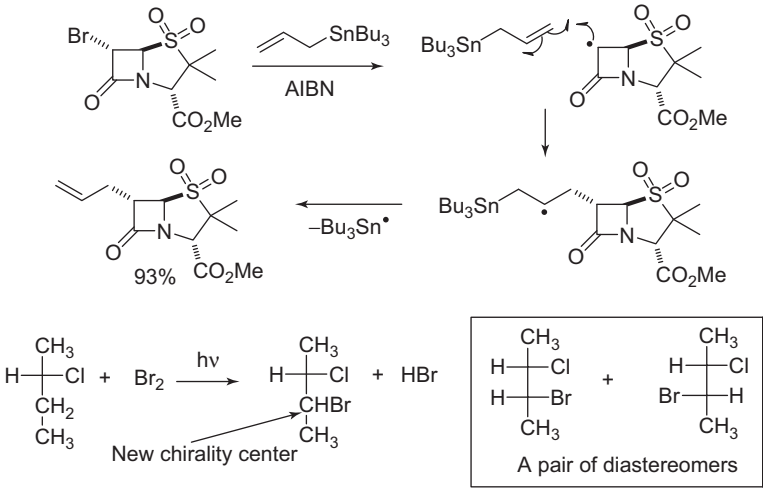
Scheme 4.49 Formation of racemic mixture.



Scheme 4.50 Formation of (*R*)- and (*S*)-enantiomers.

If the reactant already has a chirality center and the radical substitution reaction creates a second chirality center, in such a case a pair of diastereomers will be formed in unequal amounts. Diastereomers will be formed because the new chirality center created in the product can have either the (*R*)- or the (*S*)-configuration, but the configuration of the chirality center in the reactant will be unchanged in the product because none of the bonds to that chirality center is broken during the course of the reaction (Scheme 4.51). An adjacent chiral center can influence the radical reaction, leading to the predominant formation of one diastereoisomer (in a 1,2-asymmetric induction). For example, during the allylation of β-lactam using allyltributylstannane, allylation takes place selectively from the bottom face of a cyclic radical so as to avoid steric interactions with the sulfone group. This results in the diastereoselective formation of one diastereoisomer in 93% yield and, as the shape of the precursor molecule influences the approach of the incoming reagent, this is known as a *substrate-controlled reaction* (Scheme 4.51).

One of the diastereomer formed will be in greater amount than the other because the incoming Br_2 will have greater access to one side of the radical intermediate than to the other due to the presence of the original chirality center (Figure 4.16).



Scheme 4.51 Formation of diastereomers.

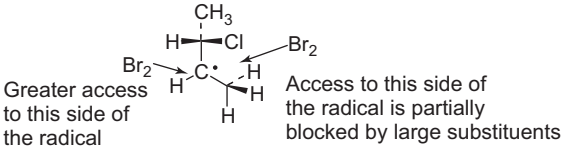
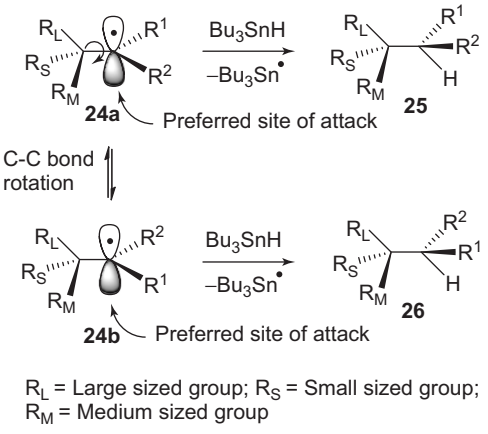


Figure 4.16 Selective formation of diastereomers.

The stereoselective reaction of an acyclic radical is usually more difficult than for cyclic radicals, as rotation about the carbon–carbon bond can lead to a mixture of diastereomers. For example, reaction of acyclic radical **24a** with Bu_3SnH is expected to selectively form **25**, as the Bu_3SnH would prefer to attack from the bottom face (to avoid the largest alkyl group, R_L, on the adjacent carbon atom – this is known as *anti attack*). However, following rotation of the central carbon–carbon bond of **24a** the alternative conformer **24b** can be formed and this would be expected to react with Bu_3SnH to predominantly form **26**. Therefore, if there is free rotation about the carbon–carbon bond in **24a/24b** a 1 : 1 mixture of the diastereoisomers **25** and **26** can be formed in a non-stereoselective reaction. It is important to note that the selective formation of **25** or **26** should strictly be discussed in terms of the relative stabilities of the transition states that lead to **25** and **26** and not the population ratio of conformers **24a** and **24b** (the Curtin–Hammett principle) (Scheme 4.52). However, as the activation energies for radical addition and abstraction reactions are usually low, and their transition states are early (or reactant-like), reactions of preferred (ground state) radical conformers are generally assumed to lead to the major products. Low-energy conformers can therefore make a good model for a reactant-like transition state. For stereoselective radical reactions, this means that

rotation around the carbon–carbon bond must be slowed down or prevented so that one particular conformation of the carbon-centered radical is favored.



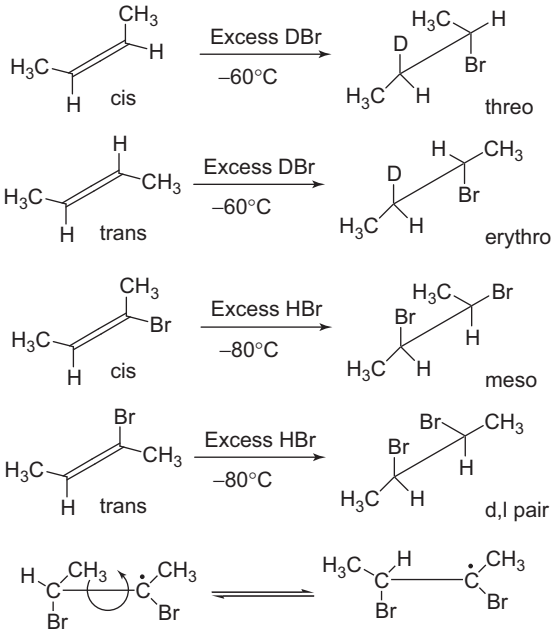
Scheme 4.52 Stereoselective reaction of an acyclic radical.

The addition of deuterium bromide to both *cis*- and *trans*-2-butene proceeds in a stereospecific *trans* manner at low temperature. The *cis*-olefin yields *threo* while the *trans* gives the *erythro* bromide. Similarly, the addition of HBr to isomeric 2-bromo-2-butenes is stereospecific at low temperature and in excess of HBr. The stereospecificity decreases as the temperature of the reaction is increased. At room temperature, both olefins yield the same mixture of products. Goering and Larsen first suggested that two different conformations are involved as intermediates from *cis*- and *trans*-olefins. The lifetime of these two conformations is so short that they cannot interconvert prior to the chain transfer step, which takes place from the less hindered side. At room temperature, however, these can obtain equilibrium rapidly because of easy C–C bond rotation, which results in the same mixture of *meso*- and *d,l*-2,3-dibromobutanes. Another reason may be that the addition of bromine radical ($Br^{\bullet}$) to noncyclic olefins is often reversible and may lead to non-stereospecific products. The second mechanism assumes a π-complex formation between olefin and HBr. A bromine atom then collides with the complex leading to its attachment and simultaneous breaking of the HBr bond, which explains the decrease in stereospecificity with rising temperature (Scheme 4.53).

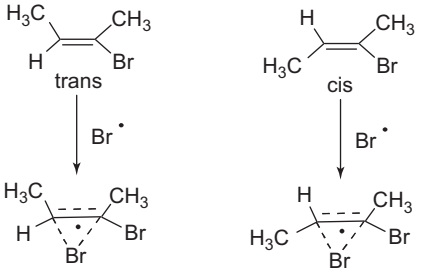
The third mechanism explains the formation of a *bridged* radical analogous to the bromonium ion. The HBr then attacks these radicals opposite the bridge to yield stereospecific products (Scheme 4.54).

A given molecular transformation is said to be *regioselective* when it takes place preferentially or exclusively at one place of a substrate (Scheme 4.55).

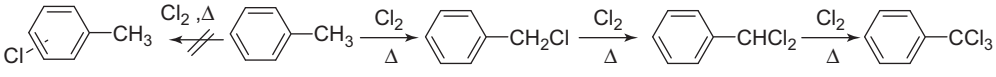
Reactions in which the reagent effects preferentially or exclusively one out of several types of possible transformations are said to be *chemoselective* (Scheme 4.56).



Scheme 4.53 Stereospecific addition reactions.

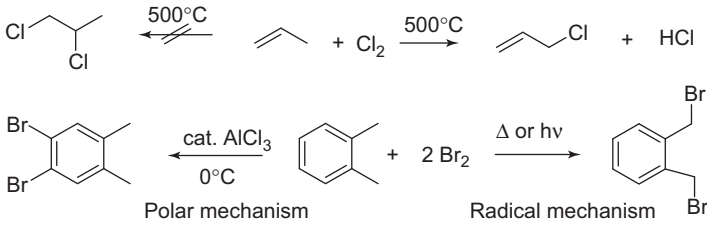


Scheme 4.54 Mechanism of stereospecific addition reaction.



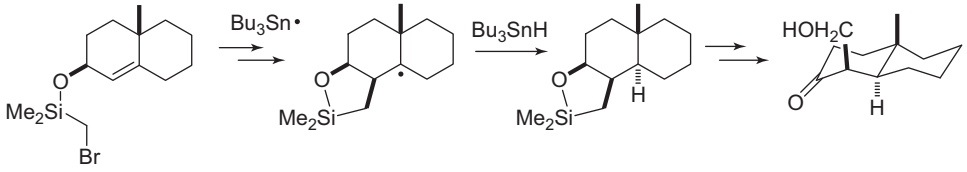
Scheme 4.55 Regioselective substitution of chlorine.

At higher temperature and lower HBr concentrations these two radicals may interconvert to give non-stereospecific products. Cyclopropyl, α-oxy radicals, and vinyl radicals tend to retain configuration and this leads to stereospecificity or stereoselectivity in many of their reactions at sufficiently low temperatures. Reactions of radicals can be very stereoselective when an additional fused ring is formed or when there is strong steric hindrance to one face of a planar radical center. In



Scheme 4.56 Chemoselective reaction.

Scheme 4.57 the radical cyclization gives a *cis* ring junction because it is difficult for the radical to reach round to the other side of the C=C. The formation of a five- rather than a six-membered ring is usually preferred kinetically for such cyclizations. The bridgehead methyl and the new ring greatly hinder the top face of radical and H is therefore added from Bu_3SnH to the other side to give the *trans*-decalin.



Scheme 4.57 Stereoselective addition of hydrogen.

4.7.1
Cyclization by Intramolecular Addition Reactions

Intramolecular radical (cyclization) reactions to form five- and six-membered rings in particular have found various synthetic applications. This flexible synthetic method can be used to prepare both carbocycles and heterocycles, and the selective formation of mono- and polycyclic products can generally be achieved in good yields. Many diastereoselective radical cyclizations have been reported over the years and the chair-like (Beckwith–Houk) transition-state model **27** (Figure 4.17) can be used to explain the stereoselectivity of most 5-*exo* radical cyclization reactions. Stereoelectronic effects have been used to explain the preference for the chair-like conformation – this allows an efficient overlap of the SOMO orbital of the radical and the HOMO of the alkene. In this conformation, the angle of attack of the radical on the alkene (106°) is close to the angle of attack of a carbon-centered radical on an alkene in an unstrained intermolecular reaction (109°). Substituents at C1 to C4 generally prefer to adopt pseudo-equatorial positions in the transition state to avoid 1,3-diaxial interactions and this governs the relative positions of the substituents observed in the cyclic products.

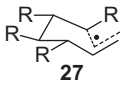


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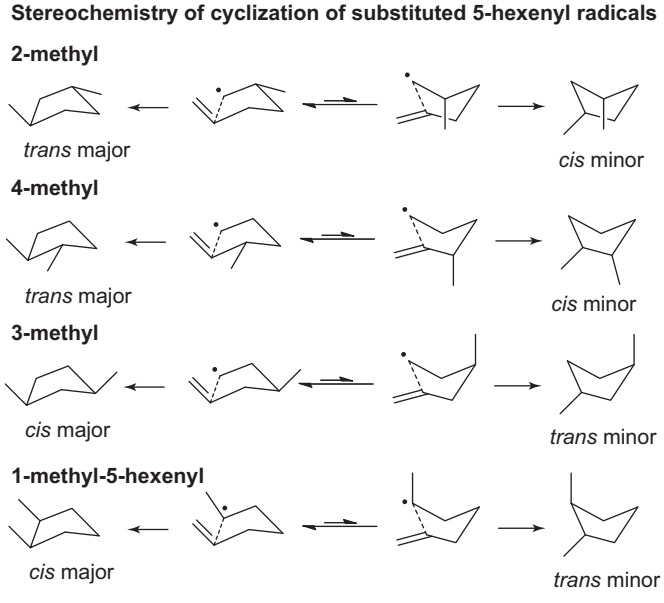
Figure 4.17 Chair-like (Beckwith–Houk) transition-state model.

The most important process (which accounts for most of the uses of radical cyclizations in synthesis) is the selective 5-exo-*cyclization of the 5-hexenyl radical* to give the cyclopentyl methyl radical. This occurs even though the alternative – a 6-endo *cyclization* to give a more stable, cyclohexyl radical – is thermodynamically more favorable. Thus, the 5-*exo*-cyclization proceeds under kinetic control. The preference for 5-*exo*-cyclization is explained by an early transition state with little product character. The transition state is a strain-free chair-like arrangement, which nicely accommodates the stereoelectronically required attack angle on the alkene. This model also nicely explains the stereochemical outcome of the cyclization reaction. Assuming that substituents prefer to adopt pseudo-equatorial positions in the chair-like transition state, we see why:

- The 2-methyl-5-hexenyl radical (and the 4-methyl-5-hexenyl radical) cyclizes to give predominantly the *trans*-dimethyl product.
- The 3-methyl-5-hexenyl radical cyclizes to give mostly the *cis*-dimethyl product.

The 1-methyl-5-hexenyl radical also gives predominantly the *cis*-product, due to a combination of steric and stereoelectronic factors. 5-*exo*-Cyclization proceeds with

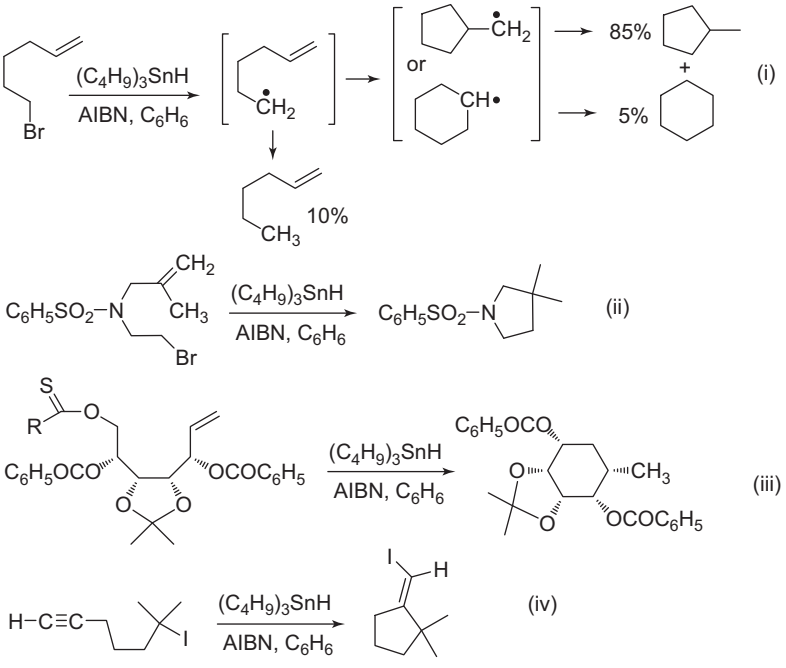


Scheme 4.58 Stereochemistry of cyclization of substituted 5-hexenyl radicals.

various substituents on the chain. However, substituents in the 5-position can retard the 5-*exo* reaction so that 6-*endo* predominates (Scheme 4.58):

1) When the alkene has a substituent at the 5-position: 6-*endo* cyclization is then faster than 5-*exo*.
2) In the cyclization of vinyl radicals. Here, the 6-ring product is formed by rearrangement of the kinetic 5-ring, via a cyclopropyl methyl radical. The ratio of 5-*exo* to 6-*endo* products can be controlled to some extent by altering the concentration of Bu_3SnH.

If a radical is joined to a double bond by a chain of three or more carbons intramolecular addition generates a ring. The regioselectivity of such additions is governed more by stereoelectronic factors than by substituents on the double bond. In the first two examples shown in Scheme 4.59, double bond substitution would favor formation of a six-membered ring, but five-membered ring formation by way of a 1°-cyclized radical dominates the products. Likewise, in reaction (iii) a six-membered ring is formed preferentially over an alternative seven-membered ring. Note that these reactions tolerate a wide variety of functional groups.



Scheme 4.59 Intramolecular addition generating rings.

The stereoelectronic factor in this reaction is defined by the preferred mode of approach of a radical as it bonds to the π-electron system of an alkene function. As shown in the Figure 4.18, this is at an angle nearly 20° off the perpendicular to the plane of the double bond. Because of this requirement, many cyclizations to moderately sized rings proceed by radical attack at the nearest carbon of the double

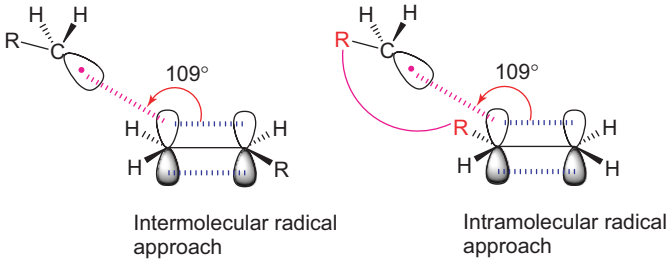


Figure 4.18 Mode of approach of a radical to the π-electron system.

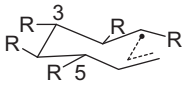


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Figure 4.19 Chair-like transition state for a six-membered ring.

bond, regardless of substitution. Bonding to the distal carbon is constrained by the structure of the connecting chain. Of course, if the carbon chain tethering the radical site to the double bond is long enough, bonding to either of the double bond carbons accommodates the stereoelectronic factor, and the product is again determined by substitution.

For the formation of six-membered rings, the chair-like transition state **28** (Figure 4.19) generally explains the stereoselectivity observed when hept-6-en-1-yl radicals undergo 6-*exo*-cyclization. Both the substituent(s) and alkene prefer to adopt pseudo-equatorial positions, therefore 1-, 3-, and 5-substituted heptenyl radicals give predominantly *trans*-disubstituted cyclohexyl products, while 2- and 4-substituted heptenyl radicals give predominantly *cis*-disubstituted cyclohexyl products.

Cyclization of the 6-hexenyl radical could conceivably be used to make cyclohexanes via 6-*exo* ring closure. However, this reaction is far less widely used in synthesis than the 5-hexenyl radical cyclization since:

1) it is about 40 times slower – hence reduction of the noncyclized radical with Bu_3SnH can compete with cyclization, leading to formation of the reduced starting material as a by-product;
2) k_{exo}/k_{endo} is only about 7 at 25 °C, so *endo*-ring closure competes to a greater extent;
3) 1,5-H abstraction is a competing process; this leads to formation of a resonance-stabilized, allylic radical.

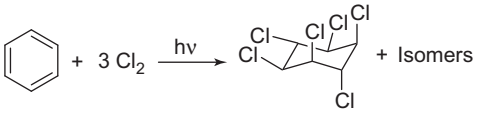
However, this 1,5-H abstraction process can be useful – it has been incorporated into some ingenious reaction sequences, for example, the ''tandem'' 1,5-H abstraction – 5-*exo* process.

Formation of medium rings by radical reactions suffers from the same difficulties as with ionic chemistry (cyclizations are enthalpically and entropically disfavored).

However, as with ionic chemistry, useful syntheses of medium rings can be accomplished by ring expansion reactions. Macrocyclization (formation of large rings) can be achieved by *endo*-cyclization of radicals onto terminal alkenes. Much current research is focused on tandem radical processes where a sequence of two or more successive radical reactions can provide extremely rapid routes to highly complex ring systems. Impressive examples include Curran's synthesis of hirsutene, and Pattenden's recent work on the formation of steroid-like systems. Many of the reactions we have seen in this book involve the use of Bu_3SnH. While this reagent participates in some extremely efficient radical chain processes, there is a major problem in that Sn reagents are highly toxic and, for example, for the synthesis of pharmaceuticals, the presence of even tiny amounts of Sn residues is unacceptable. Therefore, another major area of research is the development of alternatives to the use of Sn, or systems that use Sn in catalytic amounts. For example:

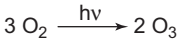
1) Atom transfer: we met the idea of halogen atom transfer earlier. This concept can also apply to Sn chemistry. An advantage over Bu_3SnH chemistry is that the product contains a potentially useful vinyl iodide unit.
2) It is possible in some cases to use catalytic Bu_3SnCl + stoichiometric $NaBH_3CN$ to prepare Bu_3SnH *in situ*.
3) $(Me_3Si)_3SiH$ has similar properties to Bu_3SnH (and can be used in catalytic amounts with stoichiometric $NaBH_4$).

Benzenoid compounds can also react by addition with chlorine atoms, for example, the irradiation of benzene and chlorine gives a mixture of stereoisomeric hexachlorocyclohexanes (Scheme 4.60).



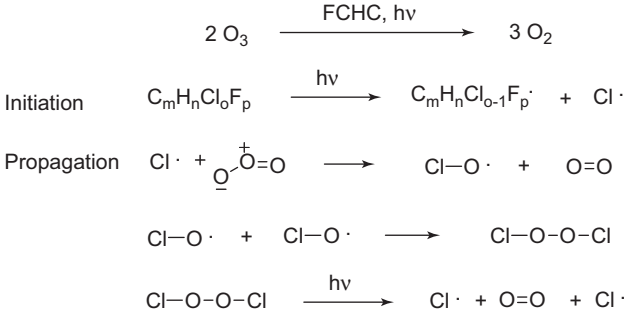
Scheme 4.60 Chlorination of benzene.

A layer of ozone surrounding the earth shields it from solar radiation that is harmful to life. The greater concentration of ozone occurs between 12 and 15 miles above earth's surface in a part of the atmosphere called the *stratosphere*. Ozone is formed in the atmosphere by the reaction of short-wavelength ultraviolet light with molecular oxygen (Scheme 4.61). This stratospheric ozone layer acts as a filter for biologically harmful ultraviolet radiation. UV light can damage DNA in skin cells, causing mutations that trigger skin cancer. Since about 1985, scientists have noted a sharp drop in stratospheric ozone over Antarctica. This area of ozone depletion is known as the "*ozone hole*."



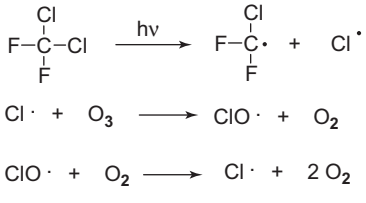
Scheme 4.61 Formation of ozone.

Strong circumstantial evidence implicates synthetic chlorofluorocarbons (CFCs) as a major cause for ozone depletion. These gases, known commercially as *Freons*, have been extensively used as cooling fluids in refrigerators and in home and automobile air conditioners, in industrial cleaning solvents, and in the manufacture of some plastic foams. They were once widely used as propellants in aerosol spray cans because of their odorless, nontoxic, and nonflammable properties and because they are chemically inert (Scheme 4.62).



Scheme 4.62 FCHC-initiated decomposition of stratospheric ozone.

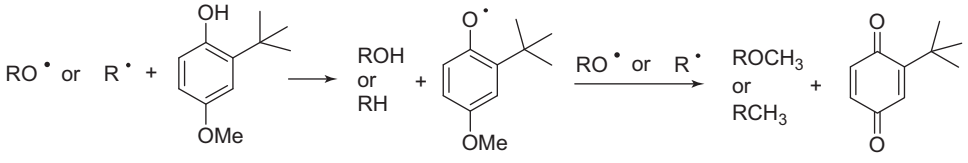
CFCs remain very stable in the atmosphere until they reach the stratosphere. There, they react with UV light, which causes their homolytic cleavage to generate chlorine radicals and, thereby, they play a major role in the destruction of the ozone layer. The chlorine radicals are the ozone-removing agents. They react with ozone to form chlorine monoxide free radical and molecular oxygen. The chlorine monoxide radicals react with ozone to regenerate chlorine radicals. These two propagating steps are repeated over and over, destroying a molecule of ozone in each step. It has been calculated that each chlorine atom destroys 100 000 ozone molecules. Because of their remarkable chemical stability, CFCs have half-lives of 70–120 years (Scheme 4.63). Although CFCs are to be phased out by international agreement, their concentration in the atmosphere continues to rise, and the concentration of ozone continues to drop. The hole in the ozone shield over the Antarctic continues to grow, and there have been indications that severe depletion is occurring over the Arctic as well.



Scheme 4.63 Decomposition of ozone by CFCs.

Chemists are creating substitutes for them that will retain their desirable properties, but will break down in the lower atmosphere so that they will not survive to reach the ozone layer. Most of the replacement compounds are being designed to contain C–H bonds, which increase the reactivity of the compounds and decrease their lifetime in the atmosphere. One solution to the problem is to replace CFCs with related compounds that contain no chlorine. Indeed, one of the most common replacements for CFCs is the family of hydrofluorocarbons (HFCs) such as 1,1,1,2,2-pentafluroethane (CF_3CHF_2). This class of compounds is less harmful to the ozone layer.

Oxygen in the air oxidizes and spoils foods, solvents, and other compounds by free-radical chain reactions. Chemical intermediates may decompose or polymerize by free-radical chain reactions. Even the cells in living systems are damaged by radical reactions, which can lead to aging, cancerous mutations, or cell-death. We often want to prevent or retard free-radical reactions. Radical inhibitors are often added to food and chemicals to retard spoilage by radical chain reactions. Butylated hydroxyanisole (BHA) is often added to food as an antioxidant. It stops oxidation by reacting with radical intermediates to form a relatively stable free radical intermediate (BHA radical). The BHA radical can react with a second free radical to form an even more stable quinone with all its electrons paired (Scheme 4.64).



Scheme 4.64 Butylated hydroxyanisole (BHA) as radical inhibitor.

4.8 Biradicals

Up to this point, we have discussed the chemistry of species with a single unpaired electron. A biradical is an even-electron chemical compound with two free radical centers that act independently (Figure 4.20). Biradicals are species with two radical centers in the same molecule containing two degenerate orbitals singly occupied. An oxygen molecule (O_2) has two unpaired electrons occupying two degenerate molecular orbitals and is thus a biradical triplet in its ground state. The lowest-energy triplet state of a biradical lies below or at most only a little above its lowest singlet state. The states of those biradicals whose radical centers interact particularly weakly are most easily understood in terms of a pair of local doublets. They are known by their higher reactivities and shorter lifetimes.

If the radical centers are close enough to each other for significant interaction (usually in the case of small molecules) there will be a splitting into singlet and triplet states, just as in the case of carbenes. The two p orbitals of the radical centers

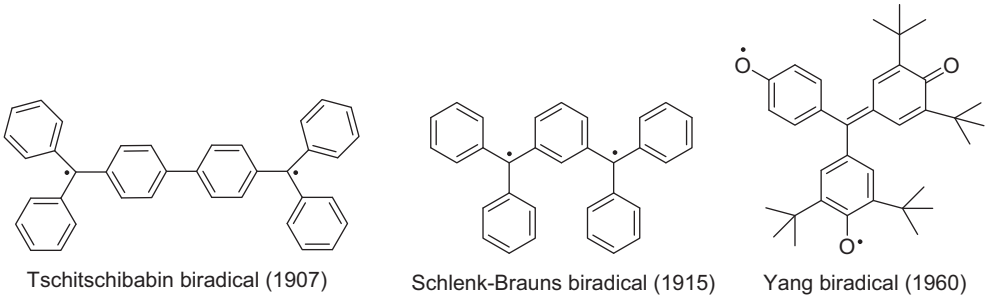


Figure 4.20 Biradicals.

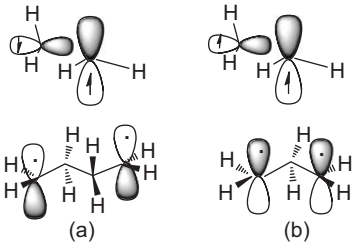
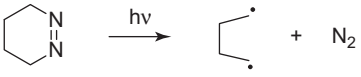


Figure 4.21 Singlet (a) and triplet (b) structures of a biradical.

will interact to give two new linear combination orbitals, one lower and one higher in energy. If the energy difference is large enough to overcome the cost of putting two electrons in the same orbital, the ground state will be singlet (Figure 4.21a); otherwise it will be triplet (Figure 4.21b). When an atom or molecule with an even number of electrons has two of them with parallel spins, it is in a **triplet state**. A molecule with all of its electrons spin-paired, irrespective of orbital occupancy, is in a **singlet state**.

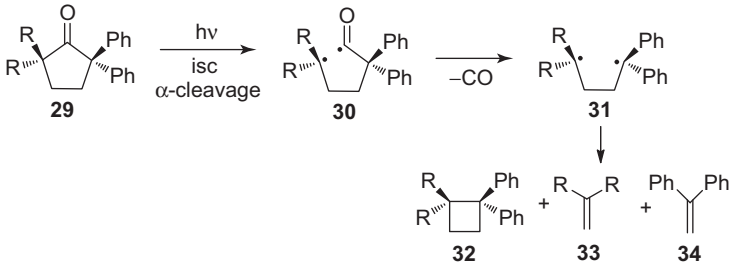
Biradicals have been proposed as intermediates mainly in pericyclic reactions. Generally, they have been obtained by the cleavage of cyclic azo compounds. The biradicals will be formed in a singlet or triplet state depending on whether the decomposition took place from the singlet or triplet state of the azo compound (Scheme 4.65).



Scheme 4.65 Cleavage of cyclic azo compound to produce a biradical.

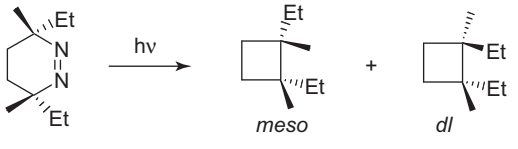
The photochemistry of cyclopentanone (**29**) is characterized in terms of disproportionation versus decarbonylation and/or cyclization versus cleavage reactions. The proposed mechanism involves electronic excitation of the ketone **29** followed by intersystem crossing (ISC) and an α-cleavage reaction in the triplet state

(Scheme 4.66). It is expected that triplet acyl-alkyl biradicals **30** formed in this manner may live long enough to undergo a spin-conserving decarbonylation (–CO) to yield triplet 1,4-biradical **31**, which may undergo coupling or disproportionation to give compounds **32**, **33** and **34**. The role of the α-substituents is to facilitate α-cleavage and decarbonylation, which must compete with excited-state deactivation and ISC, respectively.



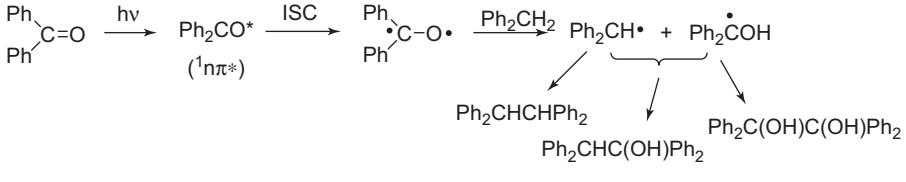
Scheme 4.66 Photochemistry of cyclopentanone.

Thermal decomposition or direct irradiation yields the singlet biradicals whereas use of sensitizer normally produces a triplet biradical. Triplet biradicals have a longer lifetime, and therefore more chance of bond rotation and loss of stereochemistry, because they must undergo spin inversion before the ring can close (Scheme 4.67).



Scheme 4.67 Non-stereospecific reaction.

Benzophenone is an excellent triplet sensitizer because its excited triplet is easily generated and is almost as energetic as the excited singlet. Therefore, irradiation of benzophenone in the presence of diphenylmethane gives three radical coupling products (Scheme 4.68).



Scheme 4.68 Irradiation of benzophenone in the presence of diphenylmethane.

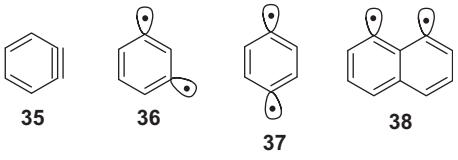
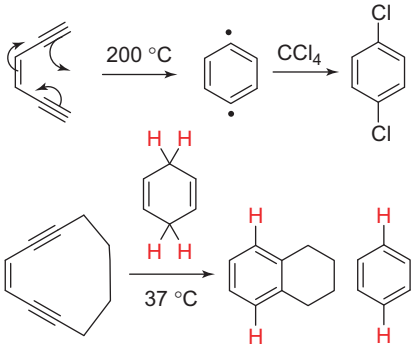


Figure 4.22 Some aromatic diyls.

Finally, we take a brief look at some aromatic diyls. 1,2-Dehydrobenzene, more easily recognized as benzyne (**35**), behaves rather as a highly strained acetylene, reacting as a powerful dienophile, and undergoing ionic addition reactions. Less familiar systems that have received attention include *meta*- (**36**) and *para*-benzyne (**37**) and 1,8-dehydronaphthalene (**38**). Of these, by far the most important is *para*-benzyne (or 1,4-dehydrobenzene). This is not because of any structural features – it acts like a bis-phenyl radical, with both radical centers being very reactive, and behaving independently. Its importance derives from the discovery in nature of a series of ''enediynes,'' powerful cytotoxic agents whose biological action depends on their ability to transform under physiological conditions into analogs of *para*-benzyne (Figure 4.22).

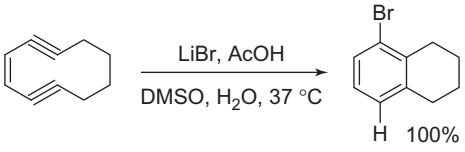
The **Bergman cyclization** (also known as the *Bergman reaction* or *Bergman cycloaromatization*, named after the American chemist Robert George Bergman, b. 1942) is an organic reaction and more specifically a rearrangement taking place when an enediyne is heated in the presence of a suitable hydrogen donor. The reaction product is a derivative of benzene. The Bergman cyclization involves the production of 1,4-dichlorobenzene when the pyrolysis of *cis*-hex-3-en-1,5-diyne is carried out at 200 °C in the presence of CCl_4 (Scheme 4.69).



Scheme 4.69 Bergman cyclization.

A biradical mechanism is also proposed for the formation of certain biomolecules found in marine *sporolides* that have a chlorobenzene unit as part of their structure. In this mechanism a halide salt provides the halogen. A model reaction with the

enediyne *cyclodeca-1,5-diyn-3-ene*, lithium bromide as halogen source, and acetic acid as hydrogen source in DMSO (dimethyl sulfoxide) at 37 °C supports the theory (Scheme 4.70).



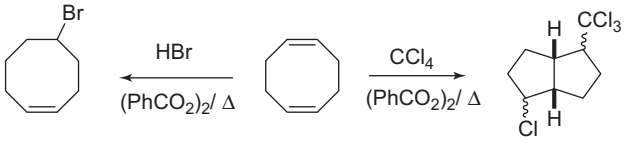
Scheme 4.70 Bergman cyclization.

4.9 Summary

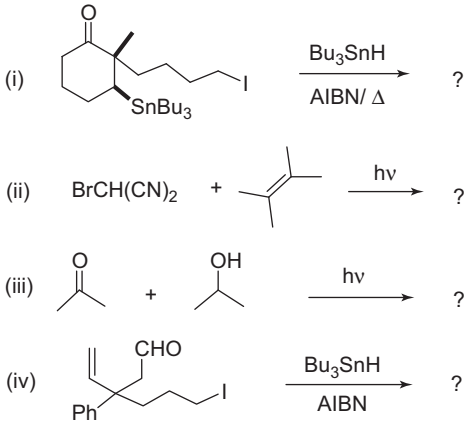
- Radicals (often referred to as *free radicals*) are atoms, molecules, or ions with unpaired electrons or an open shell.
- The frontier orbital of a free radical is called the *singly occupied molecular orbital*.
- Anything that would stabilize an anion or a cation will stabilize a radical. Radicals are also stabilized by resonance and by interaction with either filled or empty orbitals.
- Radicals are formed by homolytic cleavage or by reaction of a radical initiator with a paired-electron molecule.
- Radical reactions follow different rules to those of ionic reactions.
- Efficient reactions of radicals are chain reactions involving initiation, propagation, and termination steps.
- There are electrophilic and nucleophilic radicals. Consideration of SOMOs can tell us much about the reactivity of radicals.
- Low-energy SOMOs are more willing to accept an electron than to give one up; radicals adjacent to electron-withdrawing groups are therefore electrophilic.
- High-energy SOMOs are more willing to give up an electron than to accept an electron; radicals adjacent to electron-donating groups are therefore nucleophilic.
- More reactive radicals tend to be less selective in their reactions.
- Radicals favor conjugate addition and cyclization.
- A very important point affecting selectivity is the strength of the bonds being formed and broken.
- Radical reactions can be slowed by radical inhibitors.
- Intramolecular radical reactions are more efficient than intermolecular ones.
- Diradicals are molecules containing two radical centers. Multiple radical centers can exist in a molecule. Atmospheric oxygen naturally exists as a diradical in its ground state as triplet oxygen. The low reactivity of atmospheric oxygen is due to its diradical state.

Problems

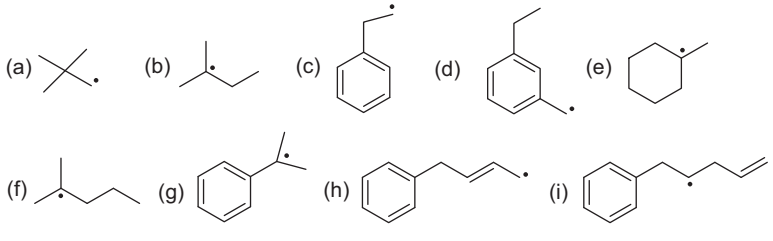
1. Rationalize the differing behavior of cycloocta-1,5-diene in the following radical addition reactions.



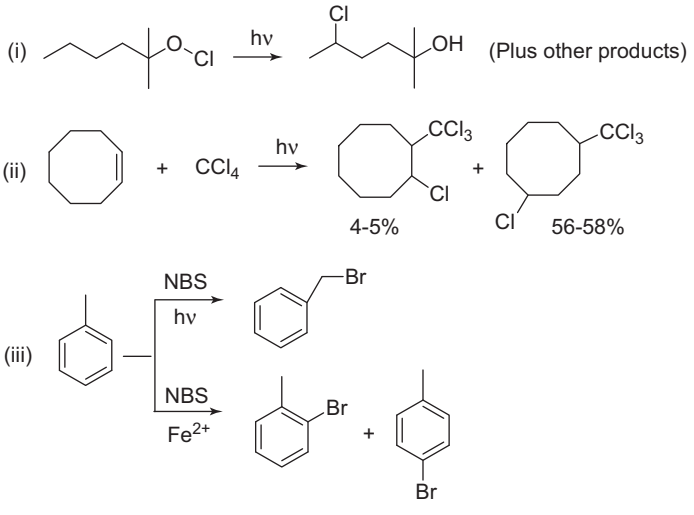
2. Propose a pathway to account for the formation of epoxides in the autoxidation of alkenes.
3. Bromination of cyclohexene with NBS (*N*-bromosuccinimide) in the presence of benzoyl peroxide gives a monobrominated product. Write down the product, along with a suitable mechanism.
4. Give the products and a suitable mechanism for each of the following reactions.



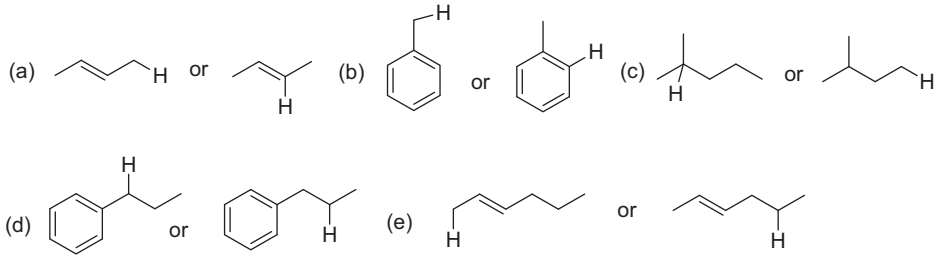
5. Classify the following radicals as primary, secondary, tertiary, benzylic, or allylic.



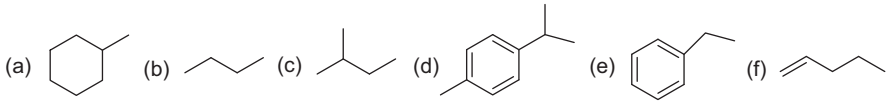
6. Explain the following observations.



7. Predict which of the two indicated C–H bonds in each of the following compounds would yield a more stable radical upon homolytic cleavage.

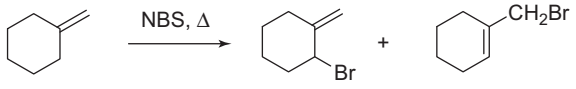


8. Predict which hydrogen will be preferentially substituted in the free radical bromination of each of the following compounds by drawing the expected product.

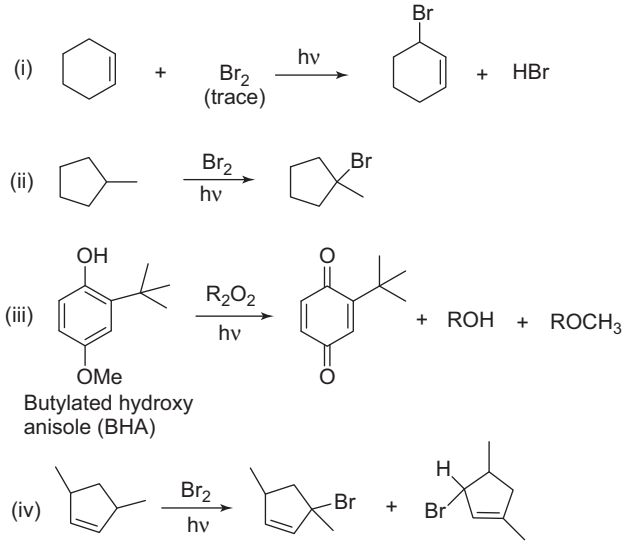


9. If cyclopentane reacts with excess Cl_2 at high temperature, how many dichlorocyclopentanes would you expect as products?

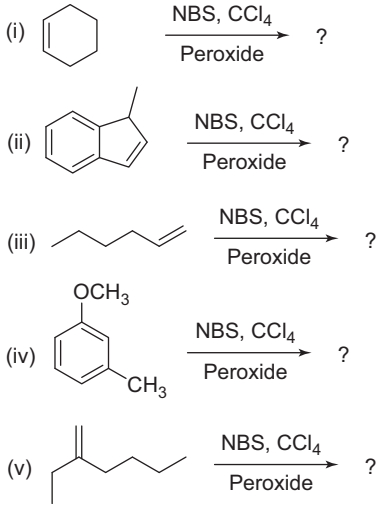
10. Rationalize the formation of the following products.



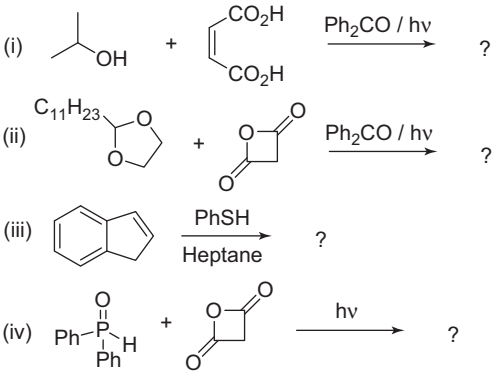
11. Rationalize the following reactions with suitable mechanisms.



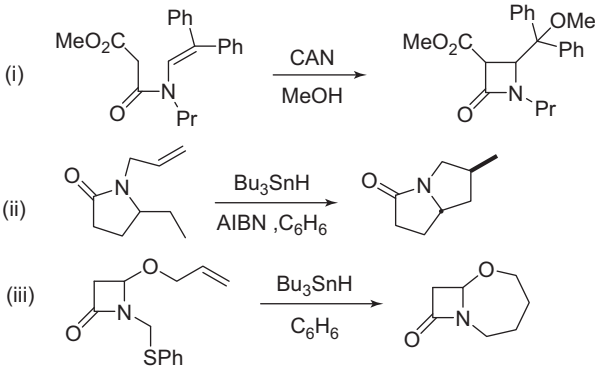
12. Write all possible products along with a suitable mechanism for the following reactions.



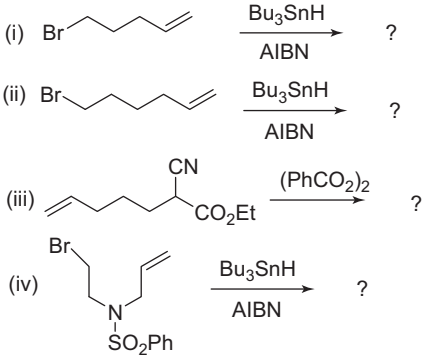
13. Complete the following reactions with suitable mechanism.



14. Discuss the mechanisms of the following reactions.



15. Write all possible products, along with a suitable mechanism, for the following reactions.



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5
Carbenes

5.1
Structure and Geometry of Carbenes

Carbene chemistry has experienced tremendous growth and broad interest in the past few decades. The investigation of divalent carbon intermediates proved to be rewarding from a theoretical as well as an experimental point of view. The long-lasting fascination of the carbene concept for organic chemists appears to have emotional rather than empirical grounds. Because they do not respect the ''octet rule,'' carbenes have long been considered as fleeting intermediates in molecular chemistry. These fascinating species are involved in many reactions of high synthetic interest. Table 5.1 presents the formal relationship of carbene to other simple carbon intermediates. With most of the intermediates mentioned in Table 5.1, the existence of moderately stable species (e.g., triarylmethyl derivatives) has provided a basis for the investigation of transient analogs.

The search for carbene began more than 150 years ago, at a time when the tetravalency of carbon was not an established fact. The French chemist Jean Baptiste André Dumas attempted to prepare methylene (CH_2) by treatment of methanol with water-abstracting reagents such as P_2O_5 or concentrated H_2SO_4, assuming that CH_3OH is a 1 : 1 adduct of CH_2 and H_2O. Carbenes were first been postulated by Eduard Buchner in 1903 in cyclopropanation studies of ethyl diazoacetate with toluene. In 1912, Hermann Staudinger (awarded the Nobel Prize in Chemistry, 1953) also converted alkenes into cyclopropanes with diazomethane and $:CH_2$ as an intermediate. The simplest chemical example of carbene is methylene ($:CH_2$), identified by Herzberg in 1959. The name carbene, apparently conceived by Woodward, Doering, and Winstein was first introduced at a meeting of the American Chemical Society in 1951. The term ''*carbene*'' refers to the specific compound $H_2C:$, the parent hydride from which all other carbene derivatives are formally derived.

Carbenes are highly reactive, neutral, divalent derivatives of carbon having only six valence electrons with a formal charge of zero. They have two covalent bonds (involving four electrons) and two nonbonding electrons localized on the carbon atom, and an empty orbital, which makes a carbene very reactive. One well-studied carbene is dichlorocarbene ($Cl_2C:$), which can be generated *in situ* from chloroform and a strong base. Doering, in 1954, demonstrated the synthetic utility

Reactive Intermediates in Organic Chemistry: Structure, Mechanism, and Reactions, First Edition.
Maya Shankar Singh.

Table 5.1 Simple intermediates of carbon compounds.

Intermediates		No of covalent bonds	No of valence electrons
Carbanions		3	8
Radicals		3	7
Carbemium ions		3	6
Carbenes		2	6

of dichlorocarbene. However, despite the explosive growth of knowledge about carbenes, attempts to isolate them before 1990 remained unsuccessful. Nowadays, the term is universally used for divalent carbon species, which are simply named as substituted derivatives of carbene. The exceptions to this are carbenes in which the divalent carbon is part of a ring or is doubly bonded. These are named using the -ylidene suffix (IUPAC system), for example, cyclohexylidene and vinylidene (Table 5.2).

Carbenes are classified as either singlets or triplets depending upon their electronic structure. The nature of the ground state depends on the relative energies of the two nonbonding orbitals. If the two orbitals are equivalent, according to Hund's rule the electron should be assigned to different orbitals with parallel spins. On the other hand, if the two available orbitals are not degenerate the two electrons would probably occupy the lower of the two orbitals with consequent spin pairing. Singlet carbenes have a pair of electrons in the highest occupied molecular orbital (HOMO) σ, the pπ orbital being vacant with a sp^2 hybrid structure.

Table 5.2 Nomenclature of carbenes.

Carbene		IUPAC
$:CH_2$	Carbene	Methylidene
$CH_3CH:$	Methylcarbene	Ethylidene
$H_2C{=}\underset{H}{C}{-}CH:$	Vinylcarbene	Propenylidene
$Ph_2C:$	Disphenylcarbene	—
$Cl_2C:$	Dischlorocarbene	—
	Cyclohexylidene	—
$H_2C{=}C:$	Vinylidene	—

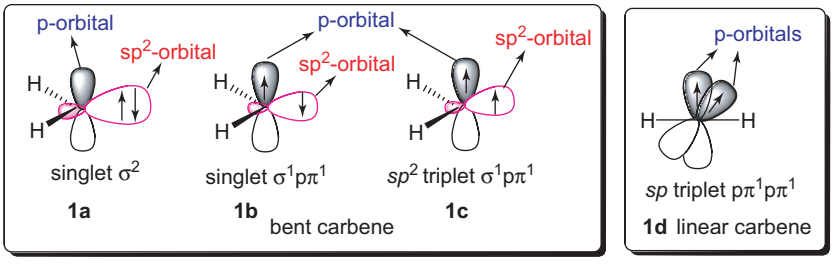


Figure 5.1 Electronic configurations of bent and linear carbenes.

As a result, singlet carbenes exhibit both nucleophilic and electrophilic character. Triplet carbenes have two unpaired electrons. They may be either sp^2 hybrid or linear sp hybrid. Most carbenes have a nonlinear triplet ground state, with the exception of carbenes with nitrogen, oxygen, sulfur atoms, and dihalocarbenes. Figure 5.1 shows some representations for different electronic states that could be proposed for methylene. Depending on whether the nonbonding electrons are of the same or opposite spin, they are triplet or singlet species. In **1a** the two nonbonding electrons are in the same orbital with opposite spin, which assumes sp^2 hybridization at carbon with two unshared electrons in a sp^2 orbital. The p orbital is unoccupied. In **1b** and **1c** they are in separate orbitals, so these two electrons may or may not have paired spins. Structures **1a** and **1b** are called *singlet states* (spin multiplicity = 1), since the nonbonded electrons have their spins paired. In **1c** one of the two unpaired electrons is in an sp^2 and the other in a p orbital, the spins of the nonbonded electrons are not paired, and so this is a triplet state (multiplicity = 3). Hence, triplet carbenes with their unpaired electrons exhibit properties of diradicals, and under suitable conditions can be detected by ESR (electron paramagnetic resonance) spectroscopy.

In linear carbenes, the carbene carbon is sp hybridized (**1d**). The bonds in the corresponding triplet carbene structure are formed from sp orbitals, with the unpaired electrons being in two orthogonal p orbitals (**1d**). Most carbenes are not linear, and the ground state multiplicity depends upon the relative energy of the triplet and singlet states. In theory all of the states in Figure 5.1 are possible, although they may have different energies, reactivities, and lifetimes under the reaction conditions, which can be analyzed in terms of steric and electronic effects. The linear geometry is an extreme case, most carbenes are bent and their frontier orbitals will be systematically called σ and $p\pi$. Regardless of the nature of the ground state, singlet carbenes are expected from most carbene precursors as a consequence of spin conservation. Intersystem crossing may or may not occur before the individual carbene reacts with a suitable acceptor.

Structure **1a** has two electrons in one orbital and no electrons in another orbital. We would expect it to be sp^2 hybridized with the nonbonded electrons in an sp^2 orbital (having $^1/_3$ s character) as the p orbital is empty. Structures **1b** and **1c** should have the same hybridization for the two singly occupied orbitals. If there were greater repulsion between pairs of electrons in the C–H bonds than there is

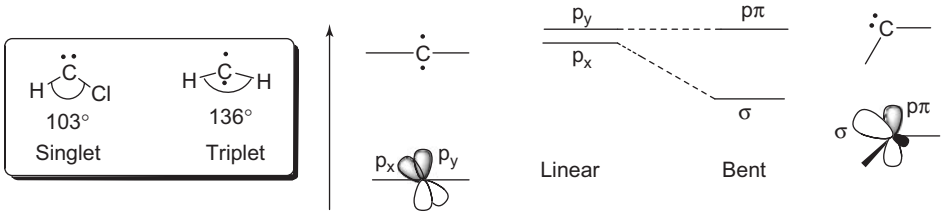


Figure 5.2 Relationship between carbene bond angle and the nature of the frontier orbitals.

between the single electrons on carbon, then VSEPR (valence shell electron pair repulsion) theory would suggest the H–C–H bond angle to be greater than 109.5°. The extreme angle of 180°, however, would be sp hybridization, and would require the two unpaired electrons be in pure p orbitals with no s character. Both theoretical and experimental determinations indicate that the lowest energy electronic state of methylene is the triplet **1c**, while the singlet **1a** is a higher energy excited state, and the singlet **1b** is an even higher energy state. However, the difference in energy between **1c** and **1a** was the subject of some debate. Most theoretical calculations indicated that the energy separation was about 10 kcal mol^{-1}, while the experimental value was reported to be about 20 kcal mol^{-1}. The issue was resolved when further experimental work gave a revised experimental value of 9 kcal mol^{-1}, which is very close to the calculated value. The unstable character of singlet carbenes by contrast has manifested itself in a lack of selectivity between reaction partners in direct reactions of these species.

The geometry of triplet methylene has been the subject of intensive theoretical and experimental work. Both theoretical calculations and experimental work (based on EPR (electron paramagnetic resonance) measurements) now suggest that triplet methylene is slightly bent, with an H–C–H bond angle between 130° and 150°, for example, $:CH_2$, :CHPh, :CHR, $:CPh_2$. Those that have bond angle of 100–110° and bond length of 1.12 Å, but cannot be observed by EPR, are called *singlet carbenes*, for example, $:CCl_2$, :CHCl, $:C(OMe)_2$ (Figure 5.2). Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media. Bulky substituents clearly kinetically stabilize all types of carbenes. Moreover, if electronic effects are negligible, the steric effects may also dictate the ground-state spin multiplicity.

At first sight, it appears that a singlet carbene has lower energy as the unshared electron pair is in a sp^2 hybrid orbital, but consideration of the electron repulsion energy that must be overcome to pair two electrons in a single orbital places it at a higher energy level than a triplet structure. The triplet is calculated to be about 8 kcal mol^{-1} (33 kJ mol^{-1}) lower in energy than the singlet. According to Hund's rule, the triplet state is a lower energy state and is more stable than the singlet, since it minimizes the electron–electron repulsions, and should be expected to be the ground state (Figure 5.3). Substituents that can donate electron pairs may stabilize the singlet state by delocalizing the pair into an empty p-orbital. If the

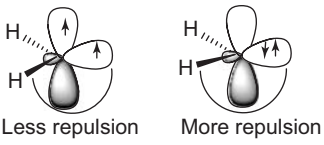


Figure 5.3 Repulsion between triplet and singlet states.

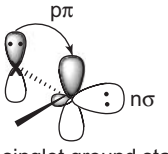
energy of the singlet state is sufficiently reduced it will actually become the ground state. No viable strategies exist for triplet stabilization.

The discussion to this point has concerned only the parent carbene and methylene. The same structural principles generally apply to other carbenes, but there are some additional considerations. For example, diphenylcarbene is more nearly linear due to the steric repulsion of the two phenyl groups. In a study of diphenylcarbene generated in diphenylethene crystals, the $C_{Ph}-C-C_{Ph}$ bond angle was found to be 148°, and the phenyl rings were twisted 36° out of the plane defined by the carbene carbon atom and two-ring carbon atoms bonded to it.

Generally, carbenes are expected to be in the singlet state from most precursors, although "intersystem crossing" to the triplet may or may not occur before the individual carbene reacts with a suitable precursor. Almost all carbenes have the potential to exist in either the singlet or the triplet state. Substituents perturb the relative energies of the singlet and triplet states. In general, alkyl groups resemble hydrogen as a substituent, and dialkylcarbenes have triplet ground states. Substituents that have electron-pair donors stabilize the singlet state more than the triplet state by delocalization of an electron pair into the empty p orbital – then the ground state changes from triplet to singlet. By appropriate choice of substituents, carbenic stability, reactivity, and philicity can be simultaneously varied, while the delicate interrelations of these properties can be understood in empirical, and, more precisely, in theoretical terms. It is now well established that s-electron-withdrawing substituents favor the singlet versus the triplet state. Indeed, σ-electron-withdrawing substituents inductively stabilize the σ-nonbonding orbital by increasing its s character and leave the pπ orbital unchanged. The s–pπ gap is thus increased and the singlet state is favored. In contrast, σ-electron-donating substituents induce a small σ–pπ gap, which favors the triplet state.

Singlet carbenes can be kinetically stabilized by introduction of bulky substituents in the α-position of the carbene center. Thermodynamic stabilization of the singlet state can be achieved, indeed, by interaction of the carbon orbitals, σ and pπ, with appropriate substituents. σ-Electron-withdrawing and π-electron-withdrawing substituents stabilize the σ orbital by inductive and mesomeric effects, respectively, while π-electron donating groups (X = OR, SR, NR_2, Br, etc.) raise the energy of the vacant pπ orbital (Figure 5.4). Combination of these effects leads to an increase in the σ–pπ gap, thus favoring a singlet ground state multiplicity.

The more electron-withdrawing a substituent is the more strongly electrophilic is the carbene. Thus, difluorocarbene is a more electrophilic intermediate than dichlorocarbene. However, if very strong electron-donor substituents such as amino groups, methoxy groups, and alkylsulfanyl groups are present then the carbene may



Stabilization of the singlet ground state by interaction of the pπ orbital with a π-electron donating X group

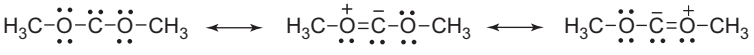
Figure 5.4 Stabilization of singlet carbene through π-electron donating group.

be nucleophilic in its reactions. Various singlet carbenes have been characterized as nucleophilic, ambiphilic (both electron-rich and electron-poor reagent), and electrophilic species (Scheme 5.1). None of these species, however, have been detected *in solution* by spectroscopic methods.

Nucleophilic	**Ambiphilic**	**Electrophilic**
$:C(OCH_3)_2$	$:C(OCH_3)Cl$	$:CCl_2$;
$:C(OCH_3)NMe_2$	$:C(OCH_3)F$	$:CCH_3Cl$
$:C(SR)_2$		:CPhCl
$:C(SPr\text{-}n)_2$		$:C(Br)CO_2Et$

Scheme 5.1 Nucleophilic, ambiphilic, and electrophilic carbenes.

For example, dimethoxycarbene is devoid of electrophilicity toward alkenes because of electron donation by the methoxy groups. A methoxy group also can be expected to stabilize a carbene, by interaction of the p orbital of the central carbon atom with a lone pair of electrons on the oxygen atom (Scheme 5.2).



Scheme 5.2 Stabilization of dimethoxycarbene.

Since triplet carbenes have unpaired electrons, they give an electron spin resonance signal. Comparatively stable carbenes in sufficient concentration have been generated by photolysis in the solid state. If the medium is a solid, rigid matrix, such as a frozen glassy hydrocarbon at 77 K, the carbenes are stable indefinitely. ESR spectroscopy has shown that the ground states for aryl carbenes are triplets. The initial photolysis of the precursor leads to the singlet carbenes, which upon spin inversion change to triplet carbenes.

Most carbenes are very short lived, although persistent carbenes are known. A **persistent carbene** (also known as a *stable carbene* or a *Arduengo carbene*) is a type of carbene demonstrating particular stability. The best-known examples are diaminocarbenes with the general formula $(R_2N)_2C$:, where the R represents various functional groups. The groups can be bridged so that the carbon with unfilled orbitals is part of a heterocycle, such as imidazole or triazole. Persistent

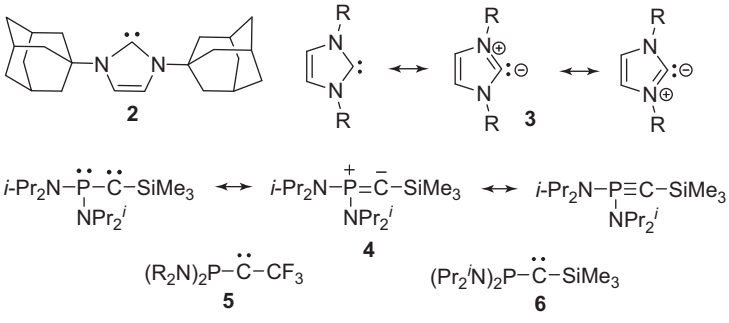


Figure 5.5 Persistent carbenes.

carbenes (Figure 5.5) are still fairly reactive substances, and many will undergo dimerization, sometimes reversibly. In the absence of oxygen and moisture 1,3-di-1-adamantylimidazol-2-ylidene (**2**) exists as stable colorless crystal with a melting point of 240–241 °C without decomposition; its structure was proved by X-ray crystallography. Cyclic diaminocarbene **3**, which could not be isolated, but has been trapped with oxygen and phenyl isothiocyanate, has a significant life time. λ^3-Phosphinocarbene or λ^5-phosphaacetylene **4**, which is in resonance with an ylide form and with a form containing phosphorus carbon triple bond, is a distillable red oil. Electronic and more importantly steric effects make these two compounds so stable. Carbene **4** adds to various electron-deficient olefins such as styrene and substituted styrenes. Bertrand *et al.* have made excellent use of the push-pull motif to produce the isolable carbenes **5** and **6**, which are stable at low temperature in solutions of electron-donor solvents (THF (tetrahydrofuran), diethyl ether, toluene) but dimerizes in pentane solution. Some persistent carbenes are used as *ancillary ligands* in organometallic chemistry and in catalysis, for example, the ruthenium-based Grubbs' catalyst and palladium-based catalysts for cross-coupling reactions.

In the last 10 years, our understanding of carbene chemistry has advanced dramatically with the preparation of persistent triplet diarylcarbenes and the isolation of heteroatom-substituted singlet carbenes. Undoubtedly, the best way to stabilize triplet carbenes kinetically consists of protecting the highly reactive carbene center by bulky substituents. Clearly, from the above discussion it is much easier to design a substitution pattern for stabilizing singlet rather than triplet carbenes. In fact, as early as 1960, Pauling realized that the *ideal* substituents to stabilize singlet carbenes should preserve the electroneutrality of the carbene center. This can be achieved in three different ways, each of which has been studied experimentally:

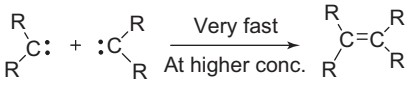
1) Two π-donor σ-attractor substituents, that is, a push, push mesomeric–pull, pull inductive substitution pattern. Good examples are diaminocarbenes in which the carbene electron deficiency is reduced by the donation of the two nitrogen lone pairs, while the carbene lone pair is stabilized by the inductive effect of two electronegative nitrogen atoms.

2) Two π-attractor σ-donor substituents, that is, a pull, pull mesomeric–push, push inductive substitution pattern; diborylcarbenes are good representatives.
3) A π-donor and a π-acceptor substituent, that is, a push, pull mesomeric substitution pattern; in this case, the inductive effects are not of primary importance. This category is illustrated by phosphino(silyl)- and phosphinophosphoniocarbenes.

5.2 Generation of Carbenes

Most commonly, photolytic, thermal, or transition metal catalyzed decomposition of diazoalkanes is used to create carbene molecules. A variation on catalyzed decomposition of diazoalkanes is the **Bamford–Stevens reaction**, which gives carbenes in aprotic solvents and carbenium ions in protic solvents. Another method is induced elimination of halogen from *gem*-dihalides or HX from a CHX_3 moiety, employing organolithium reagents (or another strong base). It is not certain that in these reactions actual free carbenes are formed. In some cases there is evidence that completely free carbene is never present; instead, it is likely that a metal–carbene complex forms. Nevertheless, these metallocarbenes (or carbenoids) give the expected products.

Carbenes are chiefly formed in two types of reactions: (i) decomposition of reactive molecules and (ii) α-elimination. Both methods provide the strong driving force necessary for the generation of molecules as reactive as carbenes. There are numerous ways of generating carbene intermediates, but all of them accomplish the elimination of two bonds from a tetravalent carbon atom. Carbenes are usually formed from precursors by the loss of small, stable molecules. Free carbenes are formed thermally or photochemically in the gas phase, and photochemically or by α-elimination under appropriate conditions in solution. The carbene intermediate is generated in the presence of its target compound, so that it can react immediately, maintaining always its concentration low. At higher concentration, the two carbenes collide and immediately dimerize to give an alkene (Scheme 5.3).

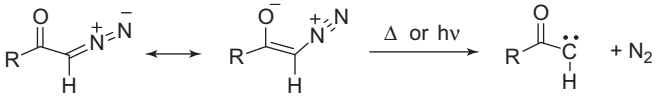


Scheme 5.3 Dimerization of a carbene.

5.2.1 Thermolysis or Photolysis of Diazo Compounds

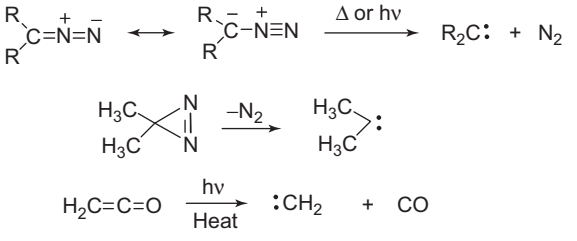
Diazo compounds constitute the most common class of carbene precursors. The stability of diazo compounds is very much influenced by the substituents present. Simple diazoalkanes such as diazomethane tend to be rather unstable and because

of their toxic and explosive nature must be handled with great care. Diazomethane is a toxic and highly explosive gas with a boiling point of −24 °C. It can detonate on contact with ground glass and its preparation requires the use of specialized glassware. It therefore has to be used in solution, usually in diethyl ether; the solution must be dilute, because concentrated solutions of diazomethane are also explosive. However, diazocarbonyl compounds are much more stable, because the electron-withdrawing carbonyl group stabilizes the diazo dipole (Scheme 5.4).



Scheme 5.4 Decomposition of diazocarbonyl compounds.

Thermal or photochemical decomposition of diazo compounds and diazirines gives carbenes. The formation of very stable gaseous nitrogen compensates for the formation of the unstable carbene. Photolysis or thermolysis of a ketene-like diazo compound eliminates a stable molecule carbon monoxide (CO) to yield a carbene. The reactions are not widely used since ketenes are not readily available precursors, and tend to polymerize under the reaction conditions (Scheme 5.5).



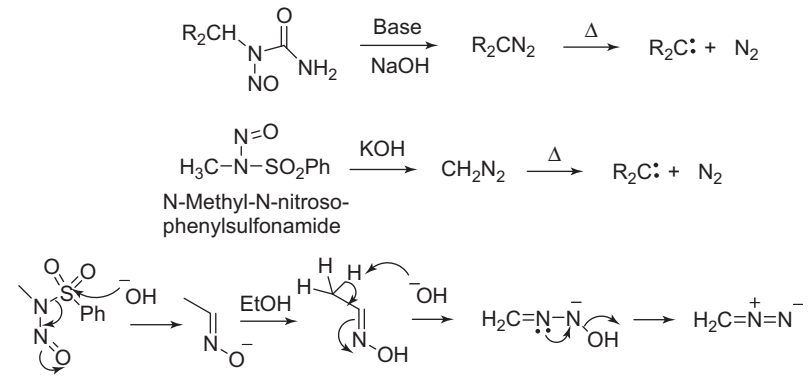
Scheme 5.5 Decomposition of diazo and ketene compounds to give a carbene.

In general, most carbenes are triplets (two electrons unpaired) in their ground states, but have excited singlet states only slightly higher in energy, and the chemical behavior of a carbene depends on which of these states it is in. If a diazo compound in an excited singlet state decomposes it will produce singlet N_2 and singlet carbene. The result will be the same for thermal decomposition. But if the azo compound is irradiated in the presence of a sensitizer, the decomposition will produce singlet N_2 and triplet carbene.

5.2.2
Reaction of N-Nitrosoureas with Base

The most general synthetic route involves base-catalyzed decomposition of N-nitroso derivatives of amides or sulfonamides. The reaction of N-nitrosoureas with base generates diazoalkanes, which can then eliminate nitrogen upon heating to

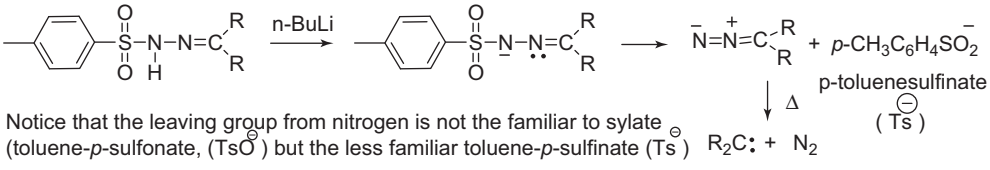
give carbene that is distilled out from the reaction mixture as an azeotrope with diethyl ether (Scheme 5.6).

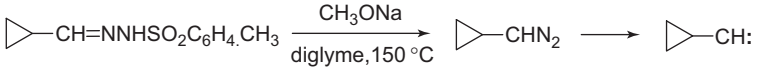


Scheme 5.6 Base-catalyzed decomposition of N-nitroso compounds.

5.2.3
Reaction of Tosylhydrazone with Base

Much more widely used carbene precursors are tosylhydrazones, which are readily prepared from aldehydes or ketones by reaction with 4-toluenesulfonyl hydrazide. Tosylhydrazones produce transient diazo compounds by base-catalyzed elimination of toluenesulfinate. The diazo compound is not normally isolated, and decomposes to the carbene on heating. The whole process is known as the *Bamford–Stevens reaction*. The leaving group is not the familiar tosylate (toluene-*p*-sulfonate, *p*.CH_3–$C_6H_4SO_3^-$, TsO^-), but the less familiar toluene-*p*-sulfinate (Ts^-, *p*.CH_3–$C_6H_4SO_2^-$) (Scheme 5.7).

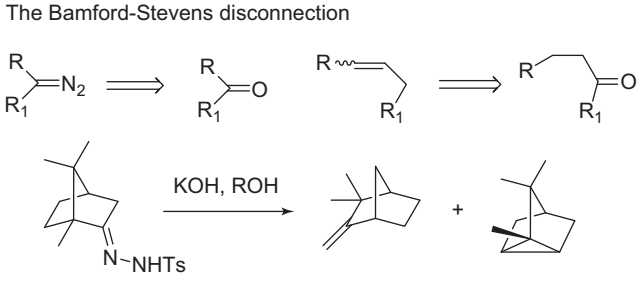




Scheme 5.7 Bamford–Stevens reaction.

The carbene nature of this intermediate was detected by examination of camphor tosylhydrazone, which on heating with hydroxide gives a mixture of camphene and tricyclene. When the reaction was performed in acidic alcohols, such as ethylene

glycol, camphene was the main product (via rearrangement). In aprotic solvents, the carbene insertion product was observed. The formation of alkenes from tosyl hydrazones under basic conditions is called the Bamford–Stevens reaction. Although it is not a carbene mechanism, but involves extrusion of nitrogen via a carbanion, it is included here for comparison with the reactions just cited. When an organolithium is used as the base, the alkene-forming reaction is sometimes called the *Shapiro reaction*, in which 2 equiv. of organolithium are required, and the reaction generates the *less substituted* alkene. The Bamford–Stevens reaction generates the *more substituted* alkenes (Scheme 5.8).



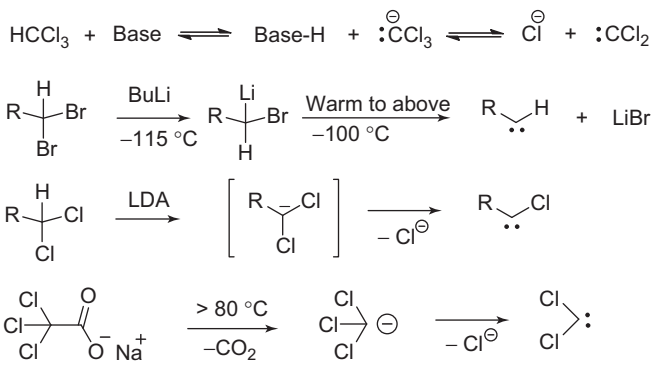
Scheme 5.8 A further Bamford–Stevens reaction.

5.2.4
Carbene Formation by α-Elimination

Historically this is one of the most important routes to carbenes. In an α-elimination reaction both the proton and the leaving group are located on the same carbon atom. The ease of elimination depends on the halide leaving group and follows the usual order: I > Br > Cl ≫ F. Thus, difluoroiodomethane ($CHIF_2$) gives exclusively difluorocarbene ($:CF_2$) with the elimination of HI. This is the most important way of making dihalocarbenes. The reactions are best carried out in an organic solvent using a strong nucleophilic base such as potassium *tert*-butoxide. Dichlorocarbene can also be generated by sonication of a solution of chloroform with powdered KOH (Scheme 5.9).

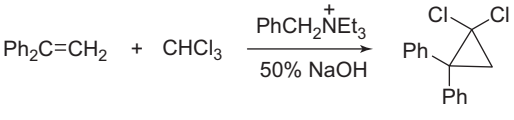
The mixture *t*-BuLi/*t*-BuOK is known as *Schlosser's base*, and is one of the most powerful bases known. It will abstract protons from allylic and benzylic positions, and will even deprotonate benzene. Similar α-eliminations may occur from trihaloacetate anions (Scheme 5.10).

Nowadays, phase-transfer catalysis has proved to be particularly effective in the generation of carbenes by α-elimination. The halomethyl anion is transported as an ion-pair with a tetraalkylammonium ion, or a crown ether-complexed alkali-metal ion, from a strongly basic aqueous solution into an organic phase, where elimination takes place and the resulting carbene reacts with the substrate in organic phase to give halocyclopropanes (Scheme 5.11).



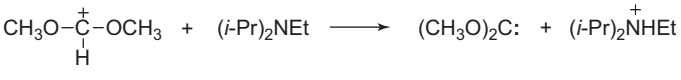
Scheme 5.9 Formation of carbene by α-elimination.

Scheme 5.10 α-Elimination of trihaloacetate.

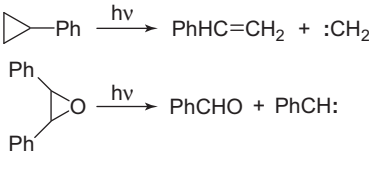


Scheme 5.11 Phase-transfer catalyst assisted α-elimination.

A highly novel method of carbene generation involves α-elimination via a carbocation intermediate. Carbene may be considered to be the conjugate base of a carbocation (Scheme 5.12). Photo-elimination also leads to carbenes (Scheme 5.13).



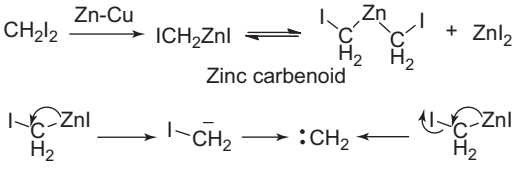
Scheme 5.12 α-Elimination via a carbocation intermediate.



Scheme 5.13 Generation of carbene via photo-elimination.

5.2.5
Generation of Carbenoids (Simmons–Smith Reaction)

Closs and Moss have suggested the term *carbenoid* to describe intermediates that exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species. When carbenes are coordinated with metals they are known as *carbenoids* that have modified reactivities. Iodomethylzinc iodide is often referred to as a *carbenoid*, because it resembles a carbene in its chemical reactions (Simmons–Smith reaction) (Scheme 5.14). Rhodium and copper carbenoids are unstable whereas some transition metals such as tungsten and chromium form stable and isolable carbenoids called *metallocarbenes* or *Fischer carbenes*. Carbenoids are structurally related to singlet carbenes and possess similar reactivity.



Scheme 5.14 Formation of carbene from carbenoid.

Carbenoids are known for almost all of the transition metals. Formally, carbenoids are carbenes directly bonded to a metal. The d-orbital electrons on the metal reduce the electron deficiency on the carbon, making the carbene more stable and easier to work with. When this electron donation is moderate, as in the low oxidation state, middle, and late d-series metals, the carbenoids still behave electrophilically, and are known as *Fischer-type carbenoids*. When electron donation from the metal to the carbenoid carbon is extreme, as in the early transition metals, the carbenes become nucleophilic in their reactivity and are known as *Schrock-type carbenoids* (Figure 5.6).

5.2.6
Formation of Carbenes under Neutral Conditions

Certain trihalomethylmercury derivatives decompose under relatively gentle conditions, and hence they are useful precursors for carbenes (Scheme 5.15).

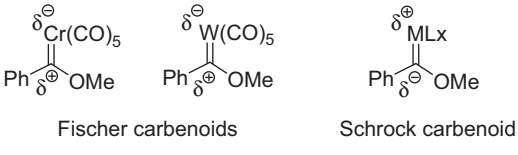
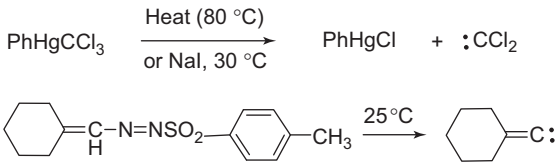


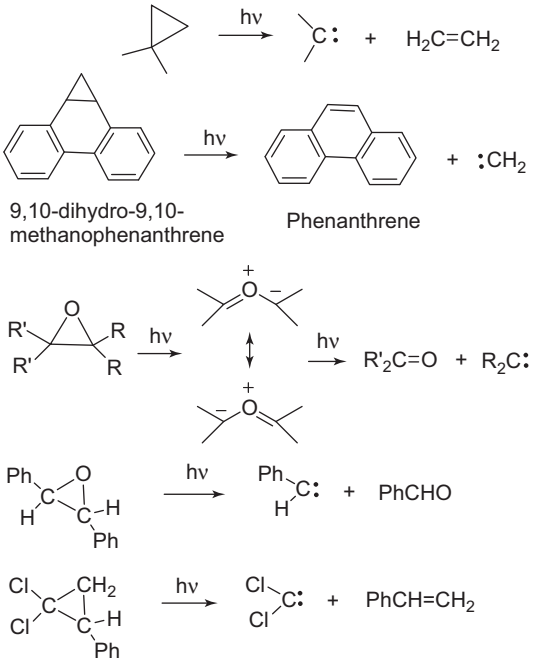
Figure 5.6 Fischer and Schrock carbenoids.



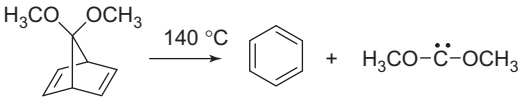
Scheme 5.15 Generation of carbene under neutral conditions.

5.2.7
Generation of Carbenes from Small Rings

Three-membered rings, which have a high ground state energy because of steric strain, will often decompose to give carbene intermediates simply on heating or irradiation, provided that a thermodynamically stable fragment is extruded. Photolysis of cyclopropanes generates carbenes via elimination of an alkene. The photodecomposition of epoxides is not a single-step process. The intermediates are carbonyl ylides, which are valence isomers of epoxides. It is believed that the second step in the process is also a photoreaction. Unsymmetrical epoxides can give rise to two carbenes and two carbonyl compounds (Scheme 5.16). 7-Norbornadienyl ketals are a good source of dialkoxycarbenes (Scheme 5.17).

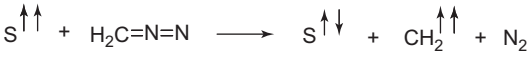


Scheme 5.16 Generation of carbene by the photolysis of cyclopropane derivatives.



Scheme 5.17 Generation of carbene from bicyclic ketal.

The carbenes produced by the means described in Sections 5.3.1–5.3.4 are initially in the singlet state, but they can relax to the triplet ground state if reaction does not occur first. The Simmons–Smith reaction produces a carbenoid, in which a carbene is stabilized by association with a metal, which reacts as a singlet carbene. It is possible to produce a triplet carbene directly through a process known as *sensitization*, in which a photoexcited triplet molecule S transfers energy to a carbene precursor and returns to its ground (singlet) electronic state. Conservation of electron spin requires that the carbene be produced in its triplet state (Scheme 5.18).



Scheme 5.18 Generation of triplet carbene.

5.3 Reactions of Carbenes

Carbene chemistry traces the evolution of carbene philicity from electrophilic to nucleophilic and ambiphilic carbenes and can be interchanged by appropriate fine tuning of the substituents. Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with an unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons, whereas singlet carbene can react in a single concerted step. Owing to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe the nature of a carbene.

Transient carbenes display a rich and diverse chemistry as stoichiometric reagents, for example, in reactions such as olefin cyclopropanation, C–H insertion, dimerization, 1,2-migration, and so on. Carbenes are important in several synthetic methods and are growing in importance, especially the intramolecular versions. Carbenes are electron deficient, and unless strong resonance interaction is possible the reactions will be electrophilic. The chemical behavior of a carbene depends to some extent on its method of preparation, electronic state, and also on the presence or absence of certain metals or metallic salts. The state in which the carbene is produced depends on the method of generation, that is, singlets

are normally generated in thermal and non-sensitized photochemical reactions, and triplets by irradiation in the presence of sensitizer, no matter which is lower in energy. These two electronic configurations possess different geometries and chemical reactivities. Because of their paramagnetic character, triplet carbenes can be observed by ESR spectroscopy provided they have sufficient lifetime.

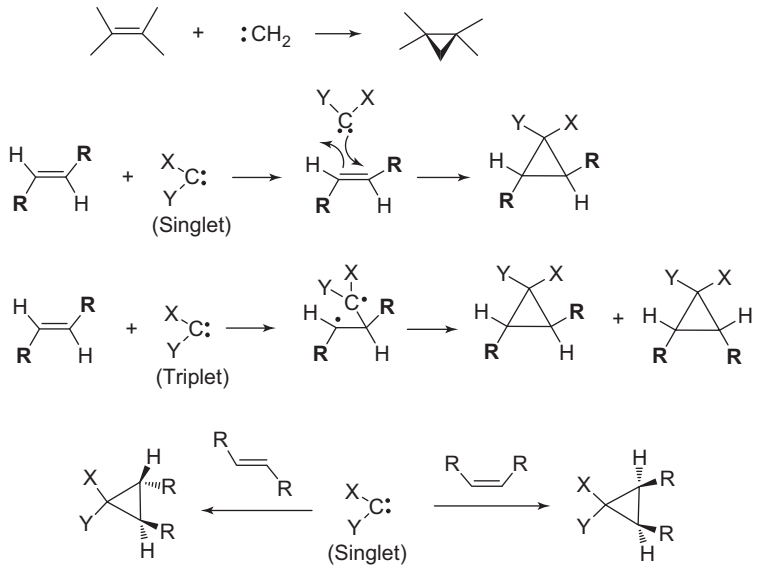
Carbenes and carbenoids undergo various reactions, that is, they can add to double and triple bonds, insert into C–H bonds, and undergo skeletal rearrangements. A carbon atom with only six electrons will do almost anything to get another two. Carbenes are too reactive to be isolated and stored; they are trapped in frozen argon for spectroscopic study at very low temperatures. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C–H bonds.

5.3.1 Addition Reactions

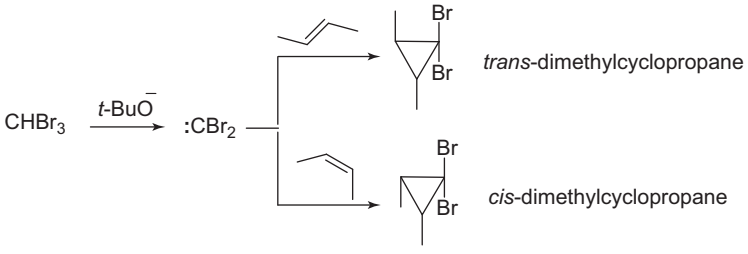
Addition reactions with alkenes to form cyclopropanes are the best-studied reactions of carbene intermediates, in terms of understanding carbene mechanisms and synthetic applications. Doering, in 1954, first reported the formation of cyclopropanes by the 1,2-addition of carbenes to alkenes. Singlet and triplet carbenes exhibit some important differences. Because it has an empty p orbital (like a carbocation) and a nonbonded pair of electrons (like a carbanion), the singlet carbene exhibits both carbocation and carbanion character. However, the triplet carbene behaves more as a diradical. These characteristics influence the types and stereochemistries of carbene reactions. A concerted mechanism is possible for singlet carbenes. As a result, the stereochemistry present in the alkene is retained in the cyclopropane.

Singlet and triplet carbenes do not demonstrate the same reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbene with its unfilled p-orbital should be electrophilic. Triplet carbenes should be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step. Addition of singlet carbenes to olefinic double bonds is more stereoselective than that of triplet carbenes. Addition reactions with alkenes can be used to determine whether the singlet or triplet carbene is involved. Reactions of singlet methylene are stereospecific while those of triplet methylene are not. For instance, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene and *trans*-2-butene is stereospecific, which proves that in this reaction the carbene generated is in the singlet state (Scheme 5.19).

The addition of dibromocarbene ($:CBr_2$) to olefins also appears to be stereospecific. From *cis*-2-butene, a derivative of *cis*-dimethylcyclopropane is obtained, whereas *trans*-2-butene yields a *trans*-dimethyl derivative (Scheme 5.20).

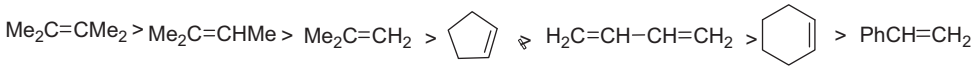


Scheme 5.19 Addition of carbenes to alkenes.



Scheme 5.20 Stereospecific addition of dibromocarbene to *cis*- and *trans*-2-butene.

In general, the following reactivity sequence applies to addition of carbene to olefins:



The precise mechanism of addition depends on the arrangement of the nonbonding electrons in the carbene. A singlet carbene (both electrons are in one orbital and the other is empty) adds stereospecifically, meaning that the *cis*-alkene gives only *cis*-cyclopropane, and the *trans*-alkene gives *trans*-cyclopropane. The addition may be regarded as [2+2] cycloaddition involving a HOMO–LUMO (LUMO = lowest unoccupied molecular orbital) interaction (Figure 5.7).

However, reaction of the triplet carbene is not stereospecific and the addition follows a radical pathway, and is stepwise, producing a mixture of diastereomeric

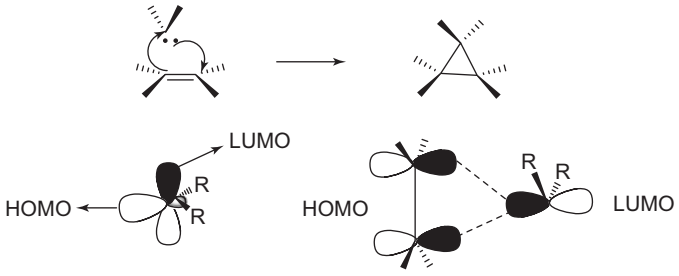
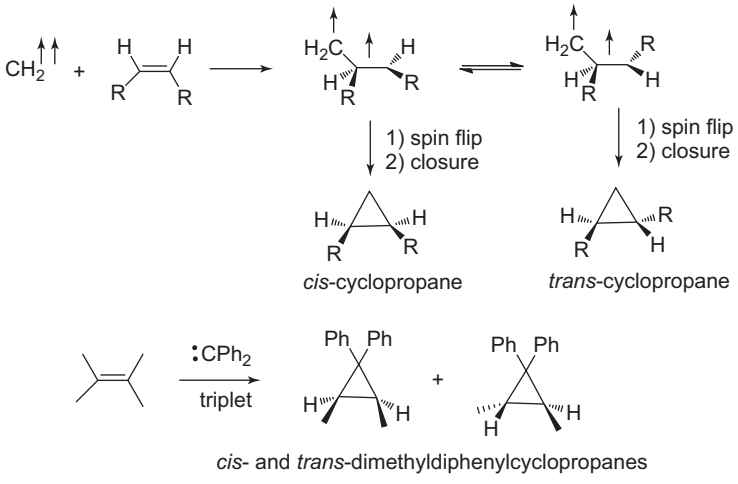


Figure 5.7 Mechanism of stereospecific addition of carbene to alkene.

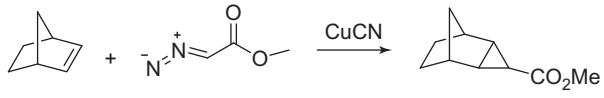
cyclopropanes. The difference in stereochemistry arises because the singlet carbene can add in one step, that is, in what is regarded as a concerted process, and therefore should obey the rules of orbital symmetry while the triplet cannot. The triplet carbene can add first to one end of the double bond to produce a diradical, which can only close to the cyclopropane after a time sufficient for one electron to flip its spin; this time may allow rotation to occur around the C–C single bond, so that a mixture of isomers results (Scheme 5.21). The rates of spin inversion and bond rotation must be of comparable magnitudes. Carbenes and carbenoids are strong electrophiles. Carbenoids are sterically more hindered and react relatively more slowly with the highly substituted alkenes than the free carbenes.



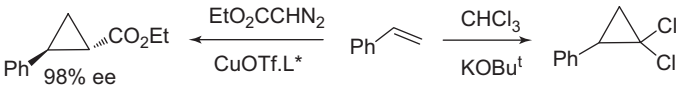
Scheme 5.21 Non-stereospecific addition of a triplet methylene to a *cis*-alkene.

The stereochemistry of these cycloadditions is so specific that it may be used as a diagnostic test for the identification of singlet and triplet carbenes. If the reaction is conducted in the presence of *triplet quenchers*, substances such as butadiene, which selectively remove any triplet carbenes, the addition is again stereospecific. Reactions involving free carbenes are very exothermic because two new σ bonds

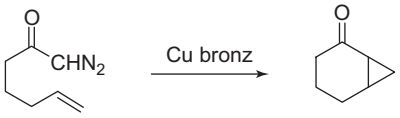
are formed and only the alkene π bond is broken. The reactions are very fast. Intramolecular additions are also possible. Schemes 5.22–5.24 give representative examples.



Cyclopropanation of bicyclo[2.2.1]hept-2-ene

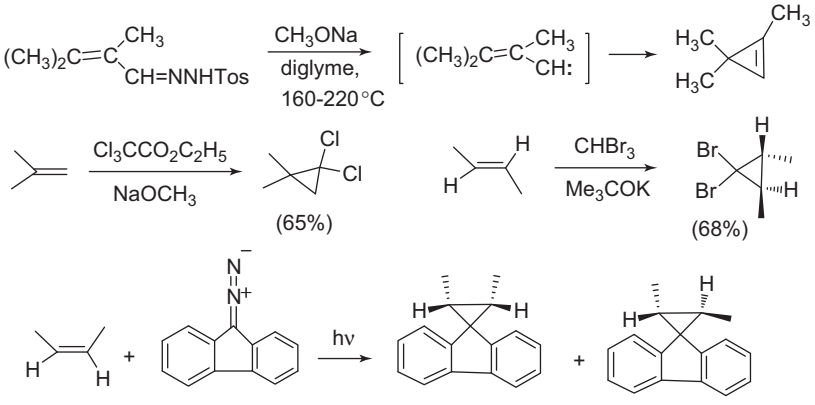


Cyclopropanation of styrene, including asymmetric variant



Intramolecular cyclopropanation of an alkene

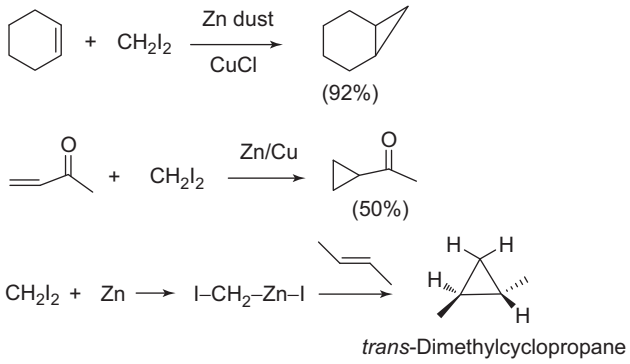
Scheme 5.22 Cycloaddition reactions of carbene.



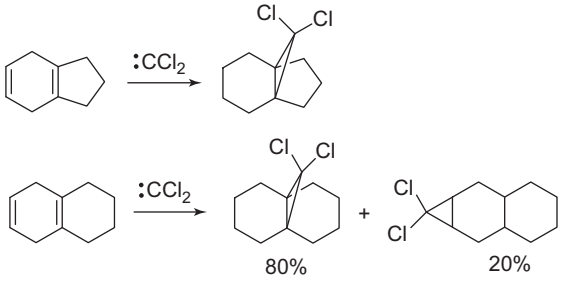
Scheme 5.23 Cycloaddition reactions of carbene.

In addition reactions, where more than one alkene moiety is present in a molecule, there is the potential for formation of isomers via addition to one or both of the double bonds. In general, carbenes add to the more electron-rich alkene (Scheme 5.25).

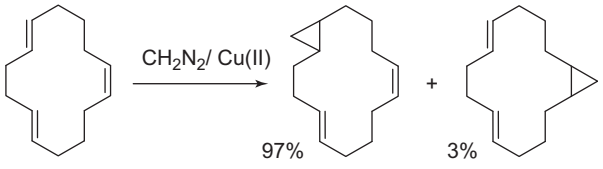
There also seems to be a preference for *trans* double bonds, as seen in the reaction of methylene with *cis,trans,trans*-1,5,9-cyclotetradecatriene. Notably, the *trans* double bond may be more sterically accessible, and this can account for the stereochemical preference (Scheme 5.26).



Scheme 5.24 Cycloaddition reactions of carbene.



Scheme 5.25 Regioselective addition of carbene.



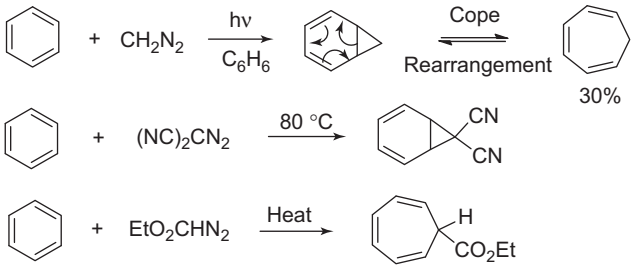
Scheme 5.26 Stereospecific addition of carbene to a trans double bond.

The high reactivity of carbenes is also essential to the addition reactions that occur with aromatic compounds. The resulting adducts are in thermal equilibrium with the corresponding cycloheptatrienes. The position of the equilibrium depends on the nature of the substituent (Scheme 5.27).

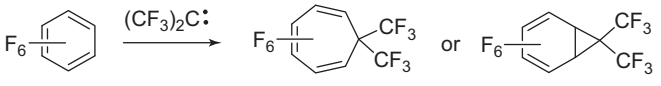
When hexafluorobenzene is treated with bis(trifluoromethyl)carbene, the tropylidene derivative or the corresponding norcaradiene are products (Scheme 5.28).

Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes. Ring expansion can also occur with aromatic and non-aromatic compounds, when the driving force is supplied by relief of strain (Scheme 5.29).

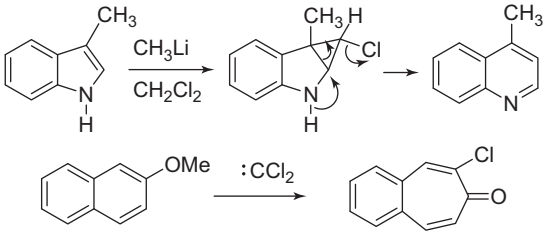
If bicyclic olefins are used, addition may occur on either side of the molecule (*exo*- or *endo*), and if the two substituents of the carbene are different, again two



Scheme 5.27 Addition of carbene to aromatic compounds.

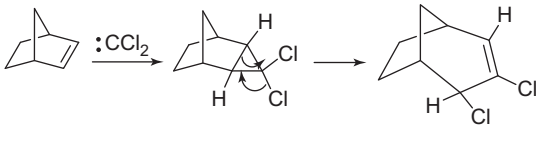


Scheme 5.28 Addition of bis(trifluoromethylcarbene) to hexafluorobenzene.



Scheme 5.29 Ring expansion of aromatic systems.

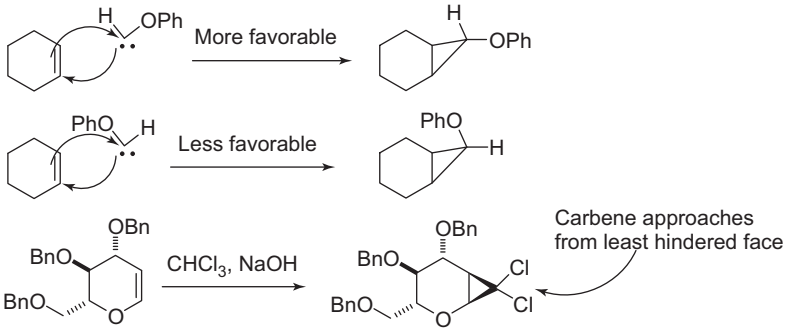
possible products may be obtained (*syn*- or *anti*-). If one approach is more favorable than the other, the reaction is said to be regioselective (Scheme 5.30).



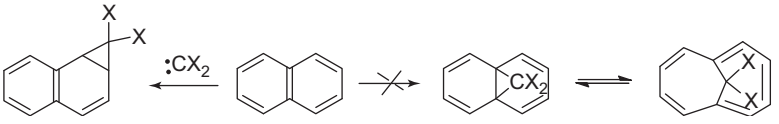
Scheme 5.30 Regioselective addition of carbene to a bicyclic system.

Moderate stereoselectivity is also seen in the addition of phenoxycarbene to cyclohexene, in which the product ratio is apparently influenced by steric factors that favor introduction of the larger group (PhO versus H) in the less crowded *exo*-position (Scheme 5.31). 1,6-Methanocyclodecapentaene is formally derived from naphthalene by addition of $:CH_2$ to the 1,2-bond of naphthalene (Scheme 5.32).

A very effective means for conversion of alkenes into cyclopropanes by transfer of a CH_2 unit involves the system CH_2I_2 and Zn–Cu couple, commonly referred to as the *Simmons–Smith reagent*. The active species is believed to be iodomethylzinc



Scheme 5.31 Stereoselective addition of carbene from less hindered face.



Scheme 5.32 Addition of methylene carbene to naphthalene.

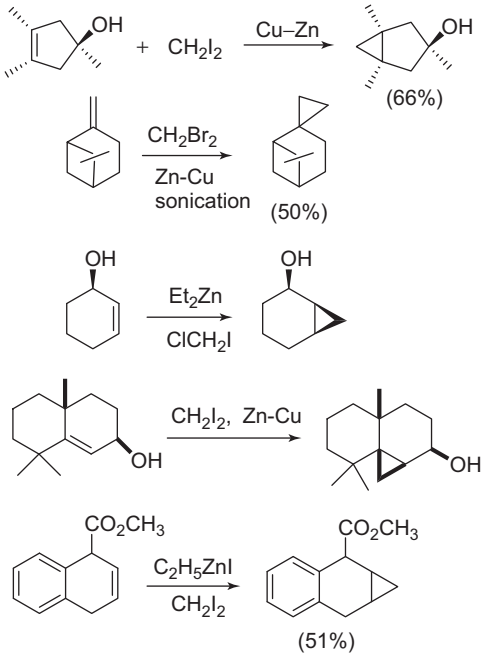
iodide in equilibrium with bis(iodomethyl)zinc (Scheme 5.33). The transfer of methylene occurs stereospecifically. Free methylene ($:CH_2$) is not an intermediate. In molecules with hydroxyl groups, the CH_2 unit is introduced on the side of the double bond *syn* to the hydroxyl group. This indicates that the reagent is complexed to the hydroxyl group and that the complexation directs the addition.

$$2\ ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

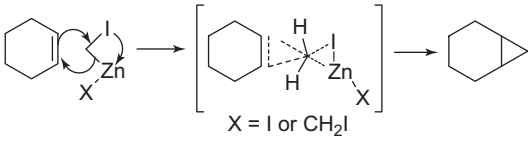
Scheme 5.33 Simmons–Smith reagent.

A modified version of the Simmons–Smith reaction uses dibromomethane and *in situ* generation of the Cu-Zn couple. Sonication is used in this procedure to promote reaction at the metal surface. Cyclopropanation can also be affected with a combination of CH_2I_2 and an alkylzinc reagent. The reaction is stereospecific and strongly regioselective. Thus, it has been found that cyclopentenol gives only the *endo*-bicyclic alcohol (Scheme 5.34). The mechanism of the Simmons–Smith reaction appears to be carbene transfer from the metal to the alkene without any free carbene being released (Scheme 5.35).

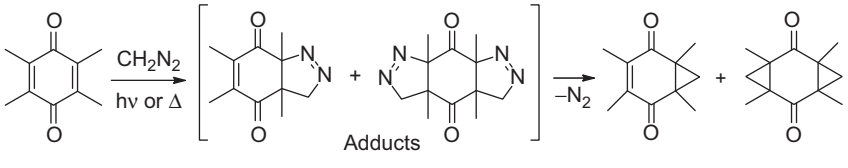
Duroquinone reacts with diazomethane to give adducts that under the action of acid catalysis, heat, or light lose nitrogen to give products (Scheme 5.36). Addition of carbene to CN double bonds has also been observed. The addition of dichlorocarbene to diazo compounds gives olefins (Scheme 5.37).



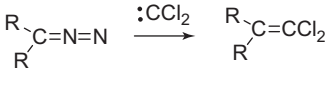
Scheme 5.34 Simmons–Smith reactions.



Scheme 5.35 Mechanism of Simmons–Smith reaction.



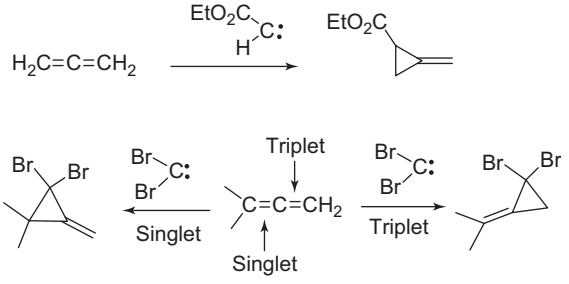
Scheme 5.36 Addition of carbene to duroquinone.



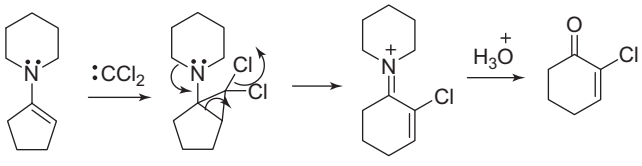
Scheme 5.37 Addition of carbene to C=N double bond.

5.3.2
Cycloaddition to 1,2-Dienes (Allenes)

Many carbenes add to cumulated systems, that is, allenes, to give alkylidenecyclopropanes in a synthetically useful reaction. Thus, allene itself reacts with ethoxycarbonylcarbene to give the ethyl ester of 2-methylenecyclopropane-1-carboxylic acid. 3-Methylbuta-1,2-diene (dimethylallene) has been proposed as a useful probe for carbene multiplicity since singlets add to the more substituted double bond, whereas triplets add to the 1,2-bond (Scheme 5.38). Carbenes react with enamines in the normal way accompanied by a ring expansion that generates ketones via rearrangement of the initially formed aminocyclopropane (Scheme 5.39).



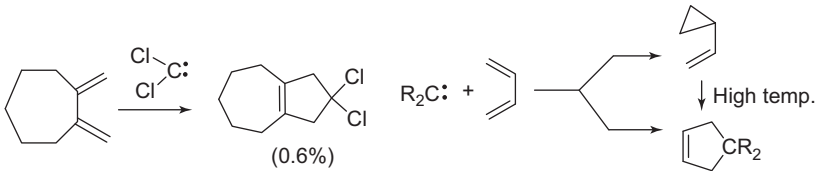
Scheme 5.38 Cycloaddition of carbene to allene.



Scheme 5.39 Addition of carbene to enamine.

5.3.3
Cycloaddition to 1,3-Diene

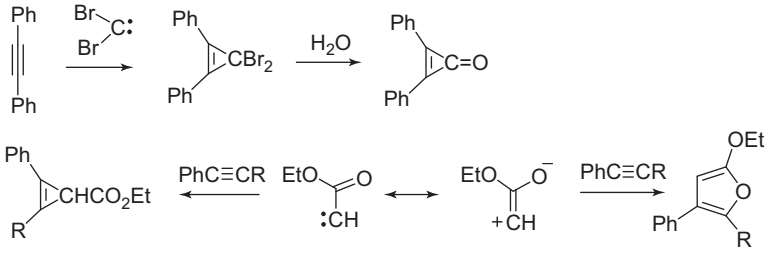
The 1,4-addition of carbenes to 1,3-dienes to give cyclopentenes is extremely rare, since 1,2-addition to give a vinylcyclopropane is much more favorable. Unfortunately, vinylcyclopropanes can be converted into cyclopentenes on heating at higher temperature. In special conditions direct 1,4-addition reactions are observed, but only in poor yield (Scheme 5.40).



Scheme 5.40 1,2-Addition of carbene to 1,3-dienes.

5.3.4
Cycloaddition to Alkynes

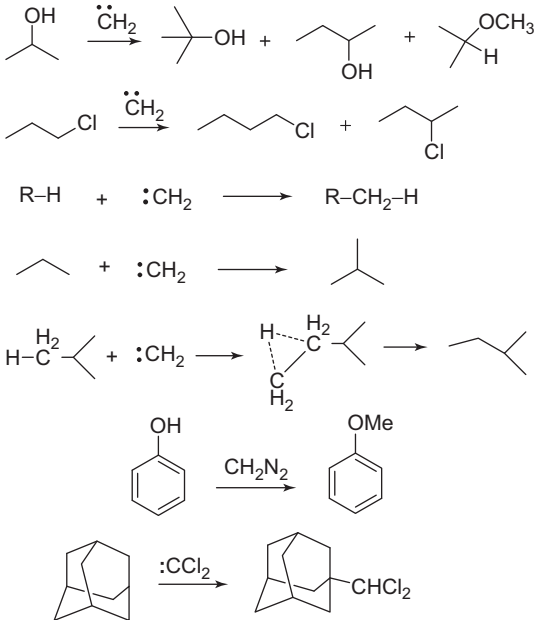
In general, alkynes are less nucleophilic than alkenes and so they are less reactive toward carbenes (Scheme 5.41).



Scheme 5.41 Addition of carbenes to alkynes.

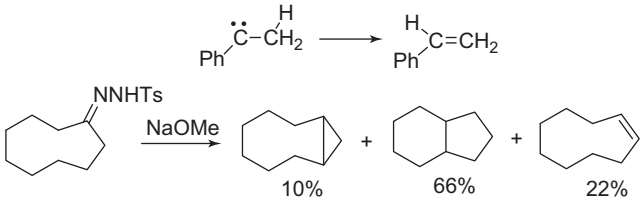
5.3.5
Insertion Reactions

Another important reaction of carbenes is their insertion into single bonds, notably C–H bonds but also O–H and C–Cl bonds. It is useful in synthesis because it leads to the formation of a new C–C bond. The attack on carbon–hydrogen bonds may be of two types. Hydrogen abstractions leading to radical pairs are usually ascribed to triplet state carbenes, and concerted insertion (i.e., a process in which a carbene interposes itself into an existing bond) is thought to characterize singlets. Insertion into carbon–hydrogen single bonds may be considered analogous to cycloaddition to alkenes. Insertion is common for methylene and carbon-substituted methylenes and can occur either inter- or intramolecularly. The singlet carbene inserts into the C–H bond in a single step with retention of configuration. Dihalocarbenes generally do not give insertion reactions. The usual mechanism for insertion is believed to be via a cyclic transition state. Diazomethane will also methylate phenols, because they are acidic enough to protonate it. Adamantane gives a high yield of 1,1-dichloromethyladamantane (Scheme 5.42).



Scheme 5.42 Insertion of carbenes into single bonds.

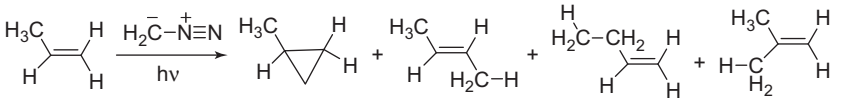
Intramolecular insertion reactions lead to rearranged structures and are equivalent to a 1,2-migration of hydrogen. Alkylcarbenes almost invariably react by intramolecular C–H insertion to give cycloalkanes, which is transannular in the case of cycloalkylidenes, or by rearrangement to give alkenes (Scheme 5.43).



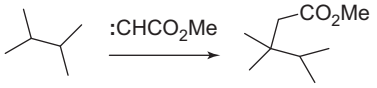
Scheme 5.43 Intramolecular insertion of carbene.

Methylene generated from diazomethane is so reactive that it inserts into C–H bonds as well as C=C bonds. For example, in the reaction of propene with diazomethane-generated methylene, several side products are obtained (Scheme 5.44). Methylene inserts into both primary and tertiary C–H bonds whereas carbomethoxymethylene reacts almost solely at the tertiary position (Scheme 5.45).

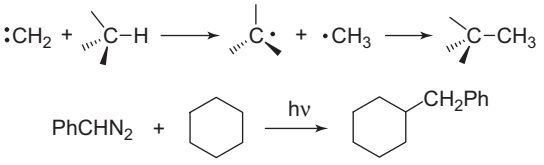
When the carbene is in the triplet state, hydrogen abstraction to yield a radical pair seems a reasonable possibility for the insertion mechanism (Scheme 5.46).



Scheme 5.44 Addition of carbene to C–H as well as C=C bonds.

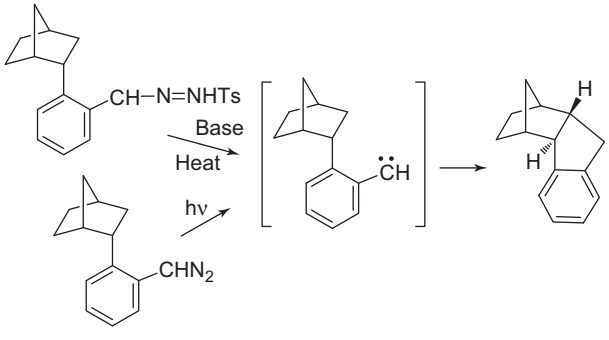


Scheme 5.45 Regioselective addition of carbomethoxymethylene.



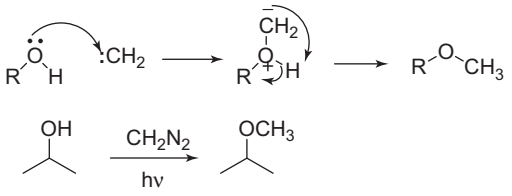
Scheme 5.46 Hydrogen abstraction by the triplet carbene to give a radical pair.

Insertion into C–H bonds is more probable than insertion into C–C bonds. Insertion into C–C bonds does not appear to occur at all. For example, photolysis of diazomethane in cyclopentane at −75 °C produced only methylcyclopentane, with cyclohexane not being observed. Singlet carbenes are thought to add to C–H bonds by a concerted process, while triplet carbenes can produce net addition through hydrogen abstraction and then recombination of the alkyl radicals. It was found that *o*-(2-*endo*-norbornyl)phenylcarbene inserts into the 3-position in such a way as to give a *trans*-junction (Scheme 5.47).



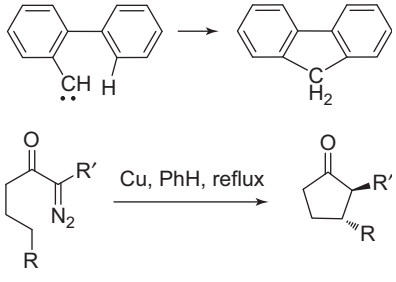
Scheme 5.47 Insertion of carbene into a C–C bond.

Carbonyl substituted carbenes insert into O–H bond, which is a useful way of making bonds in an umpolung sense. The mechanism in these cases involves initial attack on the lone pair of the heteroatoms (Scheme 5.48).

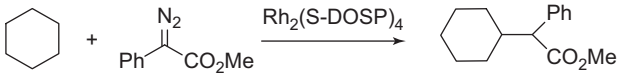


Scheme 5.48 Insertion of carbene into O–H bonds.

Intramolecular insertion reactions present new synthetic solutions. Generally, rigid structures favor such insertions. When an intramolecular insertion is possible, no intermolecular insertions are seen. In flexible structures, five-membered ring formation is preferred to six-membered ring formation. Both inter- and intramolecular insertions are amendable to asymmetric induction by choosing chiral ligands on metal centers. Arylcarbene can be inserted intramolecularly into aromatic C–H bonds (Schemes 5.49 and 5.50).

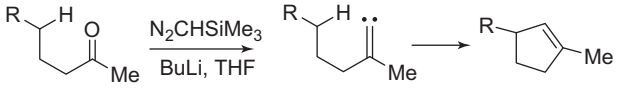


Scheme 5.49 Intramolecular insertion of carbene.



Scheme 5.50 Intermolecular insertion of carbene.

Alkylidene carbenes are alluring in that they offer formation of cyclopentene moieties. To generate an alkylidene carbene a ketone can be exposed to (trimethylsilyl)diazomethane (Scheme 5.51).

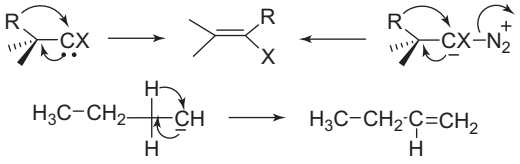


Scheme 5.51 Generation and intramolecular insertion of alkylidene carbene.

Dimerization of carbenes almost never occurs, at least not directly. The reason for the non-occurrence of the reaction is simply that the carbene concentration is so low that these species cannot find each other. Indirect dimer formation is possible in some special cases, for example, under the conditions of flash photolysis or in a warming or inert matrix.

5.3.6
Rearrangement of Carbenes

Carbenes, like other electron-deficient intermediates with a vacant p-orbital such as carbocations, undergo facile rearrangement in which an atom or group on the adjacent carbon migrates to the electron-deficient center with simultaneous formation of a new C=C bond. Such rearrangements are called 1,2-shifts and often involve migration of a hydrogen atom. The mechanism involves overlap of a migrating σ-bond with the vacant p-orbital of the carbene that requires the correct spacial alignment of orbitals, with the migrating group coplanar with the vacant orbital (Scheme 5.52).



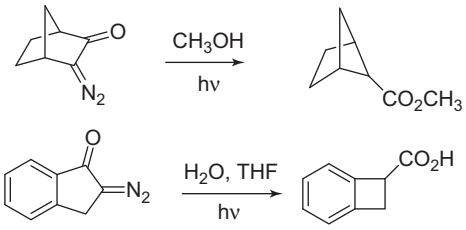
Scheme 5.52 Formation of alkenes by 1,2-shift.

The addition of dihalocarbenes to double bonds is straightforward, but the use of substrates with strained double bonds has been observed to lead to rearranged products. For example, norbornene gives the bicyclo[3.2.1]octene derivative (Scheme 5.53).

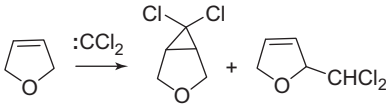
Scheme 5.53 Addition of dihalocarbenes to a strained double bond.

Cyclic diazoketones undergo rearrangement leading to ring contraction; this reaction has been widely used to prepare derivatives of strained small ring compounds such as bicyclo[2.1.1]hexane and benzocyclobutane (Scheme 5.54). CH-bonds α-to an ether linkage will also undergo this reaction to some extent, even when competing with double bonds. Thus, 1,4-dihydrofuran gives addition as well as rearranged product (Scheme 5.55).

The most common rearrangement reaction of alkyl carbenes is the shift of hydrogen, generating an alkene. For example, the carbene generated by decomposition of

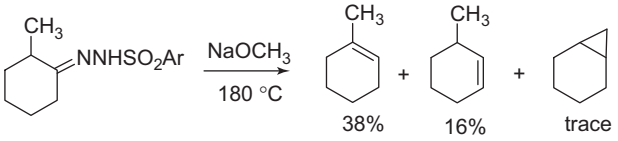


Scheme 5.54 Rearrangement leading to ring contraction.



Scheme 5.55 Addition of dichlorocarbene to 1,4-dihydrofuran to give addition as well as rearranged product.

tosylhydrazone of 2-methylcyclohexanone gives mainly 1- and 3-methylcyclohexene rather than the intramolecular insertion product (Scheme 5.56).



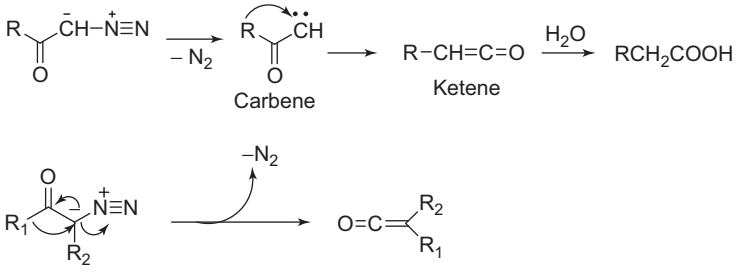
Scheme 5.56 Generation and reaction of carbene by decomposition of the tosylhydrazone.

5.3.6.1 **Wolff Rearrangement**

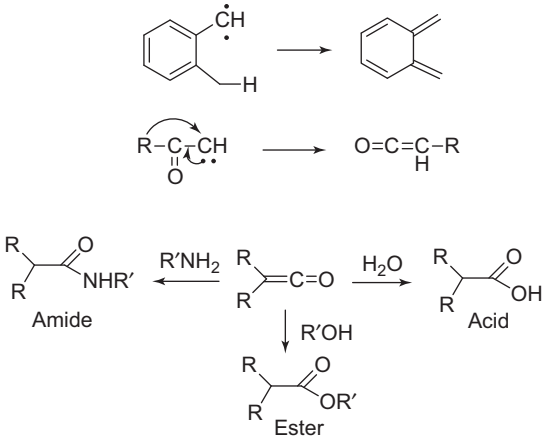
The Wolff rearrangement is an example of a nucleophilic rearrangement involving a carbene. It is a rearrangement of α-diazoketones leading to carboxylic acid derivatives via ketene intermediates. It can be achieved with metal catalysis or photochemically. There has been much debate about the timing of the mechanism and many attempts to distinguish between the two step process involving the intermediacy of a carbene or a concerted process in which migration occurs at the same time as loss of nitrogen. The general consensus appears to be that carbenes are intermediates in the photochemically induced Wolff rearrangement but there is still controversy about the thermal process (Scheme 5.57).

The above mechanism is supported by the following evidence: (i) the carbonyl carbon in the diazomethyl ketone becomes the carboxyl carbon in the resulting acid, as shown by ^{13}C studies; (ii) the migrating group R migrates with retention of configuration; and (iii) in the absence of water or alcohol, under favorable conditions the intermediate ketene may be isolated. The actual product of the reaction is thus the ketene, which reacts with water, alcohols, or amines to give carboxylic acids, esters, or amides, respectively (Scheme 5.58).

Stepwise mechanism

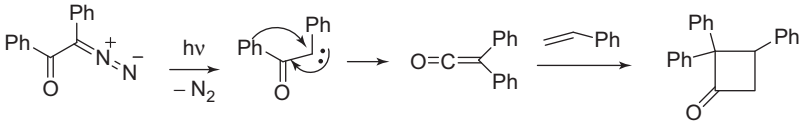


Scheme 5.57 Wolff rearrangement.



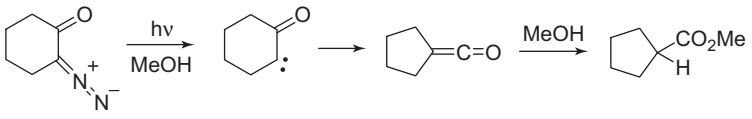
Scheme 5.58 Reaction of ketene with water, alcohols, and amines.

Carbenes from α-diazoketones have the special property that they rearrange faster than they are trapped. For example, rearrangement gives a ketene, which can be trapped by an alkene, and this forms the basis of a method for synthesizing four-membered rings (Scheme 5.59). A variant of this reaction is the ring contraction of carbenes from cyclic α-diazoketones (Scheme 5.60).



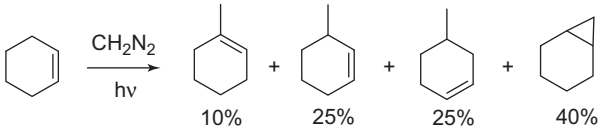
Scheme 5.59 Rearrangement of carbene to ketene.

Methylene (:CH_2) is of higher energy content than :CCl_2, and is more reactive and less selective. Its reactivity is illustrated by its reactions with cyclohexene, which include both addition to the double bond and insertion in the saturated and

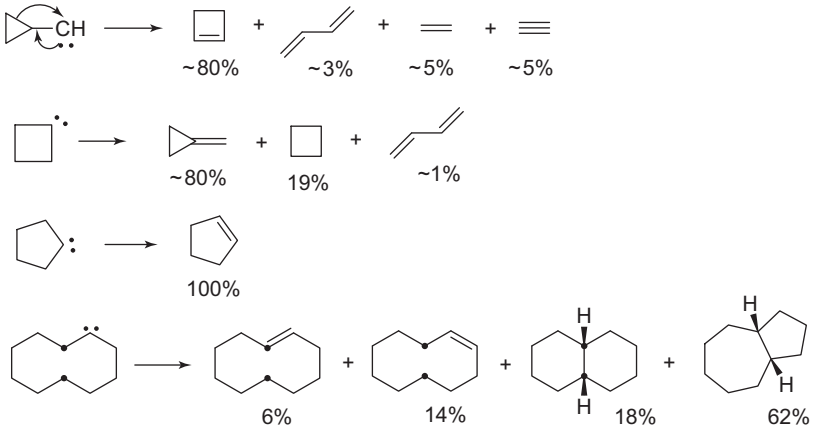


Scheme 5.60 Ring contraction of carbene to give ketene.

unsaturated C–H bonds. Irradiation of diazomethane in cyclohexene produced 1-methylcyclohexene (10%), 3-methylcyclohexene (25%), 4-methylcyclohexene (25%), and norcarane (40%) (Scheme 5.61). Cyclic carbenes undergo various possible rearrangements, depending upon ring size and experimental conditions (Scheme 5.62).

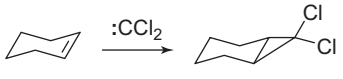


Scheme 5.61 Reaction of carbene with cyclohexene.



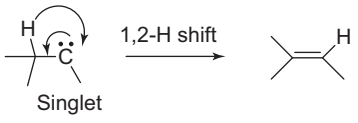
Scheme 5.62 Rearrangement of cyclic carbenes.

Different carbenes exhibit different selectivities toward insertion and cycloaddition reactions. However, the reaction of cyclohexene with dichlorocarbene resulted in a 60% isolated yield of the dichloro derivative of norcarane, that is, 7,7-dichlorobicyclo[4.1.0]heptanes (Scheme 5.63).



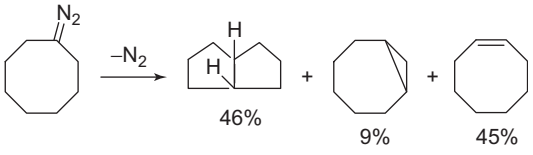
Scheme 5.63 Reaction of cyclohexene with dichlorocarbene.

Singlet carbenes will rearrange to isoelectronic structures in which all atoms have an octet of electrons if hydrogen atoms are located on adjacent carbon atoms. For example, alkyl carbenes readily rearrange by a 1,2-hydrogen shift to produce alkenes (Scheme 5.64). Evanseck and Houk determined from *ab initio* calculations that the activation energy for the rearrangement of methylcarbene to ethene was 0.6 kcal mol^{-1}.



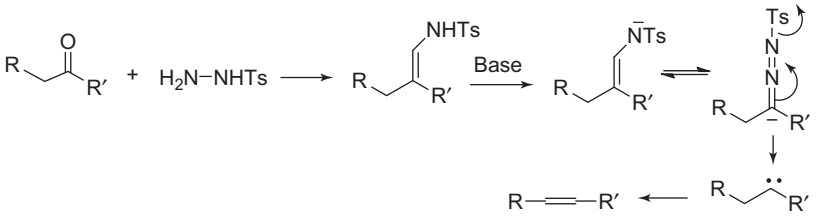
Scheme 5.64 Rearrangement of singlet carbene to alkene.

Alkyl and dialkyl carbenes undergo such rapid intramolecular reactions that intermolecular reactions are not competitive. For example, Scheme 5.65 shows products from the decomposition of diazocyclooctane.



Scheme 5.65 Competition between inter- and intramolecular reactions.

This rearrangement is the basis of the Bamford–Stevens reaction, in which the tosylhydrazone of an aliphatic ketone is converted into an alkene by the action of strong base, such as the sodium salt of ethylene glycol in ethylene glycol as solvent. The extent to which any particular carbene exhibits these reactions depends on its structure and electronic state (Scheme 5.66).



Scheme 5.66 Conversion of ketone into alkene through the Bamford–Stevens reaction.

If intramolecular reactions cannot occur, the carbanion–carbocation character of a singlet carbene can lead to reactions that occur through ionic species. Singlet carbenes react with methanol by nucleophilic abstraction of a proton, resulting in a carbocation, which subsequently reacts with the alcohol to produce an ether. For

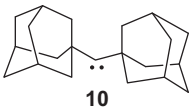


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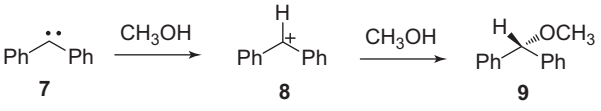
Figure 5.8 Diadamantylcarbene.

example, the diphenylcarbene singlet (**7**), which cannot undergo rearrangement to form an alkene, abstracts a proton from methanol to form the diphenylmethyl carbocation (**8**). Methanol then adds as a nucleophile to **8** to produce the ether **9** (Scheme 5.67). The propensity for intramolecular rearrangement means that the lifetime and bimolecular reactivity of carbenes depend strongly on structure. Dialkylcarbenes that do not have α C–H bond have longer lifetimes since a hydrogen shift is not possible. Two carbenes, namely, di-*tert*-butylcarbene and diadamantylcarbene (**10**), have been studied spectroscopically (Figure 5.8).

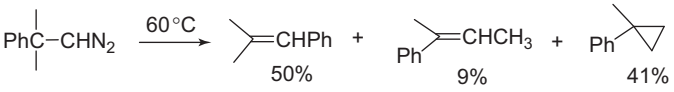


7 **8** **9**

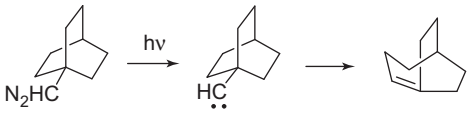
Scheme 5.67 Singlet carbene leading to carbocation.

Spectroscopic studies indicate that both carbenes are ground state triplets, but the reactions of diadamantylcarbene in solution suggested reactions involving both the singlet and triplet states. Spin-equilibrated **10** reacted with methanol ($k = 2 \times 10^7\,\mathrm{l\,mol^{-1}\,s^{-1}}$) to produce methyl diadamantylmethyl ether. In addition, reaction of the triplet state of **10** with oxygen (a triplet ground state molecule) gave a carbonyl oxide, which could be reduced to diadamantyl ketone, confirming triplet reactivity.

Moss and Mamantov found that a halogen bonded to the carbene center stabilizes the singlet state of the carbene. Because of the higher activation energy for rearrangement, alkylchlorocarbenes can take part in both intra- and intermolecular reactions and the rate constants for both processes can be measured. Carbenes can also be stabilized by migration of alkyl or aryl groups. 2-Methyl-2-phenyl-1-diazopropane provides a case in which phenyl and methyl migration, as well as intramolecular insertion, is observed (Scheme 5.68). Bicyclo[3.2.2]non-1-ene, a strained bridgehead alkene, is formed when bicyclo[2.2.2]octyldiazomethane is photolyzed (Scheme 5.69).



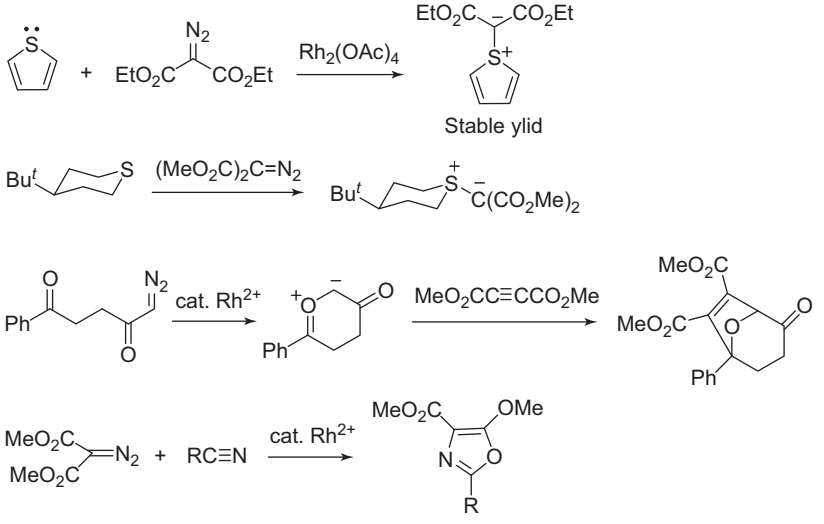
Scheme 5.68 Carbene exhibiting phenyl and methyl migration.



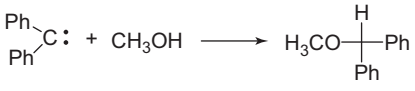
Scheme 5.69 Formation of a strained bridgehead alkene.

5.3.7 Reactions of Carbenes with Nucleophiles

Carbenes react with many nucleophiles. Tertiary amines, phosphines, ethers, sulfides, and sulfoxides all react to give ylides in the reverse of a carbene-forming reaction. Depending on the substituents present, the ylides may be isolable or may undergo rearrangement. Polarized multiple bonds such as C=O and carbon–nitrogen triple bonds also react with carbenes by attack of the heteroatom lone pair to give ylides that undergo further reaction. Scheme 5.70 gives some examples of the formation of ylides from carbenes. A common method of trapping carbenes involves insertion into the –OH bond of an alcohol (Scheme 5.71).



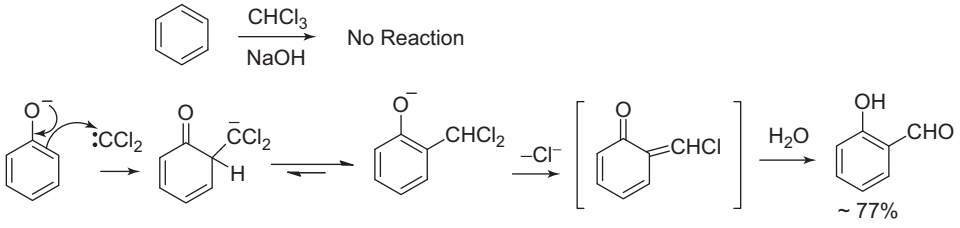
Scheme 5.70 Nucleophilic reactions of carbenes.



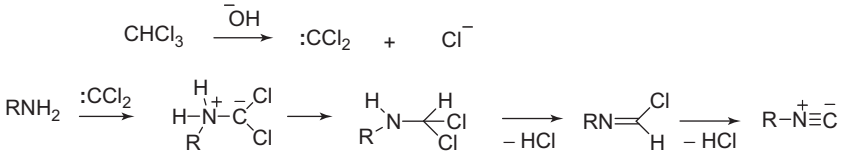
Scheme 5.71 Trapping of carbene by methanol.

Dichlorocarbene ($:CH_2$) will not add to benzene, but does attack the electron-rich aromatic ring of phenol; the product is not a cyclopropane, but an aldehyde.

Reimer–Tiemann conversion of phenoxide into *ortho*-hydroxybenzaldehyde involves an electrophilic attack by dichlorocarbene (Scheme 5.72). Carbenes also react with primary amines (carbylamine reaction) to give carbylamines (isonitriles) (Scheme 5.73).



Scheme 5.72 Reimer–Tiemann reaction.



Scheme 5.73 Carbylamine reaction.

In the vapor phase, there are two additional considerations that are very important in understanding of carbene chemistry. The first point reflects the fact that carbene reactions are normally highly exothermic (about 90 kcal mol^{-1} for insertions or additions). Thus, a product molecule is frequently produced with a large amount of excess internal energy. In the vapor phase without solvent molecules to help dissipate the excess vibrational energy, the molecule may be subject to further reactions. Such reactions are often called *"hot molecule"* reactions. Cyclopropanes from cycloaddition reactions are particularly susceptible to hot molecule decomposition to the thermodynamically more stable olefin, since E_a for cyclopropane isomerization is only 64 kcal mol^{-1}.

5.4 Carbenes and Carbene Ligands in Organometallic Chemistry

A transition metal carbene complex is an organometallic compound featuring a divalent organic ligand. The divalent organic ligand coordinated to the metal center is called a *carbene*. Carbene complexes for almost all transition metals have been reported. Many methods for synthesizing them and reactions utilizing them have been reported. The term carbene ligand is a formalism since many are not derived from carbenes and almost none exhibit the reactivity characteristic of carbenes. Often described as $M{=}CR_2$, they represent a class of organic ligands intermediate

between alkyls ($-CR_3$) and carbynes ($\equiv CR$). They feature in many catalytic reactions in the petrochemical industry and are of increasing interest in fine chemicals. The characterization of $(CO)_5Cr(COCH_3(Ph))$ in the 1960s is often cited as the starting point of the area, although carbenoid ligands had been previously implicated.

Metal carbene complexes are often classified into two types. The **Fischer carbenes**, named after Ernst Otto Fischer, feature strong π-acceptors at the metal and are electrophilic at the carbene carbon atom. **Schrock carbenes**, named after Richard R. Schrock, are characterized by more nucleophilic carbene carbon centers – these species typically feature higher valent metals (Figure 5.9). N-heterocyclic carbenes (NHCs) were popularized following Arduengo's isolation of a stable free carbene in 1991. Reflecting the growth of the area, carbene complexes are now known with a broad range of different reactivities and diverse substituents. Often it is not possible to classify a carbene complex with regards to its electrophilicity or nucleophilicity.

Fischer carbenes are found with low oxidation state metals, middle and late transition metals Fe(0), Mo(0), Cr(0), π-electron acceptor metal ligands, and π-donor substituents on the carbene atom such as alkoxy and alkylated amino groups. The chemical bonding (Figure 5.10) is based on σ-type electron donation of the filled lone pair orbital of the carbene atom to an empty metal d-orbital, and π electron back-bonding of a filled metal d-orbital to the empty p-orbital on carbon. An example is the complex $(CO)_5Cr{=}C(NR_2)Ph$.

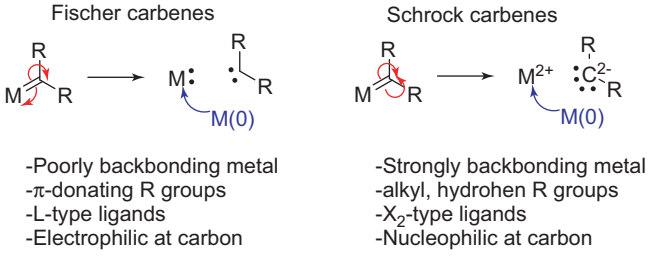


Figure 5.9 Fischer and Schrock carbenes.

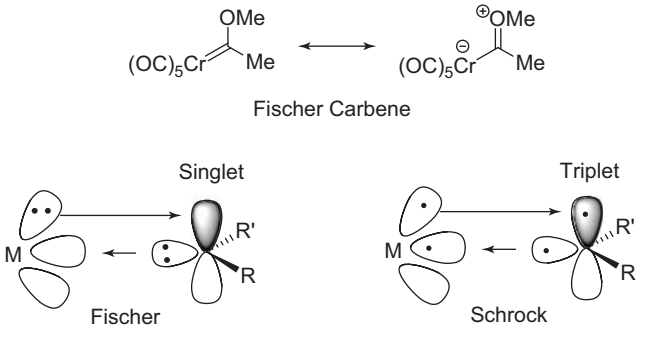


Figure 5.10 Chemical bonding in Fischer and Schrock carbenes.

Fischer carbenes can be likened to ketones, with the carbene carbon being electrophilic, much like the carbonyl carbon of a ketone. Like ketones, Fischer carbene species can undergo aldol-type reactions. The hydrogen atoms attached to the carbon α to the carbene carbon are acidic, and can be deprotonated by a base such as *n*-butyllithium to give a nucleophile, which can undergo further reaction. This carbene is also the starting material for other reactions such as the Wulff–Dötz reaction. These types of carbenes were discovered by E. O. Fischer, for which, together with other achievements in organometallic chemistry, he was awarded the Nobel Prize in Chemistry.

Schrock carbenes do not have π-accepting ligands. These complexes are nucleophilic. Schrock carbenes are typically found with high oxidation states, early transition metals Ti(IV), Ta(V), π-donor ligands, and hydrogen and alkyl substituents on the carbenoid carbon. Bonding in such complexes can be viewed as the coupling of a triplet state metal and triplet carbene. These bonds are polarized toward carbon and therefore the carbene atom is a nucleophile (Figure 5.10). An example of a Schrock carbene is the compound $Ta(=C(H)Bu^t)(CH_2Bu^t)_3$, with a tantalum(V) center doubly bonded to a neopentylidene ligand as well as three neopentyl ligands. An example of interest in organic synthesis is Tebbe's reagent (Figure 5.11). Schrock carbene complexes play a key role as both reagents and catalysts in organic synthesis. They have found widespread application as intermediates in the preparation of organometallics.

The methylene carbon of Schrock carbenes, on which electron density is piled through backbonding, is nucleophilic (the 2^- charge screams nucleophilic). On the other hand, the methylene carbon of Fischer carbons is electrophilic, because backbonding is weak and does not compensate for σ-donation from the ligand to the metal. Fischer carbenes, Schrock carbenes, and vinylidenes are usually actor ligands, but they may be either nucleophilic or electrophilic, depending on the nature of the R groups and metal. In addition, these ligands present some interesting synthetic problems, because free carbenes are quite unstable, ligand substitution does not suffice for metal carbene synthesis. When the metal possesses π-acidic ligands and the R groups are π-basic the complex is best described as an L-type Fischer carbene and the oxidation state of the metal is unaffected by the carbene ligand. When the ligands are "neutral" (R = H, alkyl) and the metal is a good backbonder – that is, in the absence of π-acidic ligands and electronegative late metals – the complex is best described as an X_2-type Schrock carbene. Notice that the oxidation state of the metal depends on our deconstruction method. Thus, we see that even the oxidation state formalism is not perfect.

Since Bertrand *et al.* and Arduengo *et al.* described the first stable carbenes in the 1990s the chemistry of carbenes has witnessed tremendous development in

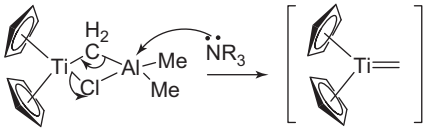


Figure 5.11 Tebbe's reagent.

the past two decades. These isolation studies built upon the early pioneering work of Ukai *et al.*, who first demonstrated the ability of thiazolium salts to promote the benzoin reaction. Breslow postulated that this transformation occurs via the formation of a carbene from the thiazolium salt, which subsequently reacts with an aldehyde to generate a key enaminol intermediate. In particular, NHCs have not only become versatile ligands for transition metals but can now be employed as true organic catalysts for various organic transformations, both in molecular chemistry and polymer synthesis. Many of these NHC-catalyzed reactions are based on activation of the carbonyl group (e.g., benzoin condensation, Stetter reaction, transesterification, etc.) though other electrophilic groups such as trialkylsilyl can also be activated (e.g., cyanosilylation or trifluoromethylsilylation reactions). This ''umpolung,'' or reversed polarity function, by which a formally electron-deficient carbonyl carbon is converted into a nucleophilic acyl anion equivalent, is the common mode of reaction induced by the action of an NHC in the archetypal benzoin and Stetter reaction processes. There are very few reliable methods for the construction of substituted benzenes. A very valuable example is the **Dötz benzannulation**, which proceeds in one step with predictable regiochemistry.

In contrast to Schrock and Fisher carbene complexes, where the carbene moiety is easily transferred to substrates, NHCs are strongly bound to the metal center and behave as ancillary ligands. In this context, NHCs have proven to be powerful in several organopolymerization reactions. They have been extensively explored for the ring-opening polymerization (ROP) of cyclic esters, mainly ε-caprolactone and lactide for the production of both cyclic and linear aliphatic polyesters. The scope of NHCs was later extended to other chain-growth polymerization reactions, including ROP of both ethylene and propylene oxides, group transfer polymerization of (meth)acrylic monomers, and to some step-growth polymerization reactions as well (e.g., for the metal-free synthesis of polyurethanes, poly(ethylene terephthalate), polysiloxanes, or polybenzoins).

On the other hand, applying the benefit of their modular reactivity, NHCs can serve as side-chain functionalizing reagents of preformed polymers featuring pendant azide groups. Their reactivity toward azides and isothiocyanates and their ability to dimerize have also enabled the synthesis of conjugated polymers through step-growth polymerization reactions involving bis(NHC) monomer substrates. Hence, owing to their inherent structural modularity and their extremely diverse chemistry, NHCs can provide highly selective polymerization reaction pathways and allow access to a wide variety of metal-free polymeric materials under relatively mild conditions. Despite these significant advances, their air and moisture sensitivities still limit the widespread adoption of NHCs in (macro)molecular synthesis. Yet, they can now be generated *in situ* (e.g., upon heating or addition of a base) from readily accessible and, in some cases, air-stable precursors.

NHCs are generally derived from persistent carbenes, which are stable compounds of divalent carbon (Figure 5.12). Being strongly stabilized by π-donating substituents, NHCs are good σ-donors, but π-bonding with the metal is weak. For this reason, the bond between the carbon and the metal center is often represented by a single dative bond, whereas **Fischer** and **Schrock carbenes** are usually depicted

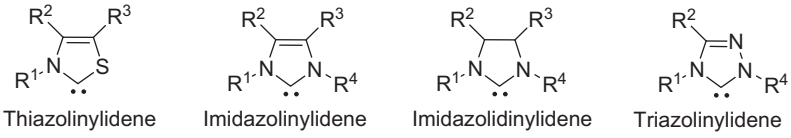
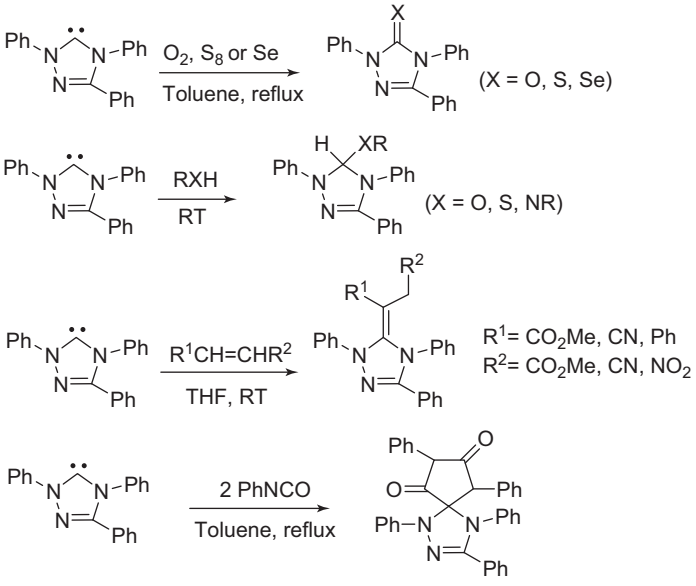


Figure 5.12 Representative NHC types.

with double bonds to the metal. Continuing with this analogy, NHCs are often compared with well-established phosphine-based ligands. Like phosphines, NHCs serve spectator ligands that influence catalysis through a combination of electronic and steric effects, but they do not directly bind substrates. Carbenes without a metal ligand have been produced in the laboratory, which promises to reduce costs as the required bonds to precious metals are no longer necessary. These are often are used as ancillary ligands in organometallic chemistry.

The chemistry of stable carbenes has not been fully explored. However, Enders and coworkers have performed a range of organic reactions involving a triazol-5-ylidene. These reactions are outlined in Scheme 5.74 and may be considered as a model for other carbenes.



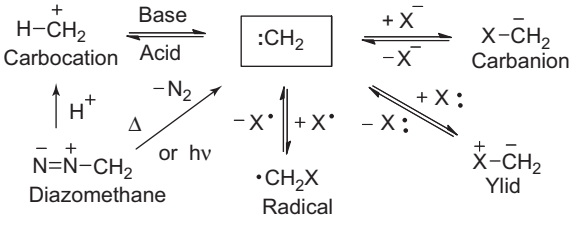
Scheme 5.74 Reactions of triazol-5-ylidene carbene.

5.5 Summary

- Carbenes are divalent carbon species, and are two electrons short of their octet.
- Most carbenes are highly reactive.

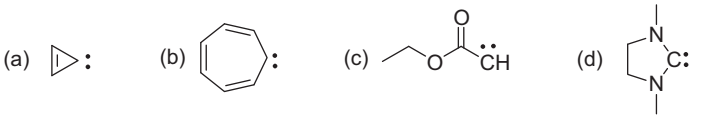
- Carbenes may exist in singlet or triplet states.
- Carbenes are formed by α-elimination or by breakdown of molecules such as diazo compounds under either thermal or photochemical conditions.
- Carbenes can insert into double or single bonds, rearrange, or abstract radicals.
- Carbenes also react with nucleophiles.
- One very common reaction for free carbenes is cyclopropanation.

This chapter has discussed how carbenes can be formed and how they can react to give stable compounds or yet more reactive intermediates. Below is a summary of the main relationships between carbenes and other intermediates:



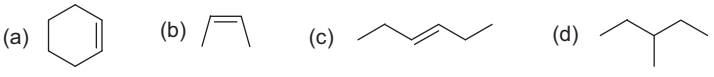
Problems

1. Each of the following carbenes has been predicted to have a singlet ground state. Indicate what structural feature in each case might lead to stabilization of the singlet state.



2. A reaction between methylene and *cis*-2-butene gave *trans*-1,2-dimethylcyclopropane. What does this tell us about the electronic configuration of the carbene in this reaction?

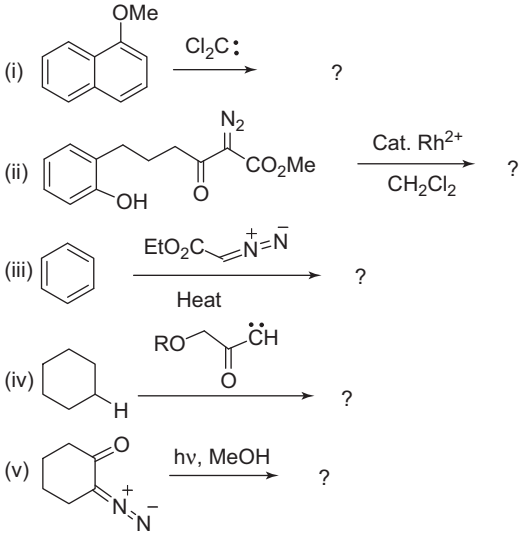
3. Predict the product(s) obtained from addition of singlet dichlorocarbene to each of the following compounds, and indicate whether they are *meso*-compounds or pairs of stereoisomers.



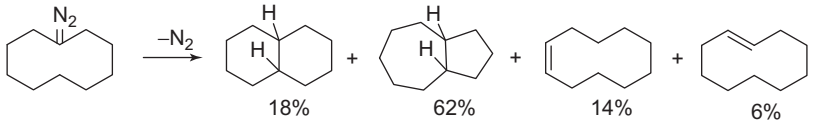
4. Why is CHI_3 less susceptible to α-elimination than $CHCl_3$?

5. Use two successive carbene reactions to synthesize 1,3-diphenylallene from stilbene (1,2-diphenylethylene).

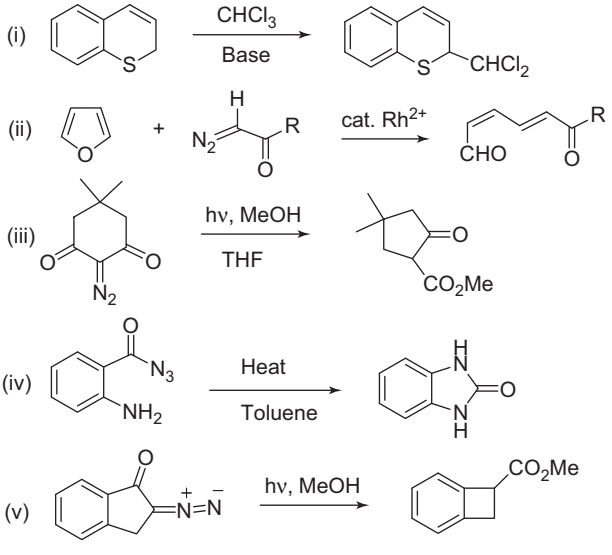
6. Predict the product(s) of the following reactions.



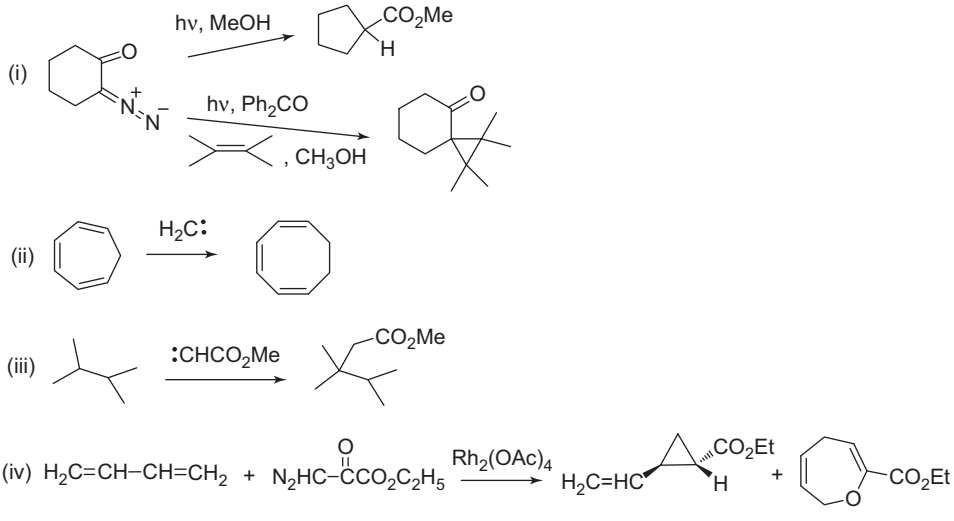
7. Propose a mechanism to account for the formation of products formed by decomposition of diazocyclodecane in the following reaction.



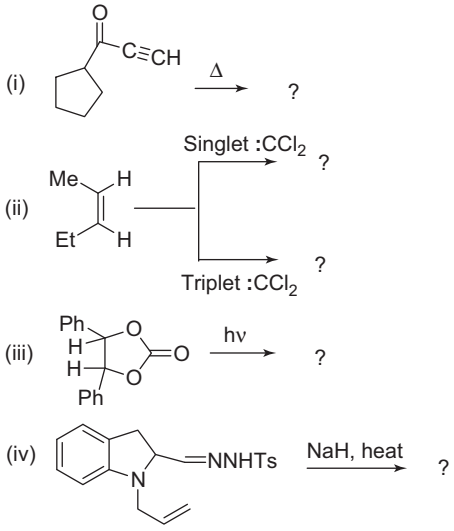
8. Write a suitable mechanism for the following transformations.



9. Rationalize the following reactions.



10. Complete the following reactions with a suitable mechanism.



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6
Nitrenes

6.1
Introduction

The diatomic molecule NH and its derivatives N–R are usually referred to as *nitrenes*; they are neutral reactive intermediates of increasing importance in both organic and inorganic chemistry. Nitrenes are molecular entities, which are usually formed thermally or photochemically from hydrazoic acid or organic azides. The name nitrene stands for the electron-deficient, electroneutral, monovalent, highly reactive molecule NH and its derivatives, which are formed by substitution of the hydrogen in NH. Thus, nitrenes are the nitrogen analogs of carbenes in which nitrogen has six electrons in its valence shell, and is therefore considered as an electrophile. There are four nonbonded electrons (two being the ''normal'' lone pair associated with nitrogen) indicated by the four dots in the drawn structure. Such univalent short-lived species were first suggested by Tiemann in 1891 as intermediates in the Lossen rearrangement, later on by Stieglitz in 1896 in the Curtius rearrangement, and were also adopted by Curtius to explain various reactions of azides. Kinetics of the cleavage of azides, spectroscopic data, and electron spin resonance (ESR) measurements constitute proof for a biradical nature of the nitrenes studied.

As a result of hydrogen shifts, nitrenes are capable of isomerization to imines, by hydrogen abstraction from neighboring molecules affording primary amines, and of ring formation by internal dehydrogenation (insertion reactions). Isomerization and hydrogen shifts are observed primarily with alkyl nitrenes; however, under favorable structural conditions, hydrogen shifts in aryl nitrenes also lead to imines. Aryl nitrenes dimerize to azo compounds and undergo intra- and intermolecular reactions with nucleophilic reactants. Thus, both stable and unstable acyl nitrenes (formed thermally or photolytically from acyl azides) add to dimethyl sulfide or dimethyl sulfoxide to furnish sulfimines or sulfoximines, respectively. Nucleophilic reagents such as alcohols and amines also react with nitrenes. Besides azides, anil-N-oxides also undergo cleavage to give nitrenes. The reaction of N-chloramines and hydroxylamine-O-sulfonic acids with nucleophilic reagents probably does not proceed via a nitrene intermediate, but rather by an S_N mechanism. Figure 6.1 shows some common nitrenes, where R could be H, Cl, F, Br, $COCH_3$, C_6H_5, alkyl, sulfonyl, and so on.

Reactive Intermediates in Organic Chemistry: Structure, Mechanism, and Reactions, First Edition.
Maya Shankar Singh.

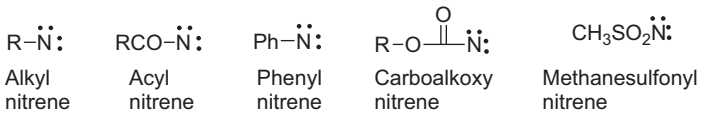
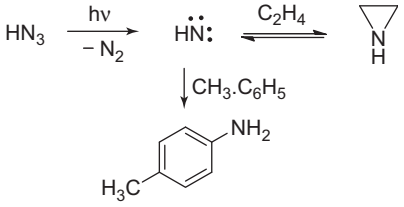


Figure 6.1 Common nitrene derivatives.

These species are isoelectronic with carbenes. The parent compound is nitrene NH (also known as *imidogen*, *azene*, or *imene*), which is formed when hydrazoic acid is irradiated with UV light in an aromatic solvent, which produces a small amount of primary aromatic amine. In the presence of ethylene, nitrene is trapped to form aziridine (Scheme 6.1). Nitrenes are also referred to as derivatives of imidogens as aminyls, azene, azylene, azacarbene, imene, or imines.



Scheme 6.1 Generation and trapping of nitrene.

6.2 Structure and Reactivity

Nitrenes are unusual molecular structures that exhibit high reactivities. Although they are isoelectronic with carbenes and can be generated and detected in a similar manner, they usually exhibit different reactivities. The chemistry of nitrenes closely parallels to that of carbenes in virtually all aspects. Like carbenes there is the possibility of two spin states for nitrenes, depending on whether the two nonbonding electrons (the normal nitrogen lone pair remains paired) have their spins paired or parallel. In general, nitrenes obey Hund's rule and are ground state triplets with two degenerate sp-orbitals containing a single electron each, although the nitrogen atom in the singlet is usually represented as sp^2-hybridized (Figure 6.2). The triplet state is usually the ground state, and lies substantially lower than the corresponding singlet states, but either species can be involved in reactions. Both nitrenes and carbenes usually have small energy separations between their lowest singlet and triplet electronic states. The energy difference between the singlet and triplet diradical states is usually much larger for nitrenes than for carbenes, being estimated at 145 kJ mol^{-1} for nitrene (NH) itself compared with 32–42 kJ mol^{-1} for methylene (CH_2). In addition, both classes of molecules seem to confirm to the idea of Skell that singlet states should insert into double bonds in a stereospecific manner, while triplets insert non-stereospecifically. These

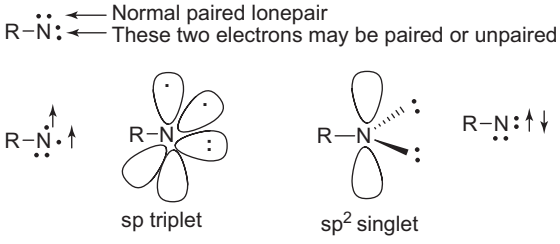


Figure 6.2 Triplet and singlet nitrenes.

species are not isolable under normal reaction conditions, although *ab initio* calculations show that nitrenes are more stable than carbenes, with an enthalpy difference of 25–26 kcal mol^{-1}. The simplest nitrene (NH) is perhaps the most thoroughly studied both from experimental and theoretical points of view. Nitrenes can be protonated to give nitrenium ions that are isoelectronic with carbenes.

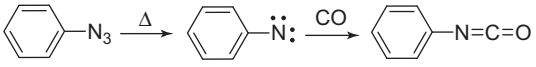
Although nitrenes are isoelectronic with carbenes there are important differences in their electronic structures, which account for their different reactivity. Nitrenes have two valence electrons that are distributed between two nearly degenerate nonbonding molecular orbitals (NBMOs), which involve the p-orbitals of the sp-hybridized nitrogen atom. Depending on the orientation of the p-orbitals with molecule they are assigned as in-plane orbital and out-of-plane orbital. As shown in Figure 6.2, this will give rise to the two electronic states of nitrenes, namely, triplet and singlet states. In the triplet state, two electrons will occupy both NBMOs with parallel spin, which will lower the coulombic repulsion between the nonbonding electrons. Whereas in the singlet states the electrons can occupy either one NBMO or both NBMOs with opposite spins resulting in a closed-shell or open-shell singlet state, respectively.

In the thermolysis of azides, obeying the spin conversion rule will initially generate the singlet nitrene, which could react with solvent or undergo intersystem crossing to give the triplet ground state. However, photochemical decomposition could generate either the triplet or singlet nitrenes. Because the chemistry is highly dependent on the reactivity, it is essential to have better knowledge of the ground and excited states of nitrenes, which can be used to control their reactivities. Information on the ground state of nitrenes can easily be determined by spectroscopic studies, but information about the excited electronic states cannot be readily obtained. In the case of nitrenes chemical reactions can take place in their ground state, in the first excited state, or the reaction surface could be a composition of both ground and first excited state. In most instances it will be the third case. As there are two possible electronic states for nitrenes, depending on which state is the ground state and the rate of intersystem crossing, they can exhibit different reactivity.

Although the triplet state is the common ground state for most simple nitrenes, they exhibit sluggish reactivity. Therefore, performing kinetic experiments with triplet nitrenes is next to impossible. However, the high-spin nature of the triplet nitrenes has made them potential candidates for organic magnetic materials. Owing

to the biradical character in the triplet state, they can undergo H-abstraction, non-stereospecific addition to a π-system, addition of radicals/radical-like structures, and dimerization to give azo compounds. In contrast, the alkyl and arylcarbonyl nitrenes have closed-shell singlets as the ground state, which exhibits high reactivity; this had led them to be used in various industrial and biological applications. For example, in the closed-shell singlets, the presence of an empty NBMO (nonbonding molecular orbital) allows them to undergo concerted insertion reactions easily. In other words, closed-shell singlet states behave as electrophiles and they would typically undergo C–H insertion reactions, stereospecific addition to π-bonds (olefin), addition of nucleophile, and 1,2-sigmatropic shift.

Alkyl nitrenes have been isolated by trapping in matrices at 4 K, while aryl nitrenes that are less reactive can be trapped at 77 K. Occasionally, a nitrene has been trapped by its reaction with CO to yield an isocyanate (Scheme 6.2). In general, aryl nitrenes abstract hydrogen from hydrocarbons more reluctantly than do triplet carbenes. For example, phenylnitrene abstracts H from toluene with a rate constant $\sim 10^3$ times lower than triplet diarylcarbenes.



Scheme 6.2 Generation and trapping of phenylnitrene.

This is in part because nitrogen is more electronegative than carbon, and therefore holds its electrons closer to the nucleus. As expected, the nature of the substituent on nitrogen affects both the multiplicity and the normal electrophilic reactivity of nitrenes. Strong π-donor substituents such as amino groups greatly stabilize the singlet as well as causing the nitrene to exhibit nucleophilic character in its reactions. A dramatic example of this effect is seen in the nitrene derived by oxidation of 1-amino-2,2,5,5-tetramethylpyrrolidine, which is a ground state singlet, stable in solution at low temperature (Figure 6.3). IR spectroscopy suggests the presence of an N=N bond ($\nu_{max.}$ 1638 cm^{-1}); the assignment is confirmed by observing the shift ($\nu_{max.}$ 1612 cm^{-1}) on isotopic labeling of the exocyclic nitrogen with ^{15}N. Aminonitrenes of this type are somewhat special, and are usually named as 1,1-diazenes, to reflect the fact that they show little nitrene character. However, other aminonitrenes, particularly those derived from N-amino-heterocycles, do show nitrene behavior.

Various techniques can be used to obtain the UV and ESR spectra of transient species. Interestingly, nitrene itself (NH) has been extensively characterized by spectroscopy, the electronic absorption at 336 nm being first observed in 1892.

Figure 6.3 Stabilization of singlet nitrene by donor substituents.

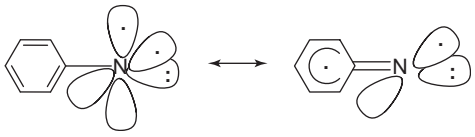
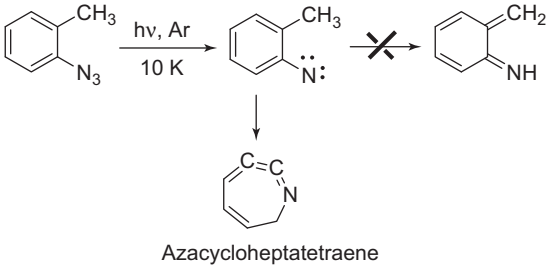


Figure 6.4 Delocalized structure of triplet phenylnitrene.

More modern techniques such as laser flash photolysis (LFP) and low temperature matrix studies allow the routine measurement of UV spectra of nitrenes. Triplet phenylnitrene, for example, shows absorptions between 300 and 400 nm at 77 K, while ESR measurements on the same species suggest that there is substantial delocalization of a single electron into the aromatic ring (Figure 6.4).

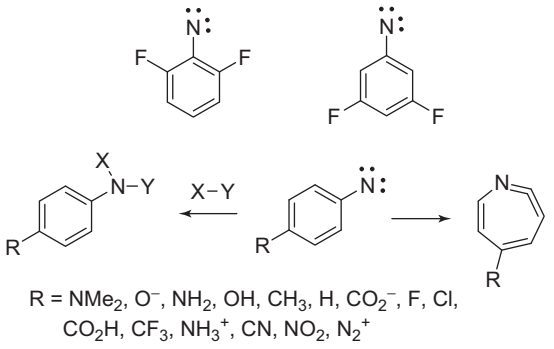
Irradiation of *ortho*-tolyl azide in inert matrices at 10 K gave the triplet nitrene, which could be characterized by IR spectroscopy. In contrast to the corresponding carbene, nitrene was stable up to 40 K in argon or 80 K in xenon matrices, giving no detectable H-shifted product. Subsequent irradiation led to ring expansion, affording azacycloheptatetraene (Scheme 6.3).



Scheme 6.3 Formation of *ortho*-tolyl-nitrene.

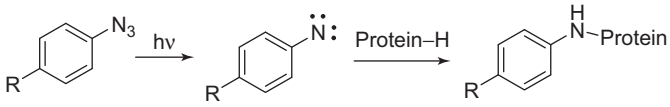
Substituents have been shown to alter the nitrene's reactivity to favor one reaction over the other. Platz has demonstrated that the barrier to ring expansion in 2,6-difluorophenylnitrene is 3–5 kcal mol^{-1} higher than for unsubstituted phenylnitrene (Scheme 6.4). The location of the fluorines on the aromatic ring is critical to this effect; 3,5-difluorophenylnitrene undergoes ring expansion at a rate similar to phenylnitrene. This substitution effect has been studied with density functional theory and multiconfigurational self-consistent field calculations. The calculations have shown that fluorine substitution at either the *ortho* or *para* positions of phenylnitrene polarizes the π-system in a manner that increases the barrier for ring opening. However, questions remain as to whether the substitution effect is mostly electronic or steric in nature. To assess the electronic effect of substituents, a series of *para*-substituted aromatic nitrenes have been studied. The substituents in this series of molecules ranged from strongly electron donating to strongly electron withdrawing. Calculations have shown that electron-withdrawing groups decrease the barrier for the ring-expansion reaction while electron-donating groups increase the barrier, that is, molecules with electron-donating groups ring

expand more slowly (Scheme 6.4). This observation is consistent with qualitative analysis based on a diabatic correlation of occupied orbitals in the reactants and products. Based on this knowledge, more effective photoaffinity labeling reagents should result from the addition of electron-donating groups.



Scheme 6.4 Electronic/steric effects of substituents in aromatic nitrene.

Most simple nitrenes have triplet ground states and exhibit sluggish reactivities. However, singlet nitrenes that have closed-shell structures have been used in many biological and industrial applications due to their ability to insert efficiently into surrounding chemical bonds. Such applications include their use as photoaffinity labeling agents (Scheme 6.5), as crosslinking reagents in photoresists, and in the modification of conductive and hydrocarbon polymers, and the high spin state of triplet nitrenes has made it possible for them to be developed into organic materials with magnetic properties. Many studies have been carried out in the last few decades using spectroscopic techniques such as LFP, ESR, time-resolved infrared spectroscopy (TRIR), and photoelectron spectroscopy (PES) to determine the electronic structures of nitrenes and their relative stabilities in solution and in the gas-phase. Furthermore, reactivity studies also have been performed as a method of identifying the electronic structures of nitrenes.

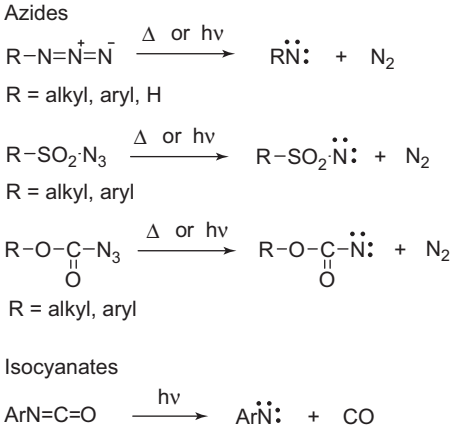


Scheme 6.5 Aryl azides for photoaffinity labeling.

6.3 Generation of Nitrenes

Understanding the chemistry revolving around reactive intermediates, including radicals, diradicals, carbenes, and nitrenes, is necessary because they play a major

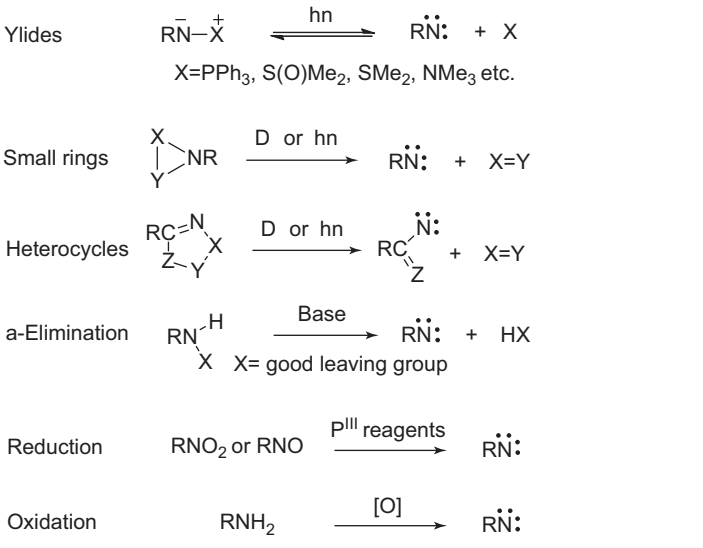
role in many organic reaction mechanisms. Furthermore, the presence of these species in combustion processes, the earth's atmosphere, and interstellar clouds has motivated extensive studies over the last few decades. General methods for the generation of nitrenes are summarized in Schemes 6.6 and 6.7 and closely parallel those used for carbenes. Because nitrenes are so reactive they are not isolated but, instead, are generated *in situ*, that is, formed as reactive intermediates during the course of a reaction. There are two common ways to generate nitrenes: (i) from azides by thermolysis or photolysis, with expulsion of nitrogen gas (this method is analogous to the formation of carbenes from diazo compounds) and (ii) from isocyanates, with expulsion of carbon monoxide (Scheme 6.6). The latter method is analogous to the formation of carbenes from ketenes. Other methods of generation of nitrenes include thermal and photochemical decomposition of nitrogen-containing precursors (Scheme 6.7).



Scheme 6.6 Generation of nitrenes from azides and isocyanates.

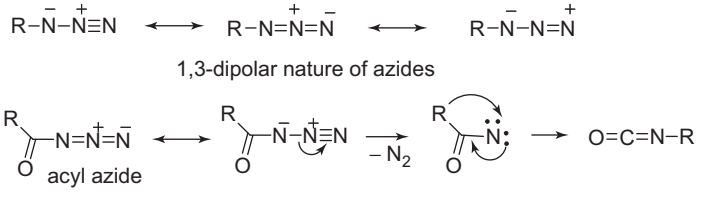
6.3.1 Azides

Azido compounds are versatile molecules. They are used extensively in both organic reactions and chemical biology. All azides are potentially explosive and must be handled with care. Azides, which have been known for over 100 years, are the most widely used precursors of nitrenes. Like diazo compounds, they possess a linear 1,3-dipolar structure and are easily prepared, often by introduction of the azide (N_3^-) ion from inorganic salts such as sodium azide. The thermal stability of azides is critically dependent on the substituent on nitrogen. Most azides decompose thermally in the range 100–200 °C to give nitrenes. Azides are also readily decomposed photochemically, and this is often the method of choice, particularly for mechanistic studies. Like diazo compounds, the decomposition of



Scheme 6.7 Generation of nitrenes from their relevant precursors.

azides can also be catalyzed by protic and Lewis acids and by transition metal salts (Scheme 6.8).



Scheme 6.8 Formation and rearrangement of acyl nitrene.

The azido group undergoes various useful reactions, including the Schmidt reaction, the Curtius reaction, and other important ring-formation or ring-expansion reactions. Reduction of azides is not only a very efficient method for the preparation of amines, amides, and sulfonamides but is also a new approach for the quantitative fluorescence detection of hydrogen sulfide in aqueous solutions. Azido compounds fragment under light and/or at elevated temperature to generate nitrenes, which can undergo insertion reaction with alkenes, yielding aziridines. Sulfonyl nitrenes are formed by heating sulfonyl azides (Scheme 6.9).

Scheme 6.9 Formation of sulfonyl nitrene.

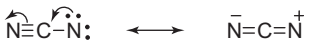
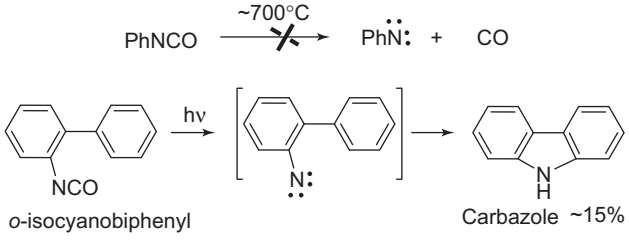


Figure 6.5 Cyanonitrene.

Cyanogen azide (NCN_3) is another special case, and is notoriously unstable, decomposing at about 50 °C. This facile decomposition is probably due to the unique nature of cyanonitrene – a symmetrical highly stabilized triplet species (Figure 6.5).

6.3.2
Isocyanates

Aryl isocyanates do not eliminate CO to give nitrenes on heating since the process is energetically unfavorable, although irradiation can provide sufficient energy for the reaction to proceed (Scheme 6.10). Hence, the generation of nitrenes from isocyanates is analogous to the generation of carbenes from ketenes. The related sulfinylamines (Ar–N=S=O), readily prepared from anilines and thionyl chloride, do decompose to nitrenes thermally with extrusion of SO.

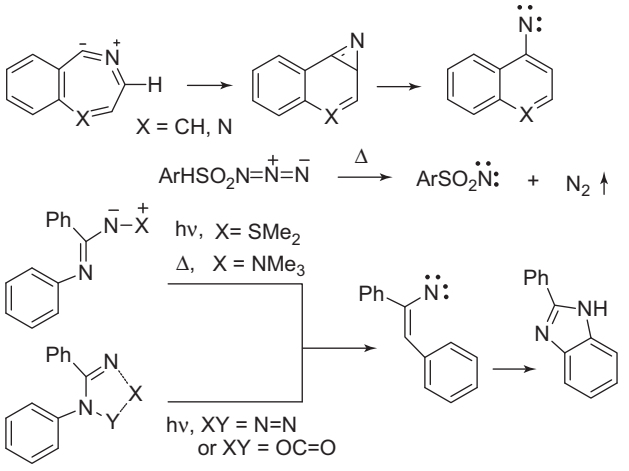


Scheme 6.10 Generation of nitrenes from isocyanates.

6.3.3
Ylides

Although the phosphorus and sulfur ylides of nitrogen, called *iminophosphoranes* and *iminosulfuranes (sulfimides)*, respectively, are less well known than their carbon counterparts they do give nitrene products on irradiation. For example, photolysis of the *S,S*-dimethylsulfimide derived from *N*-phenylbenzamidine gives a high yield of 2-phenylbenzimidazole, presumably via cyclization of the intermediate imidoylnitrene to the aromatic ring (Scheme 6.11).

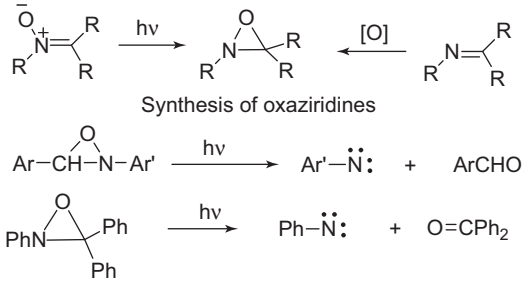
Thermolysis of the corresponding nitrogen–nitrogen ylide (an aminimide) gives the same product, as does photolysis of 1,5-diphenyltetrazole and 3,4-diphenyl-1,2,4-oxadiazol-5-one, which is strongly suggestive of a common intermediate, the nitrene. The same product is also formed by oxidation of *N*-phenylbenzamidine using lead(IV) acetate.



Scheme 6.11 Cyclization of an imidoyl nitrene generated from different precursors.

6.3.4
Small Rings

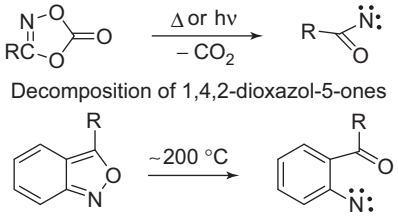
Irradiation of oxaziridines results in extrusion of a carbonyl compound and formation of a nitrene in a reaction analogous to the generation of carbenes from epoxides. Oxaziridines can be formed photochemically from nitrones or by oxidation of imines (Scheme 6.12).



Scheme 6.12 Photochemical generation of nitrenes from oxaziridines.

6.3.5
Heterocycles

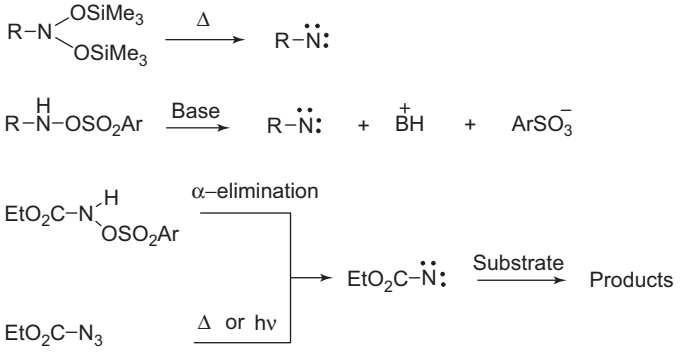
Five-membered heterocyclic rings, including those with aromatic stabilization that are able to undergo fragmentation with extrusion of nitrogen or carbon dioxide, readily decompose to give nitrenes on irradiation or vapor-phase thermolysis. For instance, 1,4,2-dioxazol-5-ones lose carbon dioxide on heating or irradiation to give acyl nitrenes (Scheme 6.13).



Scheme 6.13 Decomposition of heterocycles to give nitrenes.

6.3.6
α-Elimination

The synthetically useful α-elimination route to carbenes is less important in nitrene chemistry. Only a few substrates, such as N,O-bis(trimethylsilyl)hydroxylamines and *o*-arenesulfonylhydroxylamines, give nitrenes by an α-elimination reaction. Since N-halo compounds are often unstable and are prone to radical and ionic reactions, the most useful nitrene precursors of this type are *o*-arenesulfonylhydroxylamines ($RNHOSO_2Ar$), the reaction being best known for ethoxycarbonylnitrene. The elimination can be effected using an organic base such as triethylamine or under phase-transfer conditions. The fact that a genuine nitrene intermediate is involved is strongly suggested by the similar product distribution obtained from α-elimination of $EtO_2CNHOSO_2Ar$ and thermolysis or photolysis of EtO_2CN_3 (Scheme 6.14).

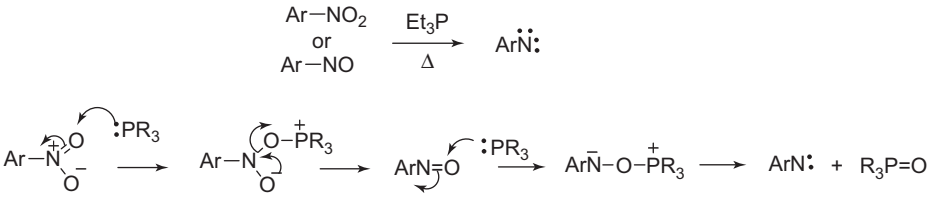


Scheme 6.14 Generation of nitrenes by α-elimination.

6.3.7
Reduction of Nitro and Nitroso Compounds

The deoxygenation of nitro and nitroso groups may generate nitrenes, which can be carried out with various reagents although trivalent phosphorus compounds, particularly triethyl phosphite, are most commonly used. The deoxygenation may

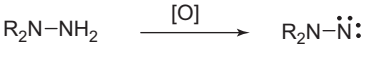
involve nucleophilic attack on oxygen by phosphorus followed by loss of the thermodynamically stable P=O compound, although alternatives are possible (Scheme 6.15).



Scheme 6.15 Possible mechanism for phosphorus(III)-mediated deoxygenation of nitro and nitroso compounds.

6.3.8
Oxidation of Amines

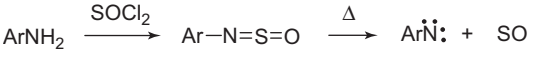
The removal of both hydrogens from a NH_2 group by oxidation formally results in generation of a nitrene although this is not a practicable route for most nitrenes. The oxidation of primary amines usually leads to many products. The oxidation of 1,1-disubstituted hydrazines is the method of choice for aminonitrenes. Various oxidants such as MnO_2, HgO, NiO_2, and phenyliodosoacetate [$PhI(OAc)_2$] can be used, but the most commonly employed reagent is lead(IV) acetate. The reactions are carried out at low temperature (typically −78 °C) in dichloromethane (DCM); with lead(IV) acetate oxidations there is the strong possibility that the true intermediate is an unstable acetoxy compound, $R_2NNHOAc$ rather than a free nitrene (Scheme 6.16).



Scheme 6.16 Generation of aminonitrenes by oxidation of 1,1-disubstituted hydrazines.

6.3.9
From Sulfinylamines

Sulfinylamines upon thermolysis produce aromatic nitrenes (Scheme 6.17).



Scheme 6.17 Thermolysis of sulfinylamines to give aromatic nitrenes.

6.4
Reactions of Nitrenes

Chemically nitrenes behave similarly to carbenes, that is, add to carbon–carbon (C=C) double bonds and insert into C–H single bonds. In addition, they isomerize to imines, abstract hydrogen atom to form primary amino groups, and effect ring closures. The singlet nitrenes add carbon–carbon double bonds stereospecifically, while the triplet nitrenes add to give both *cis*- and *trans*-aziridines. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

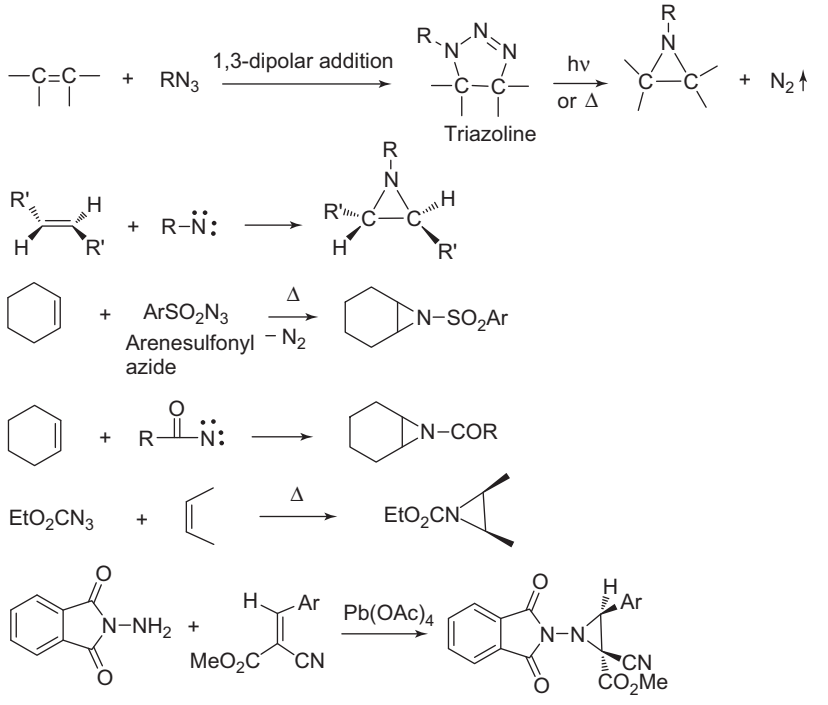
6.4.1
Cycloaddition Reactions of Nitrenes

6.4.1.1 Cycloaddition to Alkenes

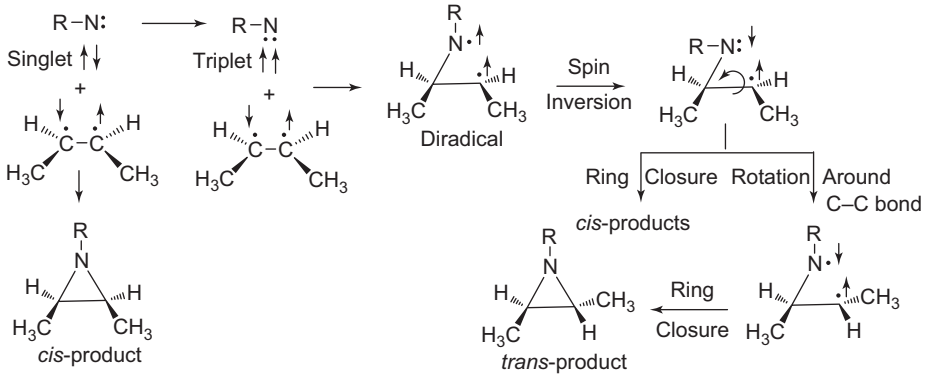
The formation of aziridines by the 1,2-addition of nitrenes to alkenes mirrors the corresponding reaction of carbenes to give cyclopropanes, although it is not as general in its scope. Since nitrenes are generally electrophilic, the reaction works best for nucleophilic alkenes, and the stereochemistry of the resulting aziridine is usually dependent on the spin state of the nitrene. Thermal decomposition of ethyl azidoformates in neat *cis*-but-2-ene gives the singlet nitrene, which adds largely stereospecifically to the alkene to give the *cis*-aziridine. Thus, singlet nitrene reacts with retention of configuration. However, as the reaction mixture is diluted with an inert solvent, collisional decay to the triplet ground state readily occurs and the reaction becomes less stereospecific. The reaction has been carried out with R = aryl, cyano, EtO_2C, and RSO_2 as well as other groups (Scheme 6.18). The mechanistic details of nitrene cycloaddition are displayed in Scheme 6.19.

Alkenyl and allyl azides give nitrenes, which undergo intramolecular addition to give highly strained compounds (Scheme 6.20). Conversely, addition of triplet (radical) traps such as dienes or α-methylstyrene increases the stereospecificity by selective removal of the triplet. Photolysis is less stereospecific since a higher percentage of the nitrenes is generated directly as triplets.

Aminonitrenes such as phthalimidonitrene, being ground state singlets, usually add stereospecifically to alkenes and because of their somewhat nucleophilic nature also add to electron-deficient double bonds. In contrast, aryl nitrenes do not usually undergo addition to alkenes, although if aryl azides are used as precursors the reaction certainly occurs. This turns out to be a general problem in azide/nitrene chemistry, since azides are reactive 1,3-dipoles, which readily undergo cycloaddition to alkenes to give the five-membered heterocycles 1,2,3-triazolines. These may subsequently lose nitrogen to give aziridines, presumably by way of a diradical intermediate, with the consequent loss of alkene stereochemistry (Scheme 6.21). Alkyl and aryl nitrenes undergo coupling to give azo compounds (Scheme 6.22).



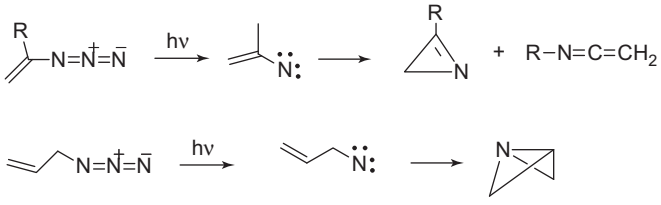
Scheme 6.18 Stereospecific addition of nitrenes to alkenes.



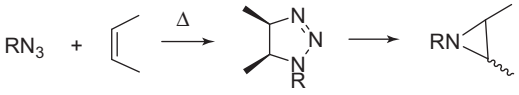
Scheme 6.19 Mechanistic aspects of nitrene cycloaddition.

6.4.1.2 **Cycloaddition to 1,3-Dienes**

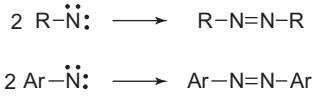
By analogy with carbenes, nitrenes undergo exclusive 1,2-addition to 1,3-dienes to give vinylaziridines, which on heating are transformed into dihydropyrroles. The reaction is known for various nitrenes, including ethoxycarbonylnitrene and



Scheme 6.20 Intramolecular addition of nitrene.

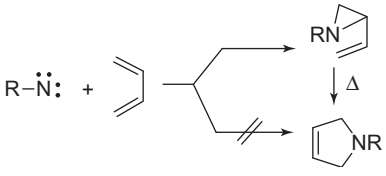


Scheme 6.21 Formation of aziridines by initial 1,3-dipolar cycloaddition of an azide.



Scheme 6.22 Coupling of alkyl and aryl nitrenes.

aminonitrenes, although when azides are used as precursors the non-nitrene 1,3-dipolar azide cycloaddition mechanisms may operate. In its intramolecular variant, the reaction has been used as a route to pyrrolizidine alkaloids (Scheme 6.23).



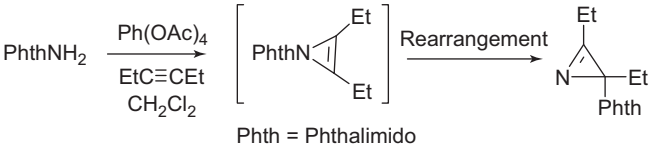
Scheme 6.23 1,2-Addition to 1,3-dienes to give vinylaziridines.

6.4.1.3 **Cycloaddition to Alkynes**

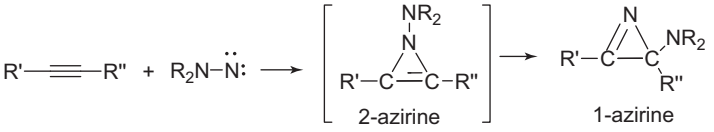
The addition of nitrenes to alkynes immediately presents a problem. The initial product of addition to the triple bond is a 1*H*-azirine, a species that is formally anti-aromatic, since it is planar and has four delocalizable π electrons (including the nitrogen lone pair). In the case of phthalimidonitrene the presumed intermediate 1*H*-azirine, formed by cycloaddition to 3-hexyne, readily rearranges to the stable 2*H*-isomer (Scheme 6.24).

Aminonitrenes (R_2NN) have been shown to add to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines, which are unstable due to anti-aromaticity (Scheme 6.25).

Attempts to add nitrenes derived by heating azides to alkynes are usually thwarted by the facile addition of the azide 1,3-dipole to the triple bond with the formation

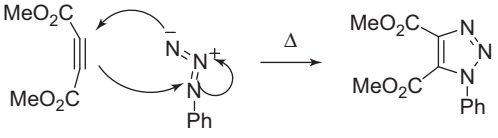


Scheme 6.24 Addition of phthalimidonitrene to an alkyne to give 2*H*-azirine.



Scheme 6.25 Addition of aminonitrene to alkynes.

of a stable aromatic 1,2,3-triazole (Scheme 6.26). Acyl-nitrenes can also act as 1,3-dipoles, and add to alkynes to give oxazoles in a reaction analogous to the formation of furans from acylcarbenes and alkynes.



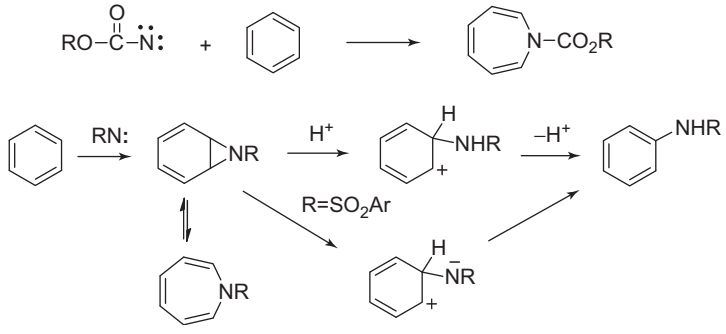
Scheme 6.26 1,3-Dipolar cycloaddition of an azide to an alkyne to give 1,2,3-triazole.

6.4.1.4 **Cycloaddition to Arenes**

Benzene and its derivatives react with nitrenes to give ring-expanded products and/or N-substituted anilines. Both types of product are formed by initial nitrene attack on the π-system, presumably by the singlet, to give an azanorcaradiene intermediate, which undergoes electrocyclic rearrangement to the azepine. In the case of ethoxycarbonylnitrene ($R = CO_2Et$) generated from the azide or by α-elimination, azepines are isolated, although rearrangement to the aniline derivative occurs readily in the presence of acid. The corresponding reaction of sulfonylnitrenes ($R = SO_2Ar$), even in the absence of acid, usually gives sulfonylanilines, which may arise from the azepine or directly from the azanorcaradiene by an alternative pathway due to the enhanced stability of the incipient sulfonamide anion (Scheme 6.27).

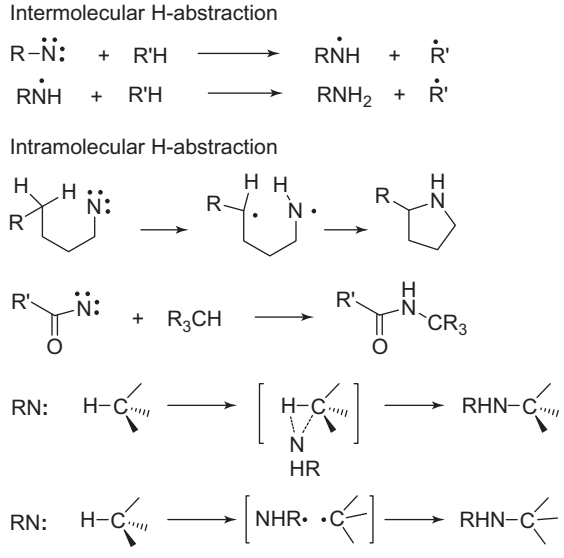
6.4.2 **Insertion Reactions of Nitrenes**

Nitrenes like carbenes readily insert into single bonds. Carbonyl nitrenes are very reactive species and insert into the C–H bonds of alkanes to give amides or carbamates. The order of reactivity among alkane C–H bonds is



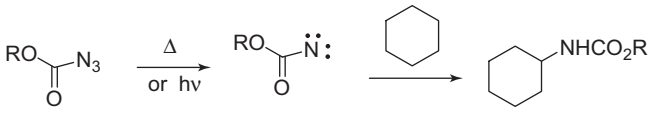
Scheme 6.27 Addition of a nitrene to an aromatic ring.

tertiary > secondary > primary. The overall process of insertion reaction can occur by different mechanisms, although most of the preparatively useful C–H insertion reactions are believed to involve direct insertion of the singlet nitrene rather than a stepwise H abstraction–recombination mechanism involving the triplet. Both mechanisms are shown below (Scheme 6.28). Retention of configuration is found at a chiral carbon. However, many reactions that lead to products with a new C–N bond that are the formal result of C–H insertion proceed by an entirely different mechanism.



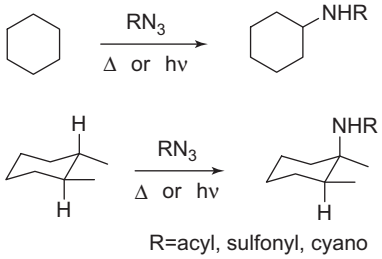
Scheme 6.28 Insertion of singlet and triplet nitrenes into a C–H bond.

Carboalkoxynitrenes generated from azidoformates undergo insertion reactions with saturated hydrocarbons (Scheme 6.29). Triplet nitrenes do not insert into alkyl C–H bonds.



Scheme 6.29 Insertion of nitrene into a saturated hydrocarbon.

The importance of the C–H insertion reaction of nitrenes lies in the fact that it is a potentially useful way of functionalizing unactivated C–H bonds, converting hydrocarbons into amine derivatives. The reaction is highly dependent on the substituents on nitrogen; for example, cyclohexane only gives good yields of aminocyclohexane derivatives with acyl-, sulfonyl-, and cyanonitrenes, generated by thermal or photochemical decomposition of the corresponding azides (Scheme 6.30). Alkyl nitrenes give very poor yields of insertion products because of the competing rearrangement by 1,2-hydrogen shift and aryl nitrenes often give anilines by hydrogen abstraction by the triplet.



Scheme 6.30 Functionalization of cyclohexanes by nitrene insertion.

For all nitrenes studied, the selectivity of C–H insertion follows the expected pattern of reactivity, decreasing in the order: tertiary > secondary > primary C–H, although there is considerable variation in the degree of selectivity. For example, the relative reactivities of tertiary, secondary, and primary C–H bonds in 2-methylbutane toward ethoxycarbonylnitrene is approximately 30 : 10 : 1, whereas the corresponding values for methanesulfonylnitrene are 10 : 4 : 1.

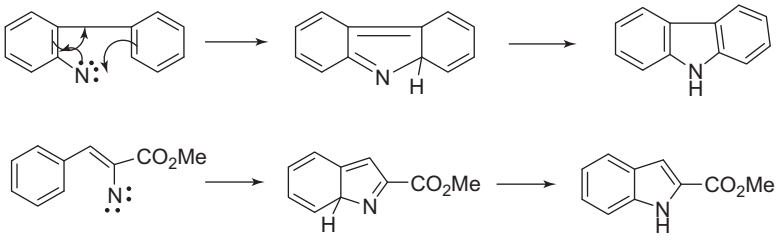
The selectivity of nitrene insertion reactions has been widely studied using substituted cyclohexanes as substrates. For aryl nitrenes exhibiting triplet reactivity, the reaction is often low yielding and non-stereospecific, but ethoxycarbonyl-, methanesulfonyl-, and cyanonitrenes all insert with retention of configuration into the tertiary C–H bond of both *cis* and *trans* 1,2-dimethylcyclohexane. When optically active substrates are used virtually complete retention is again observed, with ethoxycarbonylnitrene inserting with 98–100% retention into the tertiary C–H bond of (*S*)-3-methylhexane. The result is independent of the method of nitrene generation, and of concentration, confirming the view that only the singlet species inserts into unactivated C–H bonds.

Although aryl nitrenes often give poor yields of intermolecular C–H insertion products, the intramolecular reaction works well, and proceeds with retention

of configuration at the reacting center as shown by the example below (100% retention). Intramolecular C–H insertion reactions of other nitrenes have also found use in synthesis. The cyclization step is thought to take place by direct insertion of singlet nitrene into the C–H bond, and not through a diradical intermediate. Optically active azide gave the optically active indoline. A diradical intermediate would have been expected to give an optically inactive product. For example, heating of 2-(2-methylbutyl) phenyl azide gave 2-ethyl-2-methylindoline (Scheme 6.31).

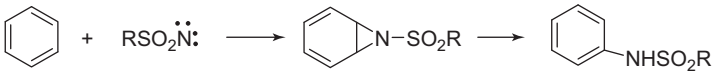
Scheme 6.31 Intramolecular nitrene C–H insertion with retention of configuration.

Formal insertions into aromatic C–H bonds often proceed by another mechanism. This is also true in intramolecular cases, and the formation of carbazole from biphen-2-ylnitrene, a well-studied example, probably occurs by an electrocyclic reaction followed by 1,5-hydrogen shift. The high yielding synthesis of indoles from azidocinnamates proceeds similarly by cyclization of a vinyl nitrene (Scheme 6.32).



Scheme 6.32 Electrocyclic ring closure of aryl and vinyl nitrenes.

Sulfonylnitrenes are formed by thermal decomposition of sulfonyl azides. Insertion reactions occur with saturated hydrocarbons. With aromatic rings the main products are formally insertion products, but they are believed to be formed through addition intermediates (Scheme 6.33).

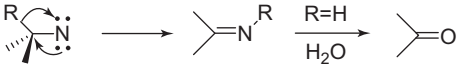


Scheme 6.33 Insertion of sulfonyl nitrene into an aromatic ring.

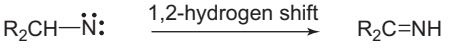
6.4.3
Rearrangement of Nitrenes

Rearrangements of aromatic and heteroaromatic nitrenes can be initiated with either heat or light. The thermal reaction is typically induced by flash vacuum thermolysis, with isolation of the products at low temperatures. Photochemical experiments are conducted either under matrix isolation conditions or in solution at ambient temperature. These rearrangements are usually initiated by ring expansion of the nitrene to a seven-membered ring ketenimine or carbodiimide (i.e., an azacycloheptatetraene).

The rearrangement by a 1,2-shift of an atom or group from the adjacent carbon to the electron-deficient center, which occurs so readily with carbenes, is also a characteristic reaction of nitrenes. When the migrating group is hydrogen, the rearrangement is particularly facile and hence other intermolecular reactions, such as cycloaddition involving alkyl nitrenes, are rarely seen. The rearrangement results in the formation of an imine, which if unsubstituted on nitrogen is easily hydrolyzed to the corresponding carbonyl compound (Scheme 6.34). Hydrogen atoms move fastest because of their low mass.

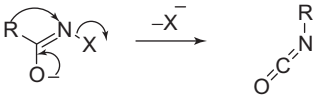


R = H>> aryl > alkyl; relative migratory apptitude of groups in nitrenere arrangements



Scheme 6.34 Rearrangement of nitrene by a 1,2-shift.

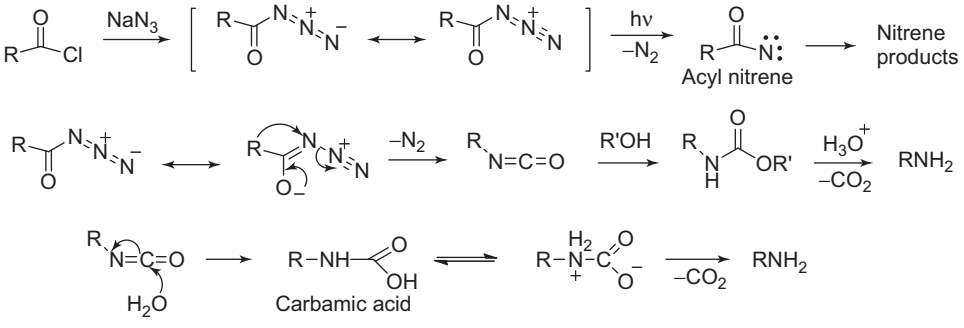
The nitrene analogs of the Wolff rearrangement are the well-known Curtius, Hofmann, and Lossen reactions. There is a group of closely related rearrangements in which carbon migrates from carbon to nitrogen, where R is an alkyl or aryl group and –X is a leaving group that may be –Br (*Hofmann rearrangement*), $–N_2$ (*Curtius* and *Schmidt rearrangements*), and –OCOR (*Lossen rearrangement*). In each case if the migrating group is asymmetric it retains its stereochemical configuration (Scheme 6.35).



Scheme 6.35 Rearrangement in nitrenes.

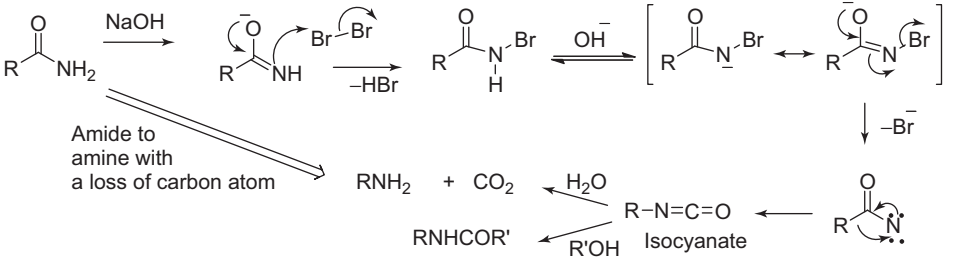
The Curtius rearrangement involves pyrolysis of an acyl azide that expels molecular nitrogen and at the same time rearranges to an isocyanate (the azides

may be made by nucleophilic substitution on an acyl chloride by sodium azide or by the reaction of acyl hydrazides with nitrous acid). Azides must be treated with caution as they may decompose explosively. The isocyanate may be isolated by carrying out the reaction in an aprotic solvent such as chloroform but, generally, alcoholic solvent is used, with which the isocyanate reacts to form a urethane. Overall, then the Curtius rearrangement converts an acid chloride into an amide with loss of a carbon atom (Scheme 6.36).



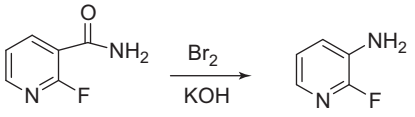
Scheme 6.36 Curtius rearrangement.

The Hofmann rearrangement occurs through a pathway similar to that for the Beckmann rearrangement. The first step in the reaction sequence is the formation of the N-bromoamide, which then undergoes removal of the remaining proton on the nitrogen, the acidity of which is enhanced due to the presence of the electronegative bromine in addition to the acyl group. The deprotonated intermediate subsequently undergoes rearrangement by what is generally accepted to be a concerted mechanism although a two-step process involving loss of bromide and formation of a nitrene would also be compatible with the data available (Scheme 6.37).



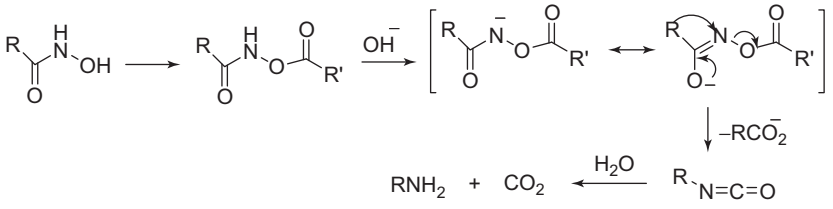
Scheme 6.37 Hofmann rearrangement.

The reaction has been useful in the conversion of aromatic amides into aromatic amines (Scheme 6.38).



Scheme 6.38 Conversion of amide into amine.

The Lossen rearrangement differs from the Hofmann rearrangement only in that the leaving group is carboxylate anion rather than bromide ion. The starting material is the ester of hydroxamic acid (RCONHOH), which is decomposed in presence of base. The hydroxamic acids exhibit tautomerism – the *keto*-form is termed *hydroxamic form* while the *enol*-form is called *hydroximic acid*. As the reaction is normally carried out in water, the process furnishes the amine directly (Scheme 6.39).



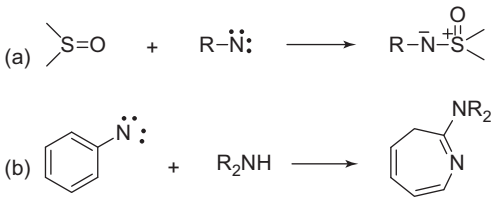
Scheme 6.39 Lossen rearrangement.

Since leaving group R′COO leaves as $R'COO^-$, the rearrangement is facilitated by the presence of electron-withdrawing groups in *meta* or *para* positions. Of these four related processes the Lossen rearrangement is the least useful in the synthesis of amines because of the unavailability of hydroxamic acids.

6.4.4
Reactions of Nitrenes with Nucleophiles

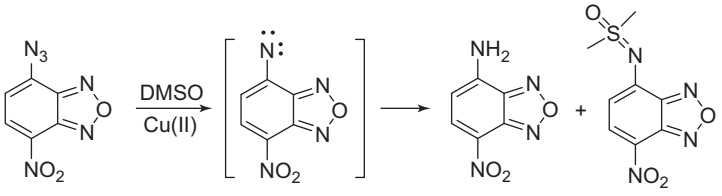
Nitrenes for the most part being electron deficient are highly electrophilic intermediates and therefore react with nucleophiles of all types. Tertiary amines, phosphines, sulfides, and sulfoxides all react with nitrenes to give ylides, in a reaction that is the reverse of their formation. In practice, dimethyl sulfoxide (DMSO) is often the most convenient nucleophilic trap since it can be used as the reaction solvent, and gives relatively stable sulfoximides (Scheme 6.40). Azo compounds, which are formally nitrene dimers, are common by-products in many nitrene reactions. However, the dimerization of two highly reactive species in solution is extremely unlikely on statistical grounds, and therefore the mechanism of azo compound formation probably involves the reaction of a nitrene, as an electrophile, with its precursor.

7-Azido-nitrobenzoxadiazole (azido-NBD) was observed to undergo a ''reduction'' reaction in the absence of an obvious reducing agent, leading to amine formation. In

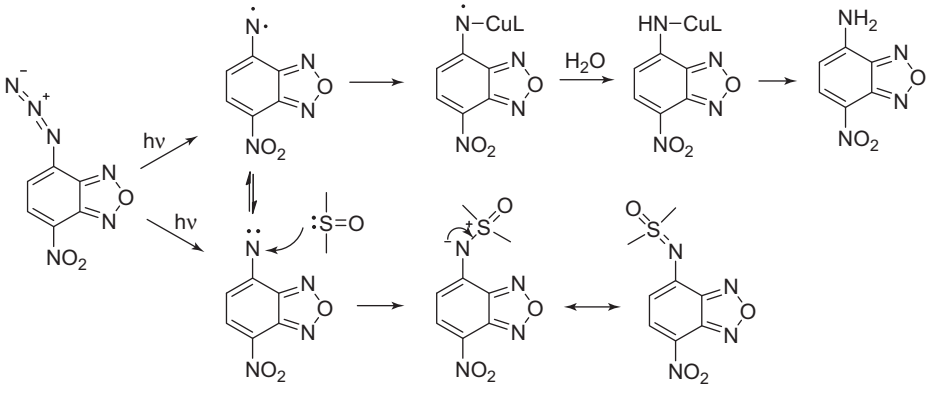


Scheme 6.40 (a) DMSO as a nucleophilic trap for nitrenes; (b) insertion of nitrene into amine.

the presence of an excess amount of DMSO, a sulfoxide conjugate was also formed. The ratio of these two products was both temperature- and solvent-dependent, with the addition of water significantly enhancing the ratio of the "reduction" product. Two intermediates of the azido-NBD reaction in DMSO were trapped and characterized by low-temperature EPR (electron paramagnetic resonance) spectroscopy. One was an organic free radical ($S = 1/2$) and the other was a triplet nitrene ($S = 1$) species (Schemes 6.41 and 6.42).



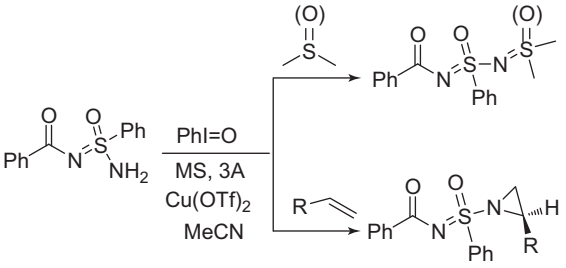
Scheme 6.41 The copper-catalyzed azido-NBD nitrene reaction in DMSO.



Scheme 6.42 Proposed mechanisms of the azido-NBD "reduction" reaction leading to the amine product via a triplet intermediate and DMSO conjugate formation.

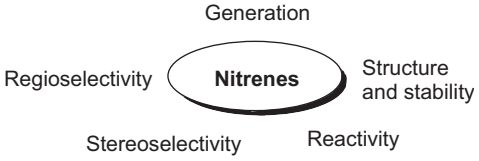
Sulfonimidamides lead efficiently to nitrenes and have been converted into sulfimides, sulfoximines, and aziridines in good yields through a copper-mediated

multicomponent reaction. The stereogenic sulfur atom and the trivalent nitrogen atom present in the molecules open the way to asymmetric synthesis (Scheme 6.43).



Scheme 6.43 Nitrene formation from sulfonimidamides.

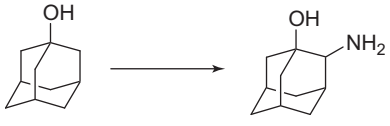
6.5 Summary



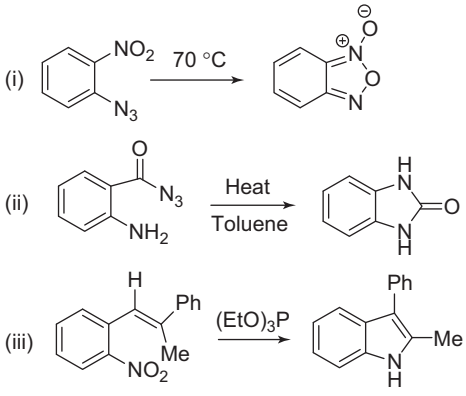
- The diatomic molecule NH and its derivatives R–N are usually referred to as *nitrenes*, with six electrons on the nitrogen.
- Nitrenes are monovalent nitrogen species, and are isoelectronic with carbenes.
- Nitrenes like carbenes are immensely reactive and electrophilic.
- The chemistry of nitrenes closely parallels that of carbenes in virtually all aspects.
- Like carbenes there is the possibility of two spin states for nitrenes, depending on whether the two nonbonding electrons have their spins paired or parallel.
- In general, nitrenes obey Hund's rule and are ground state triplets with two degenerate sp-orbitals containing a single electron each, although the nitrogen atom in the singlet is usually represented as sp^2-hybridized.
- Although nitrenes are isoelectronic with carbenes there are important differences in their electronic structures, which accounts for their different reactivity.
- Chemically nitrenes behave similarly to carbenes, that is, they add to carbon–carbon double bonds and insert into C–H single bonds. In addition they isomerize to imines, abstract a hydrogen atom to form primary amino groups, and effect ring closures.
- Substituents have been shown to alter the nitrene's reactivity to favor one reaction over another.
- Nitrenes take part in Curtius, Schmidt, Hofmann, and Lossen rearrangements.

Problems

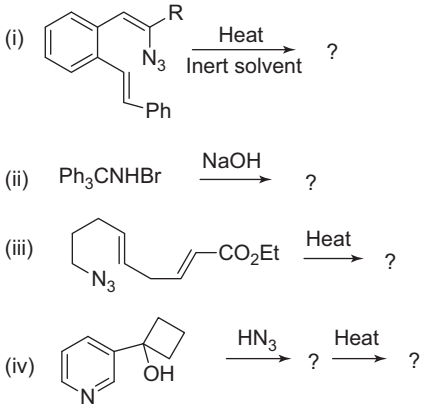
1. What are nitrenes? How they are generated? Discuss their structure and stability.
2. Discuss the electronic and steric factors influencing the stability and reactivity of triplet and singlet nitrenes.
3. Suggest a nitrene-based route for the conversion of 1-adamantol into 2-amino-1-adamantol.



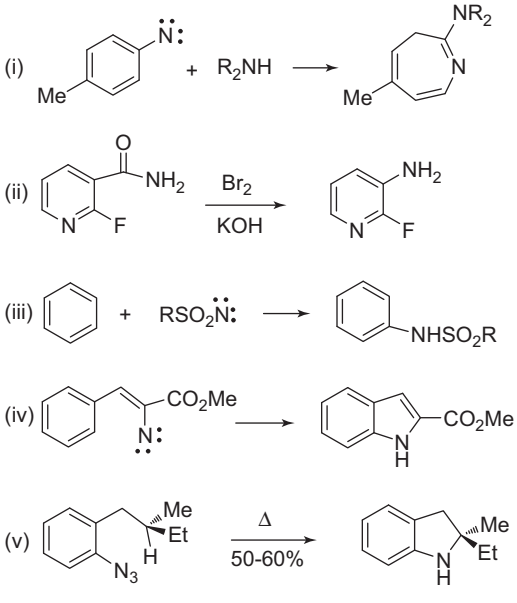
4. Write a suitable mechanism for the following transformations.



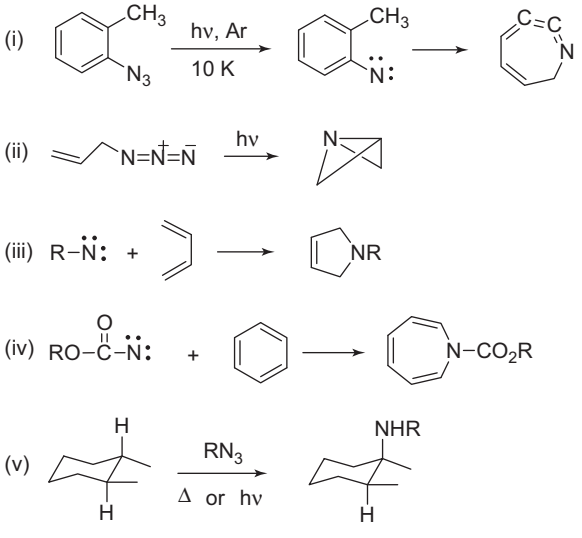
5. Predict the possible product(s) from the following reactions.



6. Discuss the state of hybridization of singlet and triplet nitrenes.
7. A reaction between nitrene and *cis*-2-butene gave a mixture of *cis*- and *trans*-1,2-dimethylcyclopropane. What does this tell us about the electronic configuration of the nitrene in this reaction?
8. Write suitable mechanisms for the following reactions.



9. Rationalize the following reactions.



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7
Miscellaneous Intermediates

7.1
Arynes

7.1.1
Introduction

More recent techniques to characterize reactive intermediates include: (i) matrix isolation spectroscopy, where a reactive intermediate is generated in a cryogenic noble-gas matrix and hence can be studied for an extended period of time; (ii) laser flash photolysis, where the reactive intermediate is generated by a very short pulse of laser light and can be investigated in real time; and (iii) specialized mass-spectrometric techniques such as ion cyclotron resonance MS. Owing to the exponential increase in computing power available to researchers, much of the mechanistic work nowadays is being carried out using the tools of quantum chemistry. In particular, the various flavors of density functional theory (DFT) have proven valuable in this respect, but high-level correlated methods such as CCSD(T) also have their place. Coupled cluster (CC) is a numerical technique used for describing many-body systems. Its most common use is as one of several post-Hartree–Fock *ab initio* quantum chemistry methods in the field of computational chemistry. It essentially takes the basic Hartree–Fock molecular orbital method and constructs multi-electron wave functions using the exponential cluster operator to account for electron correlation. Some of the most accurate calculations for small to medium sized molecules use this method.

Arynes are highly reactive species, which have attracted much attention because of their intriguing structure and properties. Various methods of aryne generation have been developed so far enabling the straightforward construction of diverse aromatic molecules with successful application to several total syntheses of complex natural products. Arynes and heteroarynes are derived formally by the removal of two adjacent (*ortho*-) substituents from aromatic or heteroaromatic rings, respectively, leaving behind two electrons to be distributed between two orbitals. Although in most cases the substituents are *ortho* to one another, this is not a prerequisite and *meta*- and *para*-arynes are also possible intermediates.

The most common aryne is based on benzene itself, although all aromatic and heteroaromatic systems can potentially give similar species. The need to postulate a

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Maya Shankar Singh.

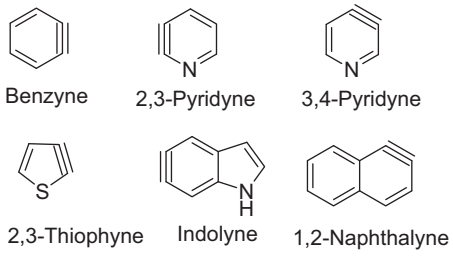


Figure 7.1 Representative examples of aryne intermediates.

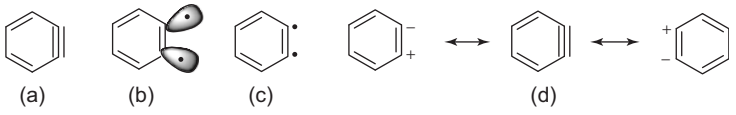


Figure 7.2 Structures of *ortho*-benzyne.

benzyne intermediate (C_6H_4) arose in the 1870s in order to explain the formation of biphenyl in certain reactions. The first correct formulation of a related intermediate from benzofuran was put forward in 1902. It was not until the 1940s when Wittig advanced clear and convincing arguments for the intermediacy of arynes. This was followed in 1953 by the classic isotopic labeling experiments of Roberts and Diels and Alder, and trapping by Wittig in 1955, which finally confirmed the existence of benzyne. Figure 7.1 displays some representative examples of aryne reactive species. While arynes are usually best described as having a strained triple bond they also possess, however, some biradical character.

The aryne nomenclature derives from the fact that the *ortho*-isomer of C_6H_4 (*ortho*-benzyne) can be represented as an alkyne, although systematically the species should be named as a didehydroaromatic compound. Hence, *ortho*-benzyne is 1,2-didehydrobenzene and 3,4-pyridyne is 3,4-didehydropyridine, and so on. Nevertheless, the aryne nomenclature remains in common use and will be used here throughout. Although many arynes have been implicated as intermediates, by far the most studied species is *ortho*-benzyne. Representations of *ortho*-benzyne showing (a) the alkyne structure resulting from (b) lateral overlap of the two *p*-orbitals, (c) diradical structure, and (d) dipolar ion structures are displayed in Figure 7.2. Dipolar structures (Figure 7.2d) explain the electrophilic character of benzyne.

7.1.2 Structure and Reactivity

Arynes were first postulated by Georg Wittig in 1940 followed by Roberts in 1953. The discovery of benzyne led to rapid developments in synthetic methodologies to make use of this highly reactive intermediate in various organic transformations. To date, various natural products have been prepared using arynes as intermediates. Examples of such natural products are cryptaustoline, (+)-liphagal,

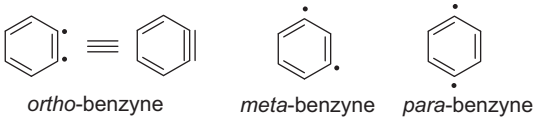


Figure 7.3 *ortho*-, *meta*-, and *para*-benzynes.

dehydroaltenuene B, herbindole A, taxodione, melleine, and many others. Perhaps one of the most famous reactions of arynes is the Bergman cyclization, which lies at the core of the mechanism of action of enediyne cytostatics. Three isomers are possible for benzyne: *ortho*-benzyne, *meta*-benzyne, and *para*-benzyne (Figure 7.3). Their energies calculated *in silico* are 106, 122, and 138 kcal mol^{-1} (444, 510, and 577 kJ mol^{-1}), respectively.

ortho-Benzyne is usually represented as a singlet molecule with a carbon–carbon triple bond. This strained π-bond is formed by lateral overlap of the two orbitals in the plane of the ring. The alternative structure is a diradical, either singlet or triplet, although most of the chemistry of the species is in accord with the alkyne structure. In fact one π bond is normal and is just part of the aromatic system. The new π bond formed by the overlap of two sp^2 orbitals outside the ring is abnormal and quite strained. This external π bond is very weak, which is why benzyne is a very unstable and highly reactive intermediate. Theoretical calculations support the view that the symmetrical triple bond structure is lowest in energy, and suggest that the structure is distorted from benzene with estimates for the carbon–carbon triple bond length in the range 1.25–1.34 Å (cf. 1.20 Å for ethyne and 1.39 Å for benzene). The geometric distortion is compensated by the greater lateral p-orbital overlap, although this overlap is still relatively poor compared with that in a normal π-bond. A direct consequence of the strained alkyne bond is that arynes have low-lying LUMOs (lowest unoccupied molecular orbitals), and hence the energy gap between the HOMO (highest occupied molecular orbital) and LUMO is small.

In accord with this, *ortho*-benzyne shows the properties of a highly reactive alkyne, participating in a range of cycloaddition reactions. In other reactions, however, *ortho*-benzyne resembles a carbene, having the similar electronic arrangement of two electrons distributed between two orbitals and behaves as a powerful electrophile, a second consequence of its low lying LUMO. Recently, with the advent of sophisticated experimental techniques, benzyne has been observed directly using laser flash photolysis, to obtain its UV spectrum, and matrix isolation to record the IR spectrum. In the latter experiment an intermediate, controversially assigned as *ortho*-benzyne with IR absorption of 2085 cm^{-1} typical of a carbon–carbon triple bond, was observed.

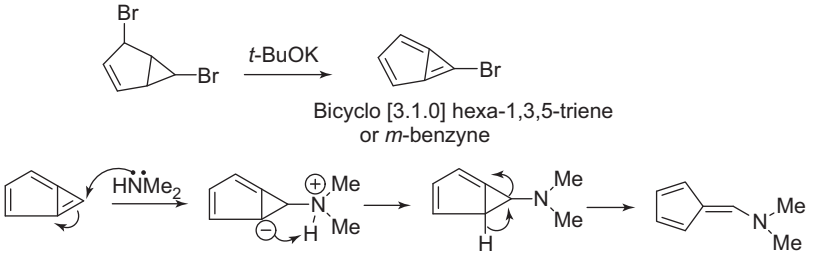
The triple bond in *ortho*-benzyne can be stabilized by complexation with transition metals. Aryne–metal complexes were originally proposed as intermediates in the decomposition of various aryl derivatives of early transition metals, and the first fully characterized mononuclear *ortho*-benzyne complex, $TaMe_2(\eta^5\text{-}C_5Me_5)(\eta^2\text{-}C_6H_4)$, was prepared. Although this method does not appear general for all transition metals, various complexes of zirconium, rhenium, and niobium have been characterized. More recently, complexes of nickel and platinum have also been

prepared. For example, oxidative addition of 1,2-dibromobenzene to a nickel(0) complex of ethene followed by reduction with sodium amalgam gives the *ortho*-benzyne nickel complex. The same complex can be prepared by generating *ortho*-benzyne from fluorobenzene in the presence of the nickel ethene complex. X-Ray crystallographic analysis shows that the metal atom and the two aryne carbons form a metallocyclopropene ring. More impressive still perhaps is the successful preparation of benzdiyne complexes. Benzdiyne is unknown in the free-state but can be stabilized on a transition metal; zirconium, nickel, and platinum complexes have been fully characterized. Although aryne transition metal complexes undergo a range of fascinating reactions, their potential in organic synthesis remains to be fully exploited.

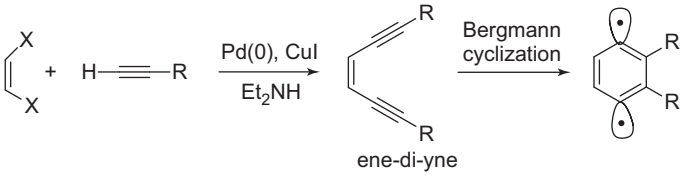
In 1953, Robert's experiments on the conversion of ^{14}C-labeled chlorobenzene with KNH_2 into aniline gave strong support to the intermediacy of *ortho*-benzyne in this and related reactions. Additional direct evidence for the existence of *ortho*-benzyne was provided by the observation of its IR spectrum, solid-state ^{13}C dipolar NMR spectrum, ^{1}H and ^{13}C NMR in a molecular container, and by UV photoelectron spectroscopy. Even at low temperatures, arynes are extraordinary reactive. The reactions of arynes can be divided into three groups: (i) pericyclic reactions, (ii) nucleophilic additions, and (iii) transition-metal catalyzed reactions. The pericyclic reactions can be divided into several categories such as Diels–Alder reactions, [2+2] cycloadditions, 1,3- and 1,4-dipolar cycloadditions, and the ene reactions. Arynes react with practically all kinds of nucleophiles. More recently, the transition-metal catalyzed reactions of arynes have been studied, in particular those involving palladium.

The removal of two substituents from the *meta*-positions of a benzene ring leaving two electrons in two orbitals should generate *meta*-benzyne. The benzyne nomenclature is still used for these intermediates despite the fact that there is no formal carbon–carbon triple bond present, and the species is more correctly named as 1,3-didehydrobenzene. The structure can be represented either as diradicals or bicyclic compounds with 1,3-bonding. In the case of *meta*-benzyne, calculations suggest that the bicyclic species bicyclo[3.1.0]hexa-1,3,5-triene, although highly strained, is more stable than the 1,3-diradical, and some experimental evidence has been obtained. *meta*-Benzyne can be trapped in a reaction mixture by dimethylamine, and the adduct thus formed is unstable and undergoes ring opening to give fulvene as the final product (Scheme 7.1). Allylic hydrogen is acidic in nature hence can be abstracted by strong base.

The removal of two substituents from the *para*-positions of a benzene ring leaving two electrons in two orbitals should generate *para*-benzyne. In contrast to *meta*-benzyne, the diradical form of *para*-benzyne appears to be lower in energy than the highly strained bicyclo[2.2.0]hexa-1,3,5-triene (butalene). Evidence for the existence of the diradical, often termed *benz-1,4-diyl*, was obtained by Bergman in the early 1970s in the specific deuterium scrambling that was observed on heating 1,6-dideuteriohexa-1,5-diyn-3-ene (Scheme 7.2). The intermediate 1,4-diradical also abstracts chlorine from CCl_4 to give largely 1,4-dichlorobenzene. Furthermore, the diradical form of *para*-benzyne can be approached by thermal cyclization reactions of enediynes.

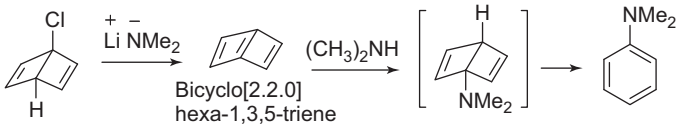


Scheme 7.1 Generation and trapping of *meta*-benzyne with dimethylamine to give fulvene.



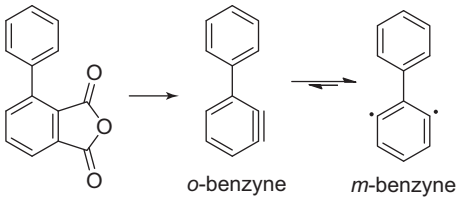
Scheme 7.2 Bergman cyclization of enediynes to give *para*-benzyne (benz-1,4-diyl).

Although the so-called Bergman cyclization has been known for over 40 years, it has very recently attained renewed significance, since a similar cyclization is believed to be the key step in the biological mechanism of action of calicheamicin/esperamicin and related enediyne antitumor agents. Upon biological activation, the enediyne cyclizes to give an intermediate *para*-benzyne, which is thought to abstract hydrogen from the DNA sugar backbone, and hence prevent replication. The chemical approach to the bicyclic form (butalene) involves a base-mediated elimination reaction. *para*-Benzyne can be prepared by the reaction of chlorobicyclo[2.2.0]hexadiene with $LiNMe_2$ at −10 °C to generates butalene, which can be trapped by dimethylamine to give an unstable compound, which further undergoes ring opening to give *N,N*-dimethylaniline (Scheme 7.3). A deuterium labeling experiment showed that the reaction is somewhat more complicated and direct displacement of chloride cannot be ruled out.



Scheme 7.3 Formation and trapping of *para*-benzyne.

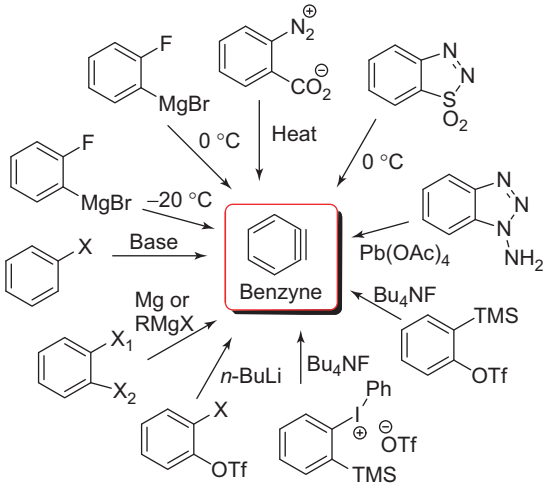
The interconversion of the 1,2-, 1,3-, and 1,4-didehydrobenzenes has been studied. A 1,2- to 1,3-didehydrobenzene conversion has been postulated to occur during pyrolysis (900 °C) of the phenyl substituted aryne precursors as shown in Scheme 7.4. Extremely high temperatures are required for benzyne interconversion.



Scheme 7.4 Interconversion of 1,2- and 1,3-didehydrobenzenes (*ortho* and *meta*, respectively).

7.1.3 Generation of Arynes

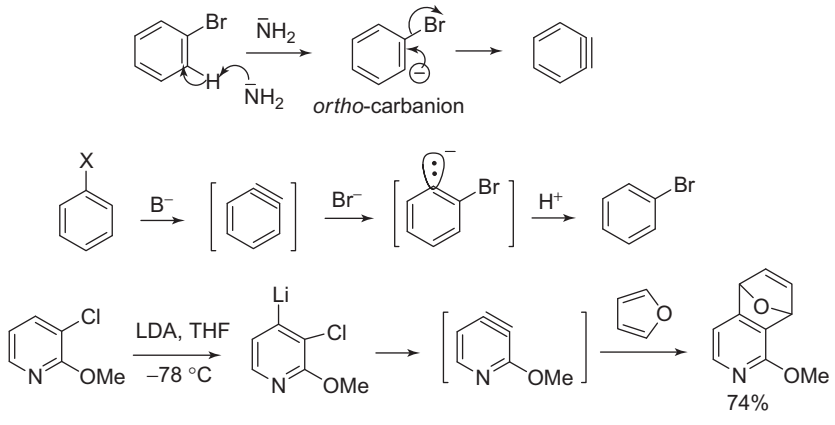
Scheme 7.5 summarizes the common methods of aryne generation, although the examples are limited to *ortho*-benzyne. Because of their extreme reactivity, arynes must be generated *in situ*. When an unactivated aryl halide is treated with a very strong base, an elimination reaction is possible, generating aryne.



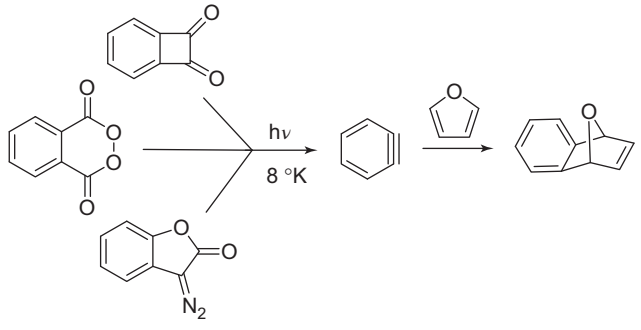
Scheme 7.5 Methods for the generation of *ortho*-benzyne.

Benzyne is electron-deficient and will be attacked by nucleophiles in a reaction that opens the π bond not part of the aromatic cloud, and produces a new carbanion. Protonation completes the sequence to give the aromatic substitution product (Scheme 7.6). Irradiation of either benzocyclobutenedione or phthaloyl peroxide or 3-diazobenzofuranone at 8 K in an argon matrix led to eventual formation of *ortho*-benzyne (Scheme 7.7).

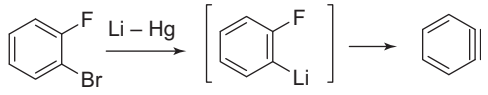
ortho-Benzyne can also be generated from *ortho*-dihaloaromatics. The reaction of lithium amalgam or magnesium affords a transient organometallic compound that decomposes with elimination of lithium halide to yield *ortho*-benzyne. 1-Bromo-2-fluorobenzene is the usual starting material in this procedure (Scheme 7.8).



Scheme 7.6 Generation and reactions of *ortho*-benzyne.



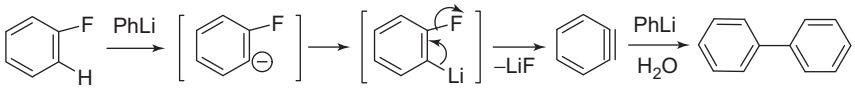
Scheme 7.7 Low-temperature photolytic generation of *ortho*-benzyne.



Scheme 7.8 Generation of *ortho*-benzyne from *o*-dihaloaromatics.

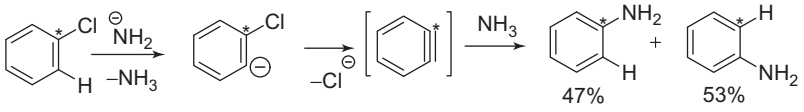
The elimination of a leaving group from the *ortho*-position of a metalated aromatic ring is historically the most important route to arynes. Although arynes had long been suggested as intermediates in such reactions, it was not until the 1940s that Wittig put the subject on a clear experimental footing. In studying the formation of biphenyl from the reaction of halobenzenes with phenyllithium he found that the rate was fastest for fluorobenzene. Since this was not the expected result for a simple displacement reaction (fluoride is a worse leaving group than chloride or bromide), an alternative mechanism was suggested whereby the strongly electronegative fluorine facilitated removal of the *ortho*-proton to give 2-fluorophenyllithium (in modern terminology this may be described as a directed lithiation reaction). Loss

of lithium fluoride from this formal anion generates benzyne, which rapidly reacts with the strongly nucleophilic phenyllithium and, finally, quenching with water during work-up gives biphenyl (Scheme 7.9).



Scheme 7.9 Generation of *ortho*-benzyne from directed lithiation.

The ^{14}C-labeling experiments of Roberts in 1953 put the existence of *ortho*-benzyne as an intermediate beyond doubt when it was found that treatment of 1-^{14}C-chlorobenzene with potassium amide in liquid ammonia gave a 1 : 1 mixture of 1- and 2-^{14}C labeled aniline. The reaction had clearly proceeded through a symmetrical intermediate *ortho*-benzyne. The overall process whereby a nucleophile apparently enters *ortho* to the leaving group is referred to as *cine substitution* (Scheme 7.10).

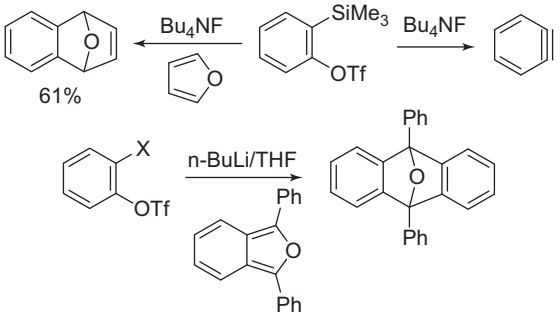


Scheme 7.10 *Ipso* and *cine* substitution through an *ortho*-benzyne intermediate.

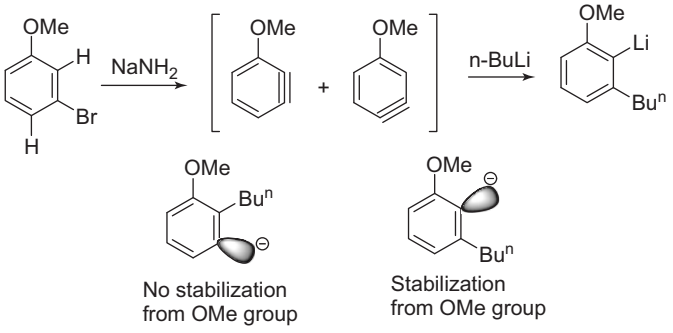
Milder methods for benzyne generation have also been developed. Aryl triflates have been widely used in synthesis. Fluoride displacement of the trimethylsilyl group allows for generation of benzyne under mild conditions (Scheme 7.11). The *ortho*-metalation of aromatic halides followed by loss of metal halide is now a firmly established route to *ortho*-arynes. Several bases can be used such as alkali metal amides ($LiNH_2$, $NaNH_2$, etc.), alkyllithiums, lithium amides ($LiNR_2$), potassium *tert*-butoxide, and so on. Some examples of *ortho*-benzyne generation are displayed in Scheme 7.11. The use of trifluoromethanesulfonate (triflate, OTf) as a superior leaving group to halide is a noteworthy modern advance, particularly when combined with the use of the trimethylsilyl group, which on treatment with fluoride ion gives the aryl anion. Precursors that can give aryl anions by other mechanisms are also potential sources of arynes, for example, base-induced cleavage of aryl ketones.

In cases where two possible arynes could be formed from a single precursor, the result will depend on the relative rates of the two steps involved in aryne generation. If the formation of the anion is rate determining then this will control which aryne is formed. For example, lithiation of 3-methoxy-1-bromobenzene occurs at the 2-position since it is directed by the oxygen substituent, and provided a single benzyne because the loss of bromide is faster (Scheme 7.12). Likewise, powerful *ortho*-directing substituents such as the oxazoline group can be used to control aryne formation.

Probably the most important of all precursors to *ortho*-benzyne is benzenediazonium-2-carboxylate. The compound is easily prepared by

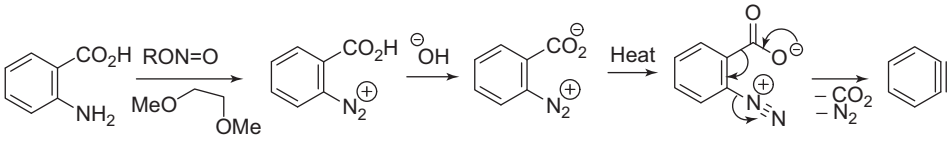


Scheme 7.11 Generation of *ortho*-benzyne from aryl triflates.



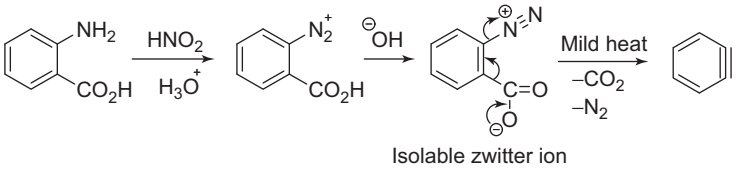
Scheme 7.12 Formation of unsymmetrical arynes.

diazotization of 2-aminobenzoic acid (anthranilic acid) using nitrous acid, and can be isolated as a solid provided it is kept moist. On no account should one attempt to obtain the salt as a dry solid because of the potential explosion risk. To avoid this problem it is quite common to carry out an *in situ* aprotic diazotization of anthranilic acid using pentyl nitrite ($C_5H_{11}ONO$). When heated in a solvent to about 80 °C, nitrogen (N_2) and carbon dioxide (CO_2) are evolved and *ortho*-benzyne is formed (Scheme 7.13). The decomposition can also be carried out photochemically, and flash photolysis of the diazonium carboxylate has been used to obtain the UV spectrum of *ortho*-benzyne. Benzenediazonium-3- and -4-carboxylates have been studied under similar conditions and UV spectra have been obtained for the transient intermediates so generated.



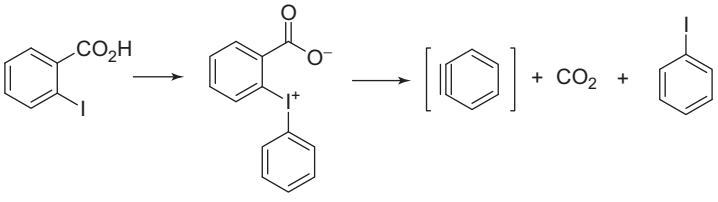
Scheme 7.13 Decomposition of benzenediazonium-2-carboxylate to give *ortho*-benzyne.

Although the decomposition of benzenediazonium-2-carboxylate can be conveniently represented as a concerted process (as above), this is almost certainly not the case since there is evidence to suggest that nitrogen is lost first (Scheme 7.14). The diazonium carboxylate method is quite general – various substituted *ortho*-benzynes, 3,4-pyridyne, and 2,3-naphthalyne can be generated from the appropriate amino acid precursors, although some of these may be difficult to prepare by diazotization and thermal decomposition. In cases where benzenediazonium carboxylates prove too thermally unstable, one can use a masked version of the diazonium group in the form of a 1,2,3-triazene. These compounds should be handled with care since they are potential carcinogens, and decompose smoothly at about 130 °C (or lower in the presence of acid) with loss of dimethylamine, nitrogen, and carbon dioxide.



Scheme 7.14 Isolable zwitterion in the case of benzenediazonium-2-carboxylate.

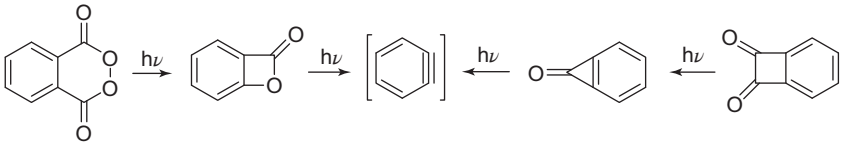
The only other useful aryne precursor of the zwitterionic type is diphenyliodonium-2-carboxylate, prepared from 2-iodobenzoic acid. It is much more thermally stable than benzenediazonium-2-carboxylate, decomposing in the range 160–200 °C with elimination of carbon dioxide and iodobenzene (Scheme 7.15).



Scheme 7.15 Decomposition of diphenyliodonium-2-carboxylate to give *ortho*-benzyne.

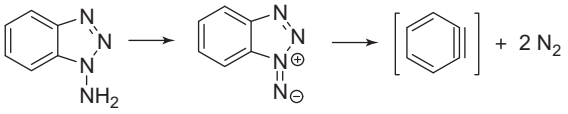
The formation of *ortho*-benzyne by fragmentation of cyclic systems by electronic rearrangement will only be energetically favorable if the other fragments so formed are extremely thermodynamically stable molecules such as CO, CO_2, and N_2. Even so, the thermal energy needed to initiate the fragmentation is often considerable, requiring high-temperature gas-phase reactions. A clue as to whether such a fragmentation is feasible can often be obtained from the mass spectrum of the precursor. If the molecule does not fragment in the desired fashion under electron impact it is unlikely to do so under laboratory conditions. Scheme 7.16 shows two successful cyclic precursors to *ortho*-benzyne, illustrating the large differences in

temperatures required to effect the ring fragmentation according to the stability of the precursor. Neither route is preparatively useful.

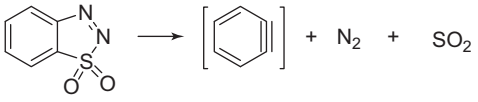


Scheme 7.16 Formation of *ortho*-benzyne by ring fragmentation reactions.

Oxidation of 1-aminobenzotriazole with lead(IV) acetate, nickel peroxide, or phenyliodosoacetate at −78 °C in dichloromethane (DCM) results in evolution of nitrogen and the generation of *ortho*-benzyne (Scheme 7.17). The reaction, originally studied by C.W. Rees and coworkers, constitutes an extremely mild route to *ortho*-benzyne, and has been extended to other arynes, notably 1,8-didehydronaphthalene, a 1,3-diradical. The mechanism formally involves generation of an aminonitrene followed by fragmentation with loss of two molecules of nitrogen. In the light of recent results, though, the intermediate in the lead(IV) acetate reaction should probably be formulated as an N-acetoxy compound. Another heterocyclic molecule that can serve as benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of SO_2 and N_2 (Scheme 7.18).

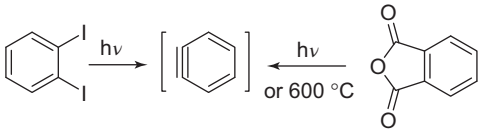


Scheme 7.17 Oxidative fragmentation of 1-aminobenzotriazole.



Scheme 7.18 Decomposition of benzothiadiazole-1,1-dioxide to give *ortho*-benzyne.

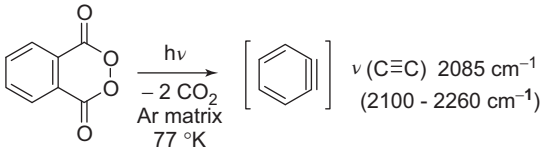
There are many other reactions that possibly involve aryne intermediates. While some are of mechanistic curiosities, some have been studied in detail, although none are generally synthetically useful. Irradiation of 1,2-diiodobenzene can lead to *ortho*-benzyne, probably via an aryl radical intermediate resulting from cleavage of the weak C–I bond (Scheme 7.19). Aryl cations, formed by the decomposition of diazonium salts are also possible intermediates to *ortho*-benzynes; provided that a large *ortho*-substituent is present, loss of a proton to give an aryne becomes competitive with the normal nucleophilic addition to the cation.



Scheme 7.19 Formation of *ortho*-benzyne from 1,2-diiodobenzene/phthalic anhydride.

7.1.4
Reactions of Arynes

Arynes are novel reaction intermediates that react with dienes or 1,3-dipoles to give the corresponding cycloadducts. Recently, many researchers have reported the reaction of benzyne prepared from 2-(trimethylsilyl)phenyl triflate or benzenediazonium carboxylate with imines, aminobenzoate, 2-aminobenzophenones, azides, and diazo compounds, which provides various N-containing cycloadducts, such as acridines, acridones, triazoles, and indazoles. Formally, the reaction proceeds in a [2+2], [3+2], or [4+2] manner. Benzyne is an extremely reactive species because of the presence of a strained triple bond and undergoes polar and pericyclic reactions. The lifetime of benzyne in the gas phase has been estimated to around 20 ns (2×10^{-8} s) by mass spectroscopic techniques. Some spectroscopic properties of benzyne have been determined by Orville Chapman using matrix isolation techniques (Scheme 7.20).



Scheme 7.20 Spectroscopic properties of benzyne.

Theoretical calculations suggest that the strained bent alkyne form of benzyne is lower in energy than the diradical alternative (Figure 7.4). The calculations suggest that the π-overlap in the strained π bond is weaker and that the π* component of the bond (i.e., the LUMO) is at lower energy than normal for a triple bond, hence arynes behave as powerful electrophiles.

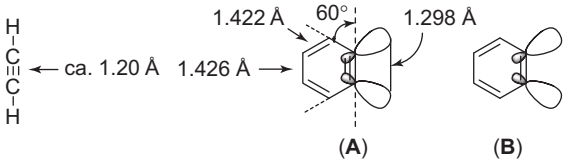
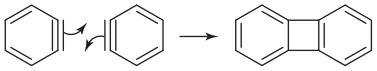


Figure 7.4 Bent alkyne form of benzyne.

The triple bond in alkynes usually results in a linear geometry to facilitate orbital overlap. In benzyne, however, the p-orbitals are distorted to accommodate the triple bond within the ring system, reducing their effective overlap. This lack of overlap results in the high reactivity of benzynes. Free benzyne is highly reactive and in the absence of suitable reagent rapidly dimerizes to biphenylene (Scheme 7.21).



Scheme 7.21 Dimerization of *ortho*-benzyne.

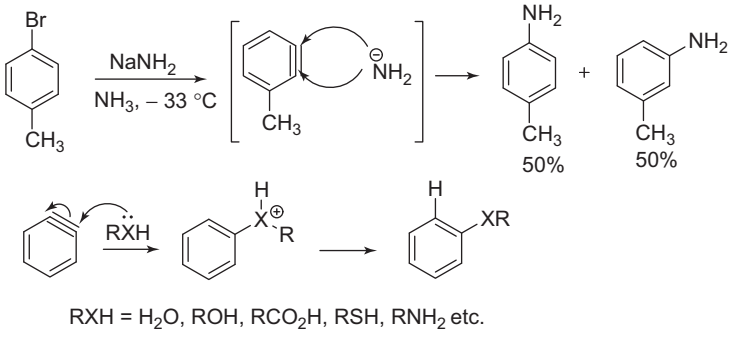
7.1.4.1 Nucleophilic Addition to Arynes

The formulation of arynes as compounds with a reactive triple bond often disguises the fact that, like carbenes, they are electron-deficient species. They are highly electrophilic and therefore react with nucleophiles of all types. Because of their low lying LUMOs and highly polarizable orbitals, arynes are, though, soft electrophiles and therefore usually react preferentially with soft nucleophiles. Thus, it can be shown that the relative reactivity of various nucleophiles follows the order: $R_3C^- \sim RS^- >$ enolates $> RO^- > I^- > Br^- > Cl^-$This facile nucleophilic addition has already been seen in the formation of biphenyl when *ortho*-benzyne is generated by the reaction of fluorobenzene with phenyllithium. Indeed, addition of aryllithiums to *ortho*-benzynes is a good way of making biaryls.

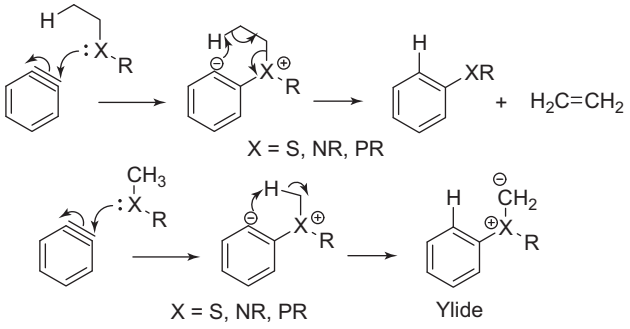
Alkyllithiums add similarly as do acetylenic and benzylic carbanions. Enolates and anions stabilized by cyano, nitro, and sulfinyl groups also add to *ortho*-benzyne (Scheme 7.22). Many of these anions are used widely in synthesis, and their arylation by arynes, usually carried out by treating a mixture of the aryl halide and the conjugate base of the anion with potassium amide (KNH_2) in liquid ammonia, is a useful reaction. Other nucleophiles of the type RXH (water, alcohols, carboxylic acids, thiols, primary, and secondary amines) add readily to *ortho*-benzyne to give the corresponding phenylated compounds RXPh, often in good yields. Under neutral conditions, where the nucleophile RXH is not deprotonated, a two-step mechanism involving nucleophilic attack followed by proton transfer probably operates (Scheme 7.22).

ortho-Benzyne also undergoes attack from tertiary amines, phosphines, sulfides, and related nucleophiles. However, in these cases the first formed intermediate cannot undergo the simple proton transfer shown above, and therefore reacts in other ways. For example, if one of the groups attached to the heteroatom carries a 3-hydrogen atom then elimination through a cyclic transition state is the usual process. If no 3-hydrogen is available but there are still α-hydrogens present, rearrangement to an ylide is the most likely pathway. Scheme 7.23 shows examples of both processes.

All the examples discussed to date have involved *ortho*-benzyne itself, and have simply served to illustrate the range of nucleophiles that react. However, one needs to know what happens when unsymmetrical arynes are attacked by nucleophiles,



Scheme 7.22 Nucleophilic addition to *ortho*-benzyne.

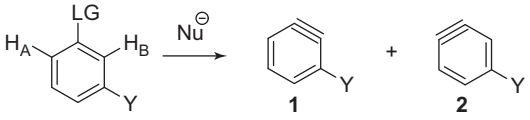


Scheme 7.23 Addition of tertiary amines, phosphines, and sulfides to *ortho*-benzyne.

where there are two possible products. The problem arises with substituted *ortho*-benzynes, arynes with an additional ring, or heteroarynes. The ratio of products formed depends on the electronic and to a lesser extent steric effects of the substituents (or additional ring or heteroatom), and the incoming nucleophile. Since the relevant orbitals of the aryne are orthogonal to the system, the electronic effect of substituents is mainly inductive, and is only relayed through the σ-bonds. If the inductive effect of the substituent can stabilize one of the two transition states to a greater extent, regioselective addition of a nucleophile may then be possible. For example, in a 3-substituted aryne, if the substituent is inductively electron-withdrawing (–I), such as methoxy or dimethylamino, it will stabilize the developing negative charge *ortho* to itself and hence nucleophilic attack at the *meta*-position is favored. Conversely, if an electron-donating (+I) substituent such as methyl is present, nucleophilic attack often occurs at the *ortho*-position. An alternative view is that the reaction is under thermodynamic control and simply proceeds to give the more stable aryl anion intermediate. Strictly, of course, neither analysis of substituent effects is correct and one should consider the frontier molecular orbitals of the aryne, but such a rigorous treatment is beyond the scope of this book.

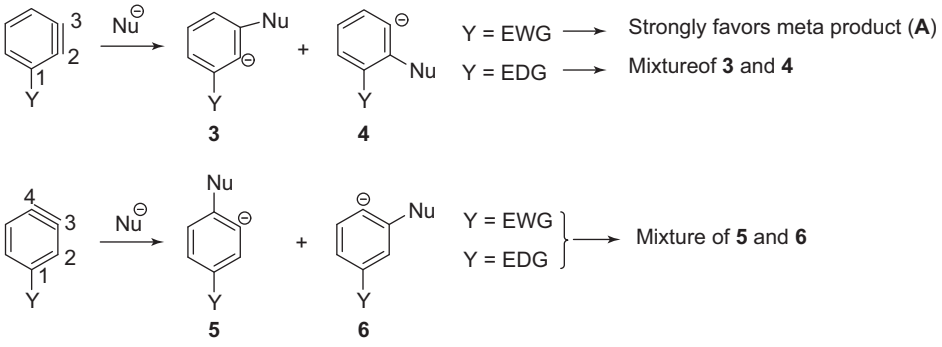
7.1.4.2 **Regiochemistry of the Triple Bond Formation**

When the leaving group (LG) and substituent (Y) are mutually *ortho* or *para*, only one benzyne intermediate is possible. However, when LG is *meta* to Y, then regiochemical outcomes of aryne **1** and **2** are possible. If Y is electron withdrawing, then H_B is more acidic than H_A resulting in regioisomer **1**. Analogously, if Y is electron-donating, regioisomer **2** is generated, since now H_A is the more acidic proton (Scheme 7.24).



Scheme 7.24 Regiochemistry of triple bond formation.

There are two possible regioisomers of benzyne with substituent (Y): the triple bond can be positioned between C2 and C3 or between C3 and C4. Substituents *ortho* to the leaving group will lead to the triple bond between C2 and C3. A *para* Y and LG will lead to the regioisomer with the triple bond between C3 and C4. A *meta* substituent can afford both regioisomers as described above. In the case where a triple bond is located between C2 and C3, an electron-withdrawing groups (EWG) will direct the nucleophile addition to place the carbanion as close as possible to the EWG. However, electron-donating groups (EDGs) will provide little selectivity between products. In the regioisomer where the triple bond is located between C3 and C4 the effect of substituent on nucleophile addition is diminished, and mixtures of *para* and *meta* products are often obtained (Scheme 7.25).



Scheme 7.25 Regiochemistry of the addition of nucleophile to the triple bond.

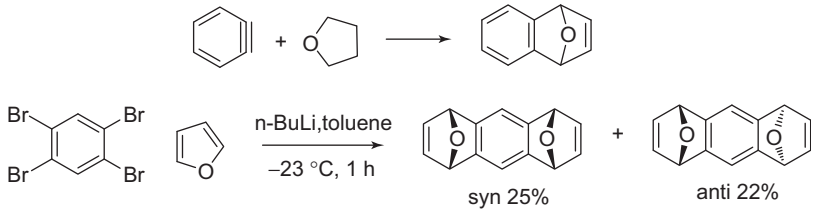
Steric effects only become important when either the attacking nucleophile or the substituent *ortho* to the aryne bond is very bulky. An example of this effect can be seen in the increased regioselectivity of addition of lithium piperidide to 3-isopropylbenzyne over 3-methylbenzyne. Likewise in the addition to 3-methylbenzyne, KNH_2 adds to both *ortho*- and *meta*-positions in approximately

equal amounts whereas the bulkier nucleophile $KNPh_2$ adds 2,3-naphthalyne indicating the *peri*-exclusively to the less hindered *meta*-position. In additions to 2,3-hydrogen naphthalyne the *peri*-hydrogen (H8) hinders the 1-position, and as the bulk of the nucleophile increases so does the selectivity for attack at C2.

One way to avoid the problem of competing sites of nucleophilic addition is to make the reaction intramolecular. In fact, intramolecular nucleophilic addition to arynes has been developed into a useful synthetic method for the preparation of benzo-fused ring systems. The substrate is usually an aryl halide bearing a side chain, which contains the potentially nucleophilic center in the *ortho*- or *meta*-position. On treatment with base the aryne is generated and simultaneously the side chain is deprotonated and provides the anion. The so-formed anion is nucleophilic enough to compete with the external base, and cyclization occurs in good yield. Note that four-, five-, and six-membered carbocyclic and heterocyclic rings are readily formed. If the alkyl side chain is sufficiently long, it allows cyclization to occur at both ends of the aryne, although the *meta*-product is the major one. Benzene rings bridged across their *meta*- and *para*-position are known as *meta*- and *para*-cyclophanes, respectively.

7.1.4.3 Cycloaddition Reactions of Arynes (Diels–Alder Reaction)

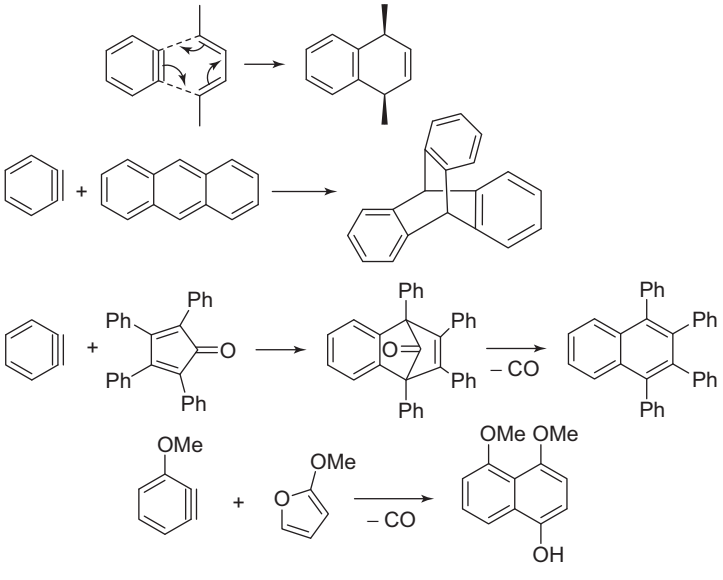
Arynes with their reactive triple bond would be expected to participate readily in cycloaddition reactions. However, as demonstrated in the previous section, the addition of nucleophiles is extremely facile, and therefore reactions with non-nucleophilic reagents cannot usually be observed unless the aryne is generated in the absence of nucleophiles. In practice this usually means that routes involving the treatment of aryl halides with nucleophilic bases cannot be used. The first cycloaddition reaction of *ortho*-benzyne, the Diels–Alder reaction with furan was observed in 1955 by Wittig and used 2-fluorobromobenzene as the precursor. The cycloadduct was obtained in almost 90% yield, and the reaction has formed the basis for numerous synthetically useful Diels–Alder cycloadditions involving arynes. Tetrabromobenzene reacts with butyllithium to give the diaryne intermediate with furan to form a tetrahydroanthracene. The mixture of *syn* and *anti* conformers can be separated based on differences in methanol solubility (Scheme 7.26).



Scheme 7.26 Diels–Alder cycloaddition involving aryne.

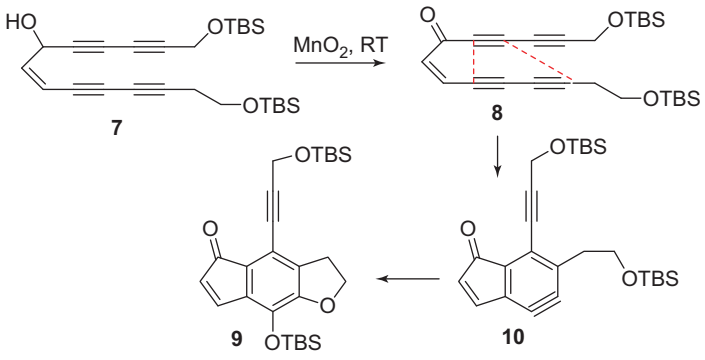
ortho-Benzyne is an extremely reactive dienophile and reacts with a large range of 1,3-dienes to give Diels–Alder products. The reaction is often used as a test for the presence of an aryne intermediate. Furan is commonly used as diene since

it is compatible with several organometallic reagents, and because it is volatile and easily removed it can be used in large excess. If the aryne is generated under high-temperature conditions, it is usually better to use the stable but reactive diene 1,2,3,4-tetraphenylcyclopenta-1,3-dien-5-one (tetracyclone). In either case isolation of the appropriate Diels–Alder adduct, which in the latter case aromatizes by loss of CO, is taken as evidence for the intermediacy of an aryne, although it should be noted that such trapping experiments are not always completely unambiguous. The concerted nature of the Diels–Alder reaction is shown by the stereospecific addition of (*E,E*)-hexa-2,4-diene. In addition to its reactions with standard 1,3-dienes, *ortho*-benzyne undergoes Diels–Alder reactions with compounds not normally considered as dienes such as benzene. Halogenated arynes such as tetrachloro- and tetrafluorobenzyne are more reactive dienophiles still, and react readily with thiophene and substituted benzenes. Many of these reactions lead to otherwise inaccessible bridged ring systems and are therefore useful in synthesis (Scheme 7.27).



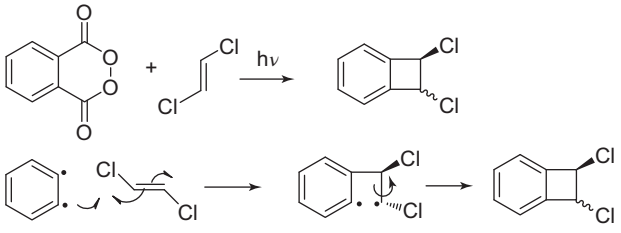
Scheme 7.27 Diels–Alder reactions involving *ortho*-benzyne.

T. Hoye *et al.* were understandably surprised when a seemingly trivial oxidation of **7** took an unexpected course (Scheme 7.28). Instead of ketone **8** the tricyclic product **9** was obtained in 53% yield. The course of the events could be rationalized readily and pointed to the unprecedented cyclization of ketone **8** to give the benzyne derivative **10** in a [4+2] cycloaddition between a diyne and an yne moiety. In fact, this intramolecular cycloaddition turned out to be a viable route to generate arynes bearing electron-withdrawing substituents, a substitution pattern that is not always amenable to the standard methods for generating arynes. Thus, this surprising reaction broadens the scope of benzyne chemistry.



Scheme 7.28 Unexpected formation of an aryne by [4+2] cycloaddition.

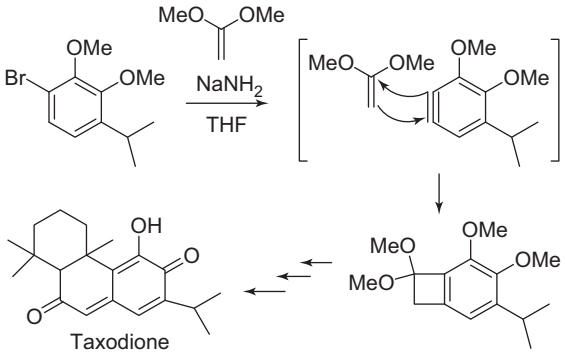
Arynes also undergo formal [2+2] additions to alkenes but many of these are stepwise rather than concerted processes. The loss of the alkene *trans*-stereochemistry in the product of the photochemically mediated cycloaddition illustrated below (Scheme 7.29) suggests that it proceeds via a photochemically generated diradical excited state of benzyne rather than by a concerted mechanism. Owing to the electrophilic nature of benzyne, olefins bearing electron-donating substituents work best for this reaction.



Scheme 7.29 [2+2] Cycloaddition via diradical excited state of benzyne.

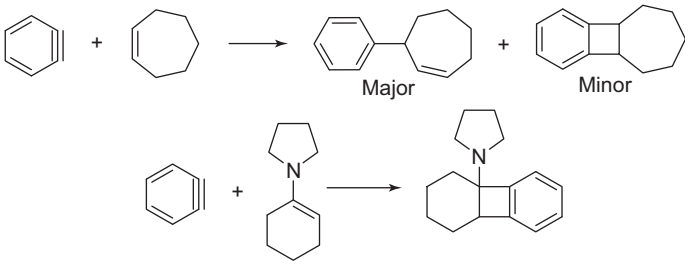
Owing to significant by-product formation, aryne [2+2] chemistry is rarely utilized in natural product total synthesis. Nevertheless, several examples exist. In 1982, Stevens and coworkers reported a synthesis of taxodione that utilized [2+2] cycloaddition between an aryne and a ketene acetal (Scheme 7.30).

Arynes react readily with simple alkenes to give either benzocyclobutenes or substituted benzenes (Scheme 7.31). The formation of benzocyclobutenes by [2+2] cycloaddition reaction of the aryne to the alkene proceeds best for strained and electron-rich carbon–carbon (C=C) double bonds. For example, dicyclopentadiene reacts to give the *exo*-isomer of the corresponding four-membered ring in good yield. The addition to cyanoethene (acrylonitrile) and the reaction with the electron-rich ethoxyethene (ethyl vinyl ether) gives the cyano- and ethoxy-benzocyclobutenes in 20% and 40% yields, respectively. The latter reaction almost certainly involves nucleophilic addition of the enol ether to the electrophilic aryne followed by collapse



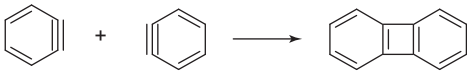
Scheme 7.30 Synthesis of taxodione utilizing [2+2] cycloaddition.

of the betaine intermediate. Likewise, addition to (*E*)- or (*Z*)-1,2-dichloroethene is non-stereospecific, in accord with a stepwise, probably diradical, mechanism.



Scheme 7.31 Cycloaddition to alkenes.

As a reactive dienophile *ortho*-benzyne also participates in the ene reaction. Thus, alkenes with allylic hydrogen can undergo concerted reaction to give substituted benzenes. However, the yields are rarely good. Cycloaddition of *ortho*-benzyne to alkynes should in principle give benzocyclobutadienes. Such intermediates are highly unstable and not surprisingly are not isolated. Instead, the products, formed in low yield, derive from further reaction with another molecule of *ortho*-benzyne or by dimerization (Scheme 7.32).

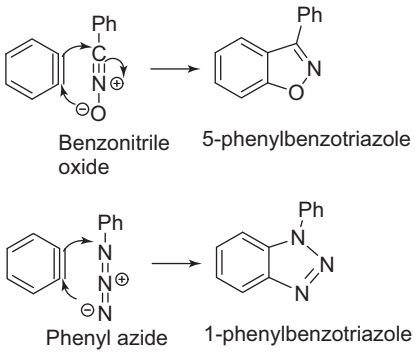


Scheme 7.32 Ene reaction of *ortho*-benzyne.

7.1.4.4 **1,3-Dipolar Cycloaddition**

The high reactivity of *ortho*-benzyne is also evident in 1,3-dipolar cycloadditions. The reaction is an extremely useful route to benzo-fused five-membered ring heterocycles. For example, azides give benzotriazoles, diazo compounds give (after

hydrogen migration) indazoles, and nitrile oxides give benzisoxazoles, all in good yield (Scheme 7.33).



Scheme 7.33 1,3-Dipolar cycloadditions.

Although the vast majority of stepwise polar additions to *ortho*-benzyne involve nucleophilic attack on the aryne, electrophilic attack is also possible provided that the aryne is generated by a method that does not involve strongly basic conditions. Few such additions are synthetically useful, with the exception of the formation of 1,2-dihalobenzenes by reactions of *ortho*-benzynes with halogens, although alternative mechanisms initiated by nucleophilic attack of halide may be envisaged. Radical reactions of *ortho*-benzyne, on the other hand, are extremely rare.

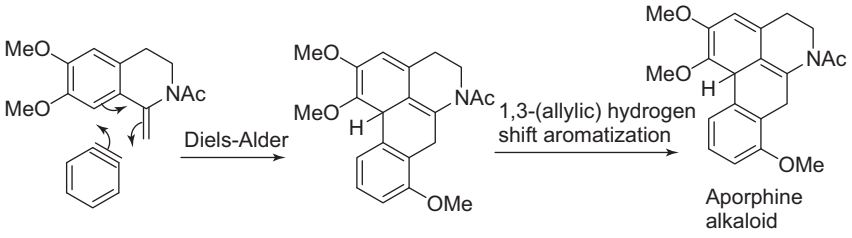
Many reactions involving *ortho*-benzyne produce its dimer and trimer, biphenylene and triphenylene, respectively. Although in some cases these hydrocarbons are formed as by-products, in others the yields can be quite high. For example, if *ortho*-benzyne is generated in solution by oxidation of 1-aminobenzotriazole in the absence of a suitable trap, biphenylene is formed in 85% yield. The reaction is highly efficient, presumably because the aryne is generated in high local concentration and therefore dimerizes before it can react by other pathways. Decomposition of benzenediazonium-2-carboxylate can also give respectable amounts of biphenylene. Both of these precursors, though, only give traces of triphenylene. High yields (over 80%) of triphenylene can be obtained, however, if *ortho*-benzyne is generated from an aryl halide. It is extremely unlikely that under these conditions in the presence of nucleophiles a concerted trimerization occurs. Much more likely is a stepwise mechanism, which involves reaction of *ortho*-benzyne with nucleophilic *ortho*-metalated aryl halide to give an intermediate metalated biphenyl that can react with a second molecule of *ortho*-benzyne to give, eventually, the observed trimer.

A four-membered ring fused to a benzyne has a sizable directing effect for the regioselective reactions with ketene silyl acetals, nucleophiles, and α-alkoxyfuran. Such findings open up an opportunity for selective syntheses of various interesting aromatic compounds.

7.1.5
Uses of Arynes in Organic Synthesis

Arynes have not been exploited in organic synthesis to the same extent as radicals or carbenes, but nonetheless do undergo some useful transformations. At the simplest level arynes are intermediates in the preparation of unusual isomers of substituted aromatic compounds. For instance, treatment of 2-methoxybromobenzene with potassium amide in liquid ammonia will result in the formation of the aryne, which will undergo regioselective nucleophilic attack *meta* to the methoxy group to give 3-methoxyaniline. This is an unusual isomer in the sense that conventional routes such as nitration of anisole followed by reduction of the nitro group do not give the *meta*-isomer.

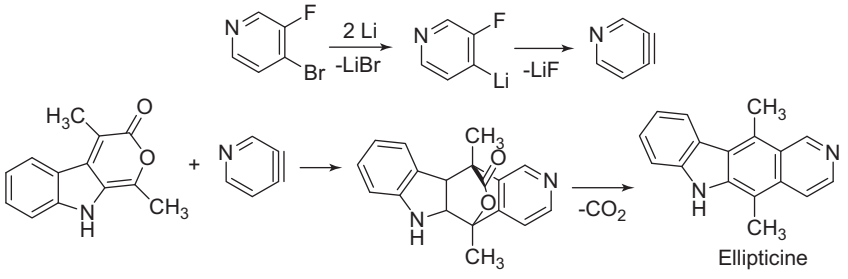
The major application of arynes in synthesis is in the construction of polycyclic systems using either the Diels–Alder or intramolecular nucleophilic addition reactions. The scope of the Diels–Alder reactions with arynes is extremely wide and compounds such as aryl-alkenes and -alkynes, which are not normally reactive 1,3-dienes, readily participate. Thus, (3,4-dimethoxyphenyl)ethyne reacts with *ortho*-benzyne followed by hydrogen migration to give the dimethoxyphenanthrene in 42% yield. A similar reaction has been used in an approach to the aporphine alkaloids, whereby 3-methoxybenzyne undergoes Diels–Alder reaction with an aryl alkene to give, after hydrogen migration, the tetracyclic ring system in 30% yield (Scheme 7.34).



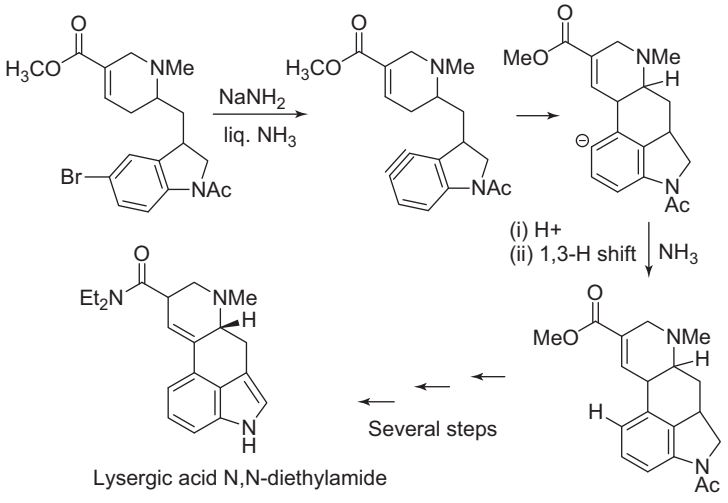
Scheme 7.34 Diels–Alder reaction of *ortho*-benzyne in the synthesis of a polycyclic system.

An intermolecular Diels–Alder reaction of 3,4-pyridyne has been used in a short synthesis of the important anticancer alkaloid ellipticine. In this case the diene is an α-pyrone; the initial Diels–Alder adduct is not isolated since it spontaneously aromatizes by loss of carbon dioxide. Unfortunately, the Diels–Alder reaction is not regioselective and an equal amount of the product arising from the alternative direction of addition to 3,4-pyridyne is formed (Scheme 7.35).

Scheme 7.36 shows a further example of the use of aryne in alkaloid synthesis, involving intramolecular nucleophilic addition reaction as a key step in the synthesis of lysergic acid ester.



Scheme 7.35 Synthesis of the antitumor alkaloid ellipticine by Diels–Alder addition to 3,4-pyridyne.



Scheme 7.36 Benzyne in a synthesis of a lysergic acid *N,N*-diethylamide precursor.

7.2
Ketenes and Cumulenes

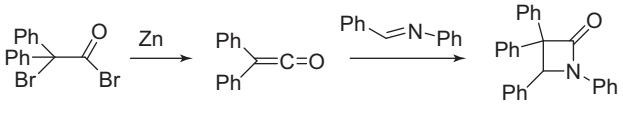
7.2.1
Introduction

A general consideration of reactive intermediates in 1956 by Leffler suggested that assignments of reaction mechanisms very often assume intermediates that have not been isolable for direct study and the physical reality of such intermediates depends on their relation to similar substances that do happen to be stable enough to study directly. Study of reactive intermediates focuses not only on ions, free radicals, and carbenes but also on other reactive species such as benzynes and ketenes, which were recognized around 1900. With advances in experimental methods of generation and detection of such species, as well as improvements in

computational methods for their study, the observation and understanding of these species has become much more comprehensive.

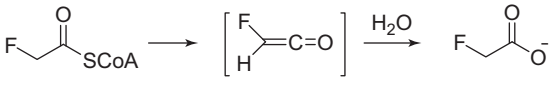
Cumulenes are a varied class of compounds, including species such as ketenes, allenes, ketenimines, and isocyanates, as well as analogs where carbon is replaced by silicon or germanium, where oxygen is replaced by sulfur or selenium, and nitrogen by phosphorus or arsenic. The distinctive bonding pattern of cumulenes consists of a central sp hybridized atom with double bonds to two other sp or sp^2 hybridized atoms, and includes carbon dioxide (CO_2), whose relative lack of chemical reactivity is a major driver of current global warming. Ketenes are unique among the cumulenes, in that they have a strong tendency for self-reaction by dimerization. Since their discovery in 1905, ketenes have maintained a separate identity and have a wide range of uses, not only in commodity applications such as the use of ketene dimers in paper sizing and in the manufacture of acetic acid, but also in vital pharmaceutical applications such as the preparation of β-lactam antibiotics.

Computational studies have compared substituent effects on the stability of ketenes, allenes, diazomethanes, diazirines, and cyclopropenes. Ketenes belong to the first generation of reactive intermediates along with carbocations, carbanions, radicals, and carbenes, and are intensively studied members of the cumulene family, with many useful synthetic applications. Ketenes were first recognized in 1905, when diphenylketene, a stable and isolable example, was obtained from the dehalogenation of the α-bromodiphenylacetyl bromide (Scheme 7.37). The most characteristic reaction of ketene is cycloaddition, as in the formation of β-lactams.



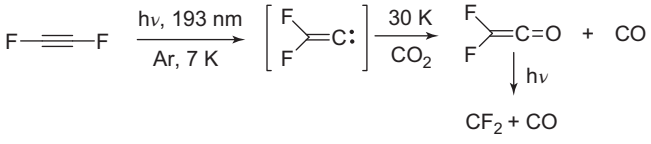
Scheme 7.37 Generation and trapping of diphenylketene.

Ketenes can be stabilized both by conjugating and by bulky substituents, and each of these factors contributes to the stability of ketene. A computational survey in 1991 provided the insight that ketenes are stabilized by electropositive substituents, and destabilized by electronegative ones, and that there is an inverse correlation of ketene stabilization with substituent electronegativity. Substituents exert major effects on ketene stabilities and properties, for example, fluoroketene (FCH=C=O) is calculated to be the least stabilized monosubstituted ketene and exemplifies the destabilizing effects of electronegative and π-donor substituents, but this ketene can nevertheless be generated and trapped in solution by reaction with imines (Scheme 7.38).



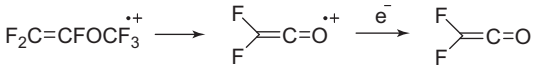
Scheme 7.38 Formation of fluoroketene by enzymatic elimination.

Difluoroketene is even more unstable but has been successfully generated in an argon matrix at 7 K by photolysis of difluoroacetylene at 193 nm, forming difluorovinylidene, which led to difluoroketene upon oxygenation by CO_2. The ketene was identified by its IR band at 2162 cm^{-1}. Upon further photolysis it underwent decarbonylation to CF_2 (Scheme 7.39). An iridium complex of difluoroketene has also been characterized.



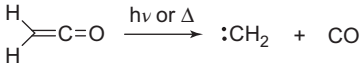
Scheme 7.39 Generation of difluoroketene.

Difluoroketene is also generated in the gas phase by electron impact mass spectrometry of perfluoro methyl vinyl ether and neutralization–reionization of the resulting ion (Scheme 7.40). Electropositive substituents have the opposite effect and stabilize ketenes, as found computationally and experimentally and as exemplified by silyl-substituted ketenes.



Scheme 7.40 Gas-phase formation of difluoroketene.

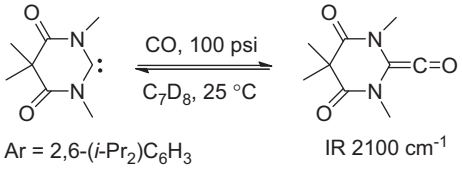
Dissociation of the parent ketene to the carbene and carbon monoxide is one of the most characteristic reactions of ketenes (Scheme 7.41), and has long been a subject of experimental and theoretical investigations.



Scheme 7.41 Dissociation of parent ketene.

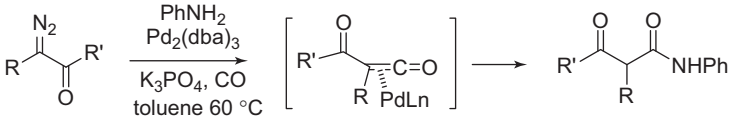
7.2.2
Generation of Ketenes

The reaction of stable N-heterocyclic carbenes (NHCs) with carbon monoxide and the carbonylation of diazo compounds also provide routes to ketene formation. Ketene formation by carbon monoxide addition to a stable carbene (with 55% conversion) has been confirmed by the characteristic IR absorption, and the ketene has been isolated as a purple solid at low temperature with the structure determined by X-ray crystallography (Scheme 7.42).



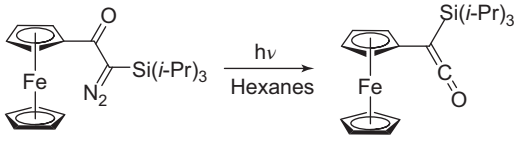
Scheme 7.42 Formation of an N-heterocyclic ketene.

Diazoalkane carbonylation using palladium catalysis gives unobserved acylketenes, which are captured *in situ* with nucleophiles (Scheme 7.43). The reactions are suggested to involve palladium complexed ketenes and are carried out with various substrates and nucleophiles.



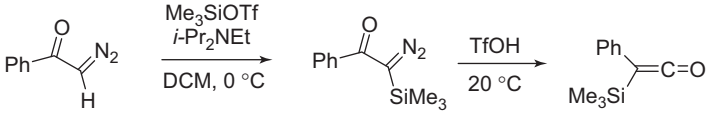
Scheme 7.43 *In situ* formation of acylketene.

A stable silyl-substituted ferrocenyl-ketene has been generated by Wolff rearrangement (Scheme 7.44). This ketene with the bulky silyl group is less reactive toward *n*-butylamine than the parent ferrocenyl-ketene by a factor of 7×10^8, showing the steric protection provided by the large substituents.



Scheme 7.44 Formation of silyl-substituted ferrocenyl-ketene.

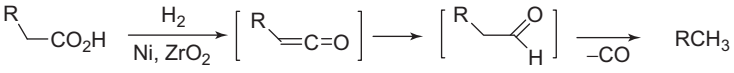
Aryl diazo ketone conversion into the silylated diazo ketone in a one-pot procedure using a silyl triflate and then Wolff rearrangement catalyzed by triflic acid generates the stable aryl(trialkylsilyl)ketene (Scheme 7.45).



Scheme 7.45 Generation of stable aryl(trialkylsilyl) ketene.

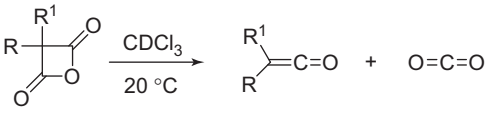
Ketenes are most often prepared from carboxylic acid derivatives, and a novel reductive pathway has been described for the conversion of biomass derived fatty acid esters in microalgae oils into hydrocarbons through intermediate ketenes. The conversion into alkanes using ZrO_2-promoted Ni catalysis is explained as involving conversion of the esters into acids and dehydration to ketenes (observed by strong

IR absorption at 2050–2150 cm^{-1}) followed by hydrogenation to aldehydes and then decarbonylation with hydrocarbon formation (Scheme 7.46).



Scheme 7.46 Formation of ketene using ZrO_2-promoted Ni catalysis.

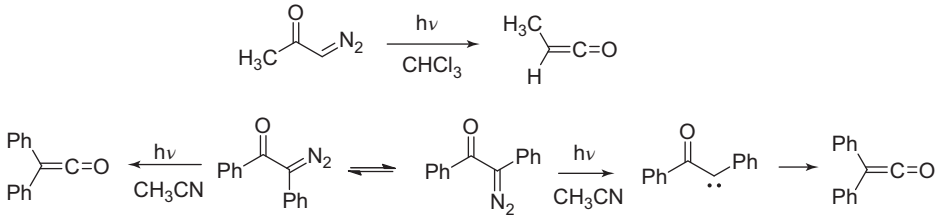
A unique preparation of ketenes is by thermal decomposition of malonic anhydrides, which form ketenes and carbon dioxide (Scheme 7.47). Ketene, methylketene, and dimethylketene are formed by this methodology. Surprisingly, the monomethyl malonic anhydride is the most reactive and the dimethyl is the slowest.



Scheme 7.47 Formation of ketenes by thermal decomposition of malonic anhydrides.

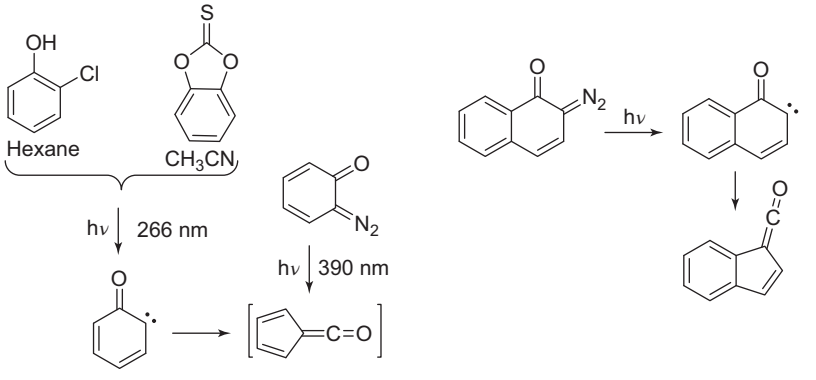
7.2.3
Photochemical Generation of Ketenes

Photolysis at 270 nm of diazoacetone with ultrafast IR detection gives ketene generation in a concerted process, interpreted as showing a predominance of the *syn*-conformation of the diazo ketone (Scheme 7.48). Photolysis of azibenzil with UV-visible detection shows formation of the singlet benzoylcarbene in acetonitrile. The IR absorbance at 2100 cm^{-1} shows formation of the ketene by a concerted process arising from the *syn*-conformation and also from the carbene, which then forms the ketene (Scheme 7.48).



Scheme 7.48 Photochemical formation of ketenes.

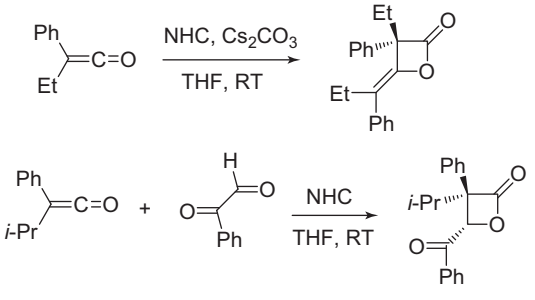
Femtosecond photolysis of diazocyclohexadienone, *o*-phenylene thioxocarbonate, and 2-chlorophenol each give rise to cyclopentadienylideneketene, either by a direct conversion or through an intermediate singlet 2-oxocyclohexa-3,5-dienylidene observed by UV (Scheme 7.49).



Scheme 7.49 Formation of ketenes by femtosecond photolysis.

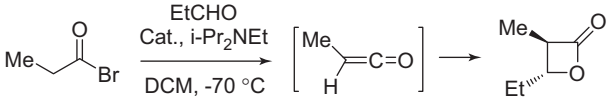
7.2.4
Reactions of Ketenes

Aryl(alkyl)ketenes in the presence of the chiral NHC catalyst with Cs_2CO_3 undergo stereoselective dimerization (Scheme 7.50). A one-pot procedure with *in situ* generation of the ketene and dimerization was also successful.



Scheme 7.50 Dimerization of phenyl(ethyl) ketene.

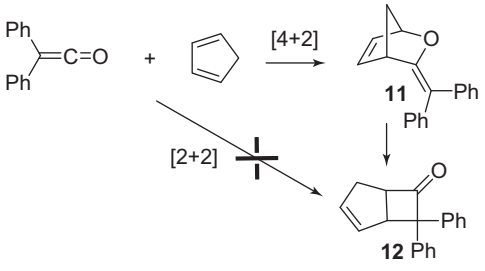
Ketenes generated by dehydrobromination of acyl bromides undergo *trans*-selective [2+2] cycloaddition with carbonyl groups, using the chiral catalyst bis-pyridinium aluminum-salen complex, to form β-lactones (Scheme 7.51).



Scheme 7.51 *trans*-Selective [2+2] cycloaddition of ketene with aldehyde.

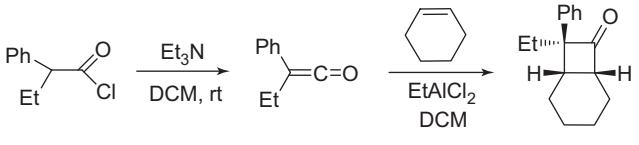
The cycloaddition of diphenylketene with cyclopentadiene is a classic reaction in ketene chemistry that has long been studied, but the interpretation of this

reaction has evolved substantially over the years. It was reported by Machiguchi and coworkers to proceed by an initial [4+2] cycloaddition to **11** followed by rearrangement to **12**, and not by direct [2+2] cycloaddition (Scheme 7.52).



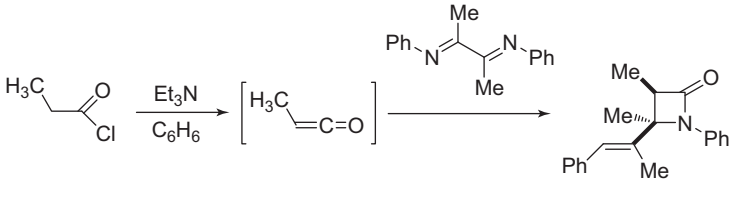
Scheme 7.52 Cycloaddition of diphenylketene with cyclopentadiene.

The first reported examples of Lewis acid-catalyzed ketene-alkene [2+2] cycloadditions provide efficient and diastereoselective routes to cyclobutanones (Scheme 7.53). In this procedure, the alkene is added to a ketene solution generated by dehydrochlorination but is not reactive until the mixture is added to the catalyst solution. Catalyzed reactions with conjugated alkenes such as cyclopentadiene favor the opposite diastereoselectivity to that of the corresponding thermal reactions.



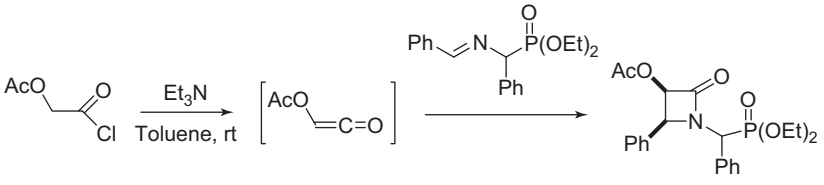
Scheme 7.53 Lewis acid catalyzed ketene–alkene cycloaddition.

The [2+2] cycloaddition of ketenes with imines to form β-lactams is perhaps the most studied of ketene reactions, and because of the continued search for new drugs continues to attract close attention. The reaction of methylketene with the bis-imine forms the *cis*-monoadduct as the only observed mono-addition product (Scheme 7.54).



Scheme 7.54 Reaction of methylketene with a bis-imine to form a *cis*-monoadduct.

Ketenes generated by acyl chloride dehydrochlorination give [2+2] cycloaddition with imines bearing a phosphonate-substituted side chain to form the corresponding β-lactams (Scheme 7.55).



Scheme 7.55 Reaction of acylketene with imine to give a β-lactam.

7.3 *ortho*-Quinone Methides

When describing the chemistry of an entity that is difficult to isolate and identify its mere existence may be questioned. However, there is abundant indirect evidence for the *in situ* formation of *ortho*-quinone methides (*o*-QMs). Most indirect evidence comes from the structural identification of products that result from dimerizations, trimerizations, and intramolecular and intermolecular [2+2] cycloadditions, as well as the nucleophilic trapping of *o*-QMs. Quinone methides (QMs) are short-lived, highly reactive powerful intermediates used for the synthesis of complex natural products, modern materials, fine chemicals, and pharmaceuticals. The *o*-QM, which is generally formed through the condensation of phenol with aldehyde in the presence of acid or base catalyst, was first suggested by Fries in 1907. The first direct evidence was given by Gardner in 1963 by trapping it at −100 °C. After 1963, its use as intermediate increased enormously in many tandem and cycloaddition reactions with various dienophiles.

QMs have been proposed as intermediates in numerous chemical and biological processes. Moreover, they have been implicated as the ultimate cytotoxins responsible for the functions of such agents as antitumor drugs, antibiotics, and DNA alkylators in biological chemistry. As a consequence, some strategies have been successfully developed for generating *o*-QMs. In the past decade, the most popular methods were photochemical initiation of *o*-(α-phenyl) substituted phenols or thermal initiation of various substituents on the benzene ring of *o*-methyl (ene-acetoxy)-phenols. Lewis acid, base, and chemical oxidants have also been used to generate *o*-QMs.

QMs exist in three isomeric forms, namely, *o*-, *m*-, and *p*-quinone methides (also known as *o*-, *m*-, and *p*-QMs) (Figure 7.5). The importance of *o*- and *p*-QMs in organic synthesis and their role in biochemistry have been studied in detail. Unlike benzoquinones, *o*- and *p*-QM derivatives are highly polarized compounds, usually observed with difficulty or postulated as reactive intermediates because of facile reactions driven by the formation of aromatized phenol derivatives.

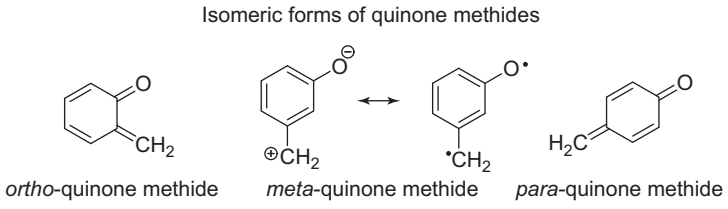


Figure 7.5 Structure of quinone methides.

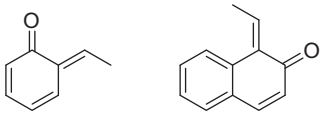


Figure 7.6 *ortho*-Quinone methides.

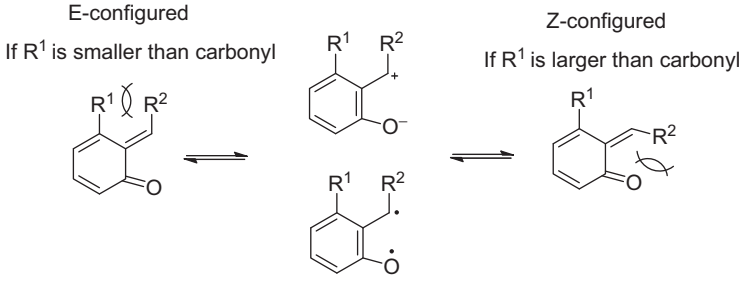


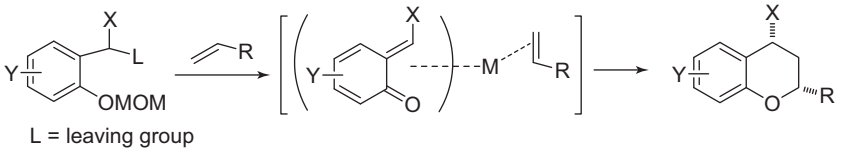
Figure 7.7 *ortho*-Quinone methide behaves as a combination of charged zwitterions and the biradical.

o-QMs are highly reactive intermediates that have been extensively harnessed by nature (Figure 7.6). Various plants, animals, and insects capitalize upon these types of compound as a means of defense. However, despite general knowledge of *o*-QMs for over a century these intermediates still lie outside the synthetic mainstream. Very recently, Pettus described the methods by which *o*-QMs are prepared, the benefits and limitations associated with each method, and current applications in total synthesis. The pseudo three-component condensation reaction of 2-naphthol with aldehydes in the presence of various catalysts to form xanthenes has been studied widely. The reaction proceeds through the *in situ* formation of *o*-QMs with 2-naphthol acting as a nucleophile. However, the three-component condensation reactions of 2-naphthol and aldehydes with other nucleophiles are rarely reported in the literature.

An *o*-QM behaves as a combination of charged zwitterions and the biradical (Figure 7.7). The contribution of these canonical forms lead to the idea that the (*E*/*Z*) geometries of *o*-QM are fluxional. The distribution among these geometric isomers is believed to result from the differences between nonbonded interactions (Figure 7.7). If from a steric point of view R^1 substituent is smaller than oxygen, then

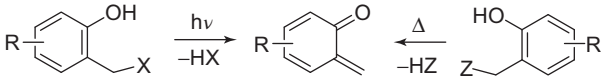
the (*E*)-configuration is preferred. However, increasing the size of R^1 substituent can cause the (*Z*)-configuration to predominate. The (*E*/*Z*) ratio is important in governing the diastereoselective outcome for Diels–Alder cycloadditions.

Several methods have been developed to generate the transient highly reactive *o*-QMs. In addition to thermal and base initiation, some Lewis acids and transition-metal salts/complexes of Os, Rh, Ir, Mn, and Pd have been reported to mediate the generation of *o*-QMs. The resulting 2-aryl-chromans can be functionalized to provide the core structures of natural and synthetic compounds exhibiting a wide array of biological properties (Scheme 7.56).



Scheme 7.56 Metal-catalyzed generation of *o*-quinone methides and subsequent cycloaddition reactions.

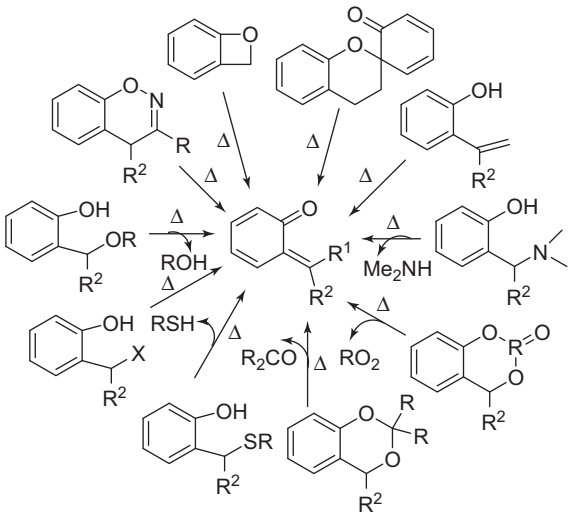
Very recently, Bharate and coworkers developed a Knoevenagel-type condensation to furnish *o*-QMs. In addition, some efficient methods for generating *o*-QMs involving the use of transition-metal complexes were also successfully documented. The generation of *o*-QM formation showed a strong dependence on the leaving group attached at the benzylic position of their precursor. Intramolecular elimination of HX from the suitable precursor yields *o*-QM (Scheme 7.57). Furthermore, the generation of QMs has been proven to be highly responsive to the presence of electron-withdrawing and electron-donating groups. In more detail, electron-donating groups greatly facilitate QM generation, whereas electron-withdrawing substituents strongly suppress such a process.



Scheme 7.57 Photochemical and thermal generation of *o*-quinone methide (*o*-QM).

Various precursors have been utilized for the thermolytic generation of *o*-QMs. Notably, all thermal generation techniques preclude the application of nucleophiles that are thermally unstable. With any given precursor, there is a substantial temperature range for initiation that depends upon the substituents. In general, if the process involves significant nonbonded interactions, then the temperature requirements are higher, while extended conjugation or other stabilizing factors lowers the overall temperature requirements (Scheme 7.58).

o-QMs, being a powerful intermediates, have been stabilized by metal coordination. Examples of simple isolated QMs are scarce. In fact, in condensed phases the parent compound has only been characterized spectroscopically at temperatures

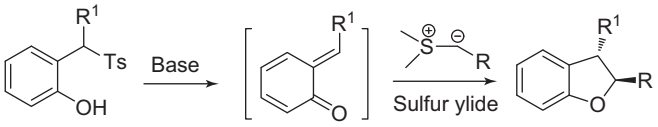


Scheme 7.58 Thermal generation of *o*-quinone methides.

below −100 °C, because it is extremely reactive. Spectroscopic evidence of the zwitterionic form of the *o*-QM derived from vitamin E has only been possible at −78 °C through stabilization by interaction with *N*-methylmorpholine *N*-oxide. These results show how difficult it has been to isolate QMs. *para*-QMs have been discussed as intermediates in the chemistry of lignins and have been used in organic synthesis as electrophiles or electron acceptors. Because the parent *o*-QM molecule is unstable, NMR spectroscopic data are not available. Therefore, metalated parent *o*-QM complexes have been examined using two-dimensional NMR spectroscopic techniques to understand its structure and reactivity. *o*-QMs are also believed to be key intermediates in the action of several antitumor and antibiotic drugs. Owing to their highly electrophilic character, they can act as alkylating agents of DNA.

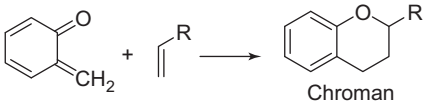
Recently, as a good leaving group under basic conditions or with acidic reagents (Lewis type), an arylsulfonyl group has been used in organic synthesis. The sulfonyl moiety at the benzylic position of 2-substituted phenol would also serve as a good leaving group, and the *o*-QM intermediates can be generated *in situ* under mild basic conditions. Ylides act as a nucleophile under basic conditions; meanwhile, ylides could react with *o*-QMs to give the intermediate followed by intramolecular nucleophilic attack of the oxygen anion on the carbon atom of ylides to furnish 2,3-dihydrobenzofuran derivatives (Scheme 7.59). In this process, a base has dual functions, generating both *o*-QM intermediates and ylides. First, the reaction was initiated by the formation of the *o*-QM intermediate in the presence of a base, which reacts with sulfur ylides followed by *trans*-elimination–cyclization to afford the product *trans*-dihydrobenzofurans.

o-QMs are versatile intermediates involving a minimum of seven carbon atoms, which are mainly involved in 1,4-Michael-type additions as well as aza-Michael



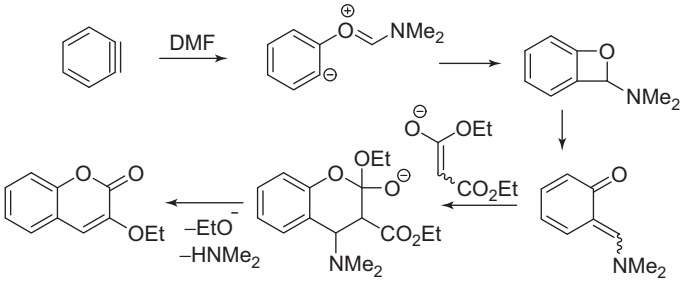
Scheme 7.59 Generation of *o*-quinone methides and synthesis of *trans*-2,3-dihydrobenzofurans.

reactions with various nucleophiles. *o*-QMs also give Diels–Alder (Scheme 7.60) and hetero-Diels–Alder cycloaddition products. *o*-QMs especially derived from 4-hydroxycoumarin undergo a [4+2] cycloaddition reaction with pentafulvenes to afford pyranocoumarins and pyranopyrones.



Scheme 7.60 Reactivity of *o*-quinone methide with alkenes.

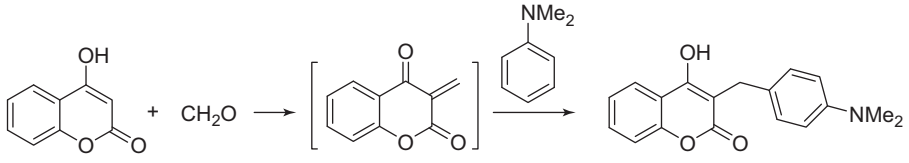
o-QMs are labile and transient intermediates, which have been widely utilized as defensive chemicals in nature. Their structural motifs also play vital roles in vitamin E chemistry and metabolism, and in the anticancer properties of anthracyclines. Despite universal knowledge about *o*-QMs as biologically active components, there appear to be several unexploited reactions of potential synthetic value, which would be feasible by suitable combination of *o*-QMs and designed reagents (Scheme 7.61).



Scheme 7.61 Synthesis of coumarins using substituted arynes.

A novel green process for intermolecular hydroarylation of *in situ* generated *o*-QMs with electron-rich arenes in aqueous medium under catalyst-free conditions at room temperature has been developed. The reaction is efficient and highly regioselective (Scheme 7.62).

However, limited work has appeared with the carbon nucleophiles. Recently, an efficient tandem process has been developed that would allow the reaction of *o*-QM intermediates with carbon/nitrogen nucleophiles *in situ* to provide xanthene, naphtho(pyrano)pyridine/amidoalkyl naphthol derivatives under solvent-free and simple reaction conditions (Scheme 7.63). Xanthenes and benzoxanthenes are



Scheme 7.62 Example of intermolecular Michael-type hydroarylation of *in situ* generated *o*-quinone methides with tertiary aromatic amines.

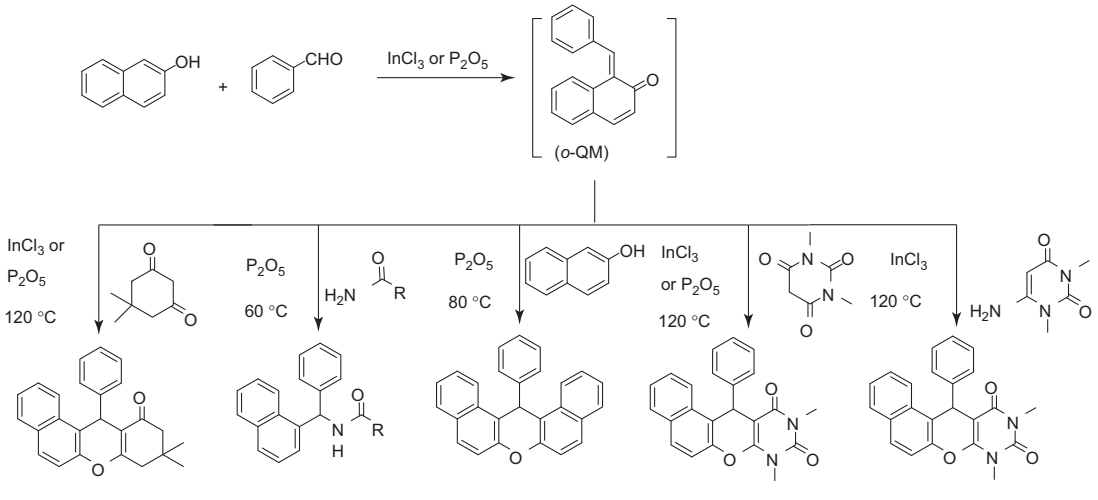
important biologically active heterocyclic compounds. They are also used as dyes, in laser technologies, pH-sensitive fluorescent materials as antagonists for the paralyzing action of zoxazolamine, and in photodynamic therapy. Compounds having 1,3-amino-oxygenated functional groups are present in various biologically important natural products and potent drugs, including several nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lopinavir. Naphtho(pyrano)pyrimidines are biologically interesting compounds with antibacterial and antifungal activities. These are also neuropeptide S receptors (NPSRs). A series of benzoxanthene, naphtho(pyrano)pyrimidine, and amidoalkylnaphthols have been synthesized under solvent-free conditions in good to excellent yield. $InCl_3$ and P_2O_5 have been used as catalyst for these transformations (Scheme 7.63).

An efficient and environmentally friendly approach for the synthesis of (2-aminobenzothiazolomethyl)-2-naphthols or 5-(2-aminobenzothiazolomethyl)-6-hydroxyquinolines via condensation of an aldehyde, 2-naphthol or 6-hydroxyquinoline, and 2-aminobenzothiazole using water as the solvent has been reported that opens up an important alternative to the use of volatile organic solvents (Scheme 7.64).

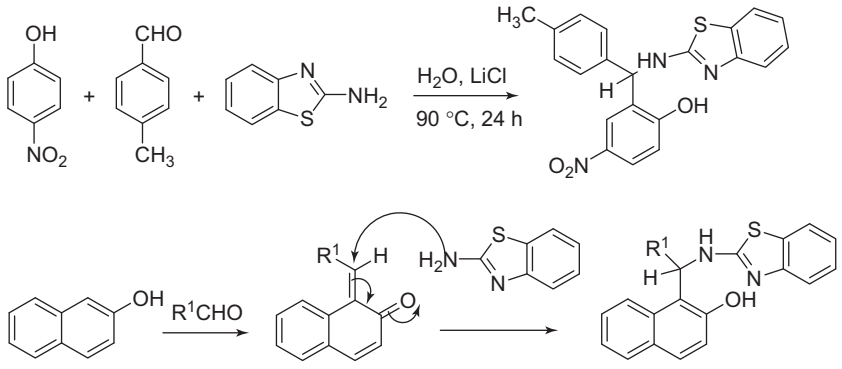
7.4 Zwitterions and Dipoles

In chemistry, a zwitterion (formerly called a *dipolar ion*) is a neutral molecule with a positive and a negative electrical charge, distinct from dipoles at different locations within the molecule. However, some chemists restrict the term to compounds with the charges on non-adjacent atoms. While all zwitterions are dipoles, not all dipoles are zwitterions. To be a zwitterion, the dipole must have specific (non-contiguous) atoms, each with a permanent (partial) charge. The best-known examples of zwitterions are the free amino acids found in cells. These compounds contain an ammonium and a carboxylate group and can be viewed as arising via a kind of intramolecular acid–base reaction, the amine group deprotonates the carboxylic acid (Scheme 7.65).

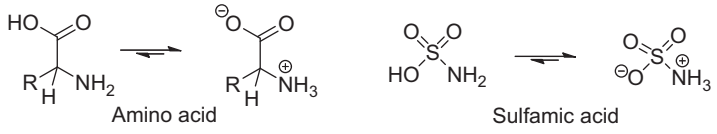
Amino acids, peptides, and proteins typically contain both acidic and basic functional groups such as carboxyl and amino groups. Carboxylic acids with a pK_a of ~5 can easily protonate an amine ($pK_b \approx 4$) in aqueous solution, and therefore molecules containing both carboxyl and amino groups are found to be zwitterions



Scheme 7.63 Reactions of *o*-quinone methide with various reagents.



Scheme 7.64 Synthesis of 2′-aminobenzothiazolo-(4-methylphenyl)methyl-4-nitrophenol and 2′-aminobenzothiazolomethyl-2-naphthols via *o*-quinone methide intermediate.



Scheme 7.65 Examples of zwitterions.

(both cations and anions) under near neutral pH conditions. At pH values near neutrality, a proton transfer reaction takes place that results in the –COOH becoming $-COO^-$ and the $-NH_2$ becoming $-NH_3^+$. A large favorable (stabilizing) electrostatic interaction now develops between these two parts of the molecule. This interaction is favorable enough to shift the equilibrium constant for the proton transfer reaction toward the formation of the charged species, by a factor of between 10- and 50-fold. In addition to the favorable electrostatic interaction between the charged regions, these same charged regions have very favorable electrostatic interactions with surrounding water molecules. Water molecules solvate these regions of the amino acid in a manner very similar to their solvation of cations and anions.

The physical properties of crystalline amino acids are consistent with their existence as zwitterions. Their melting points are relatively high, often above 200 °C (392 °F), and they are far more soluble in water than in nonpolar solvents such as ether or chloroform. Measured dipole moments for crystalline amino acids are fairly large, reflecting the significant degree of charge separation.

While the naturally occurring amino acids are not zwitterions in the vapor phase, they are in aqueous solutions, implying that water plays an important role in inducing zwitterion formation. Together, these observations inspire the question, How many water molecules are required to induce zwitterion formation in a given amino acid molecule? Calculations suggest that five water molecules are needed to transform glycine into its zwitterion, while four each are required for phenylalanine and tryptophan. Since the excess electron may also make a

contribution to zwitterion stabilization, these numbers are lower limits for how many water molecules are needed to induce zwitterion formation in these amino acids when no extra net charges are involved. Zwitterions strongly influence the structure and function of peptides and proteins. For this reason, it is important to understand zwitterion formation in amino acids themselves. All of the 20 common naturally occurring amino acids can form zwitterions in solution due to the stabilizing effects of solvation and/or counterions.

Glycine zwitterion is intrinsically (i.e., in the gas phase) not very stable, and solvation is a major contribution to stabilizing zwitterion. For instance, the glycine zwitterion has been calculated to be unstable by ~18 kcal mol^{-1}, whereas the zwitterion solvated by water molecules is more stable than neutral glycine by ~11 kcal mol^{-1}. Amino acids exist as zwitterions in solution and in their canonical forms in the gas phase. The zwitterionic form can be stabilized in the gas phase by salt bridge interactions when a net charge is present, or by shielding of the charges either by the addition of water molecules or by complex formation.

In addition to the amino acids, many other compounds that contain both acidic and basic centers tautomerize to the zwitterionic form. For example, bicine and tricine contain a basic secondary or tertiary amine fragment together with a carboxylic acid fragment. Neutron diffraction measurements show that solid sulfamic acid exists as a zwitterion. Many alkaloids, such as lysergic acid and psilocybin, exist as zwitterions because they contain carboxylates and ammonium centers. Many zwitterions contain quaternary ammonium cations. Since it lacks N–H bonds, the ammonium center cannot participate in tautomerization. Zwitterions containing quaternary-ammonium centers are common in biology, for example, betaines, which serve as electrolytes in fish. The membrane-forming phospholipids are also common zwitterions. The polar head groups in these compounds are zwitterions, resulting from the presence of the anionic phosphate and cationic quaternary ammonium centers.

In organic chemistry, a dipolar compound, or simply a dipole, is an electrically neutral molecule carrying a positive and a negative charge in at least one canonical description. In most dipolar compounds the charges are delocalized. Unlike salts, dipolar compounds have charges on separate atoms, not on positive and negative ions, that make up the compound. Dipolar compounds exhibit a dipole moment and can be represented by a resonance structure. Contributing structures containing charged atoms are denoted as zwitterions. Some dipolar compounds can have an uncharged canonical form (Figure 7.8).

Electrically neutral molecules carrying a positive and a negative charge in one of their major canonical descriptions are also called as *dipolar species*. In most dipolar

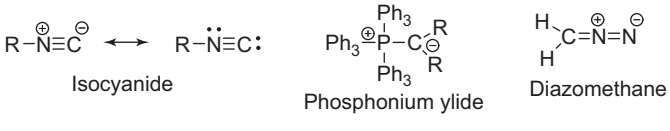
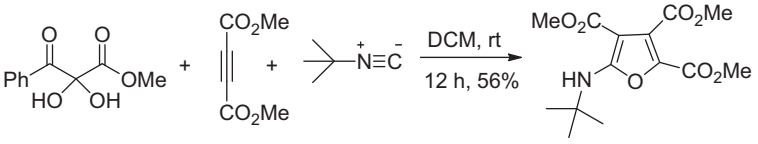


Figure 7.8 Common examples of dipolar species.

compounds the charges are delocalized; however, the term is also applied to species where this is not the case. 1,2-Dipolar compounds have the opposite charges on adjacent atoms (Scheme 7.66). The term *1,3-dipolar compounds* is used for those in which a significant canonical resonance form can be represented by a separation of charge over three atoms (in connection with 1,3-dipolar cycloadditions). Subclasses of 1,3-dipolar compounds include: allyl type, propargyl type, and carbene type.



Scheme 7.66 Formation of furan derivatives via isocyanide zwitterion.

7.5 Antiaromatic Systems

In 1965 Breslow coined the term antiaromaticity to describe cyclic compounds that are energetically destabilized by conjugation. This concept was rapidly and widely adopted, but it is hard to define and has generated considerable controversy, largely relating to quantifying the antiaromatic destabilization energy of a given species. Over the subsequent half-century various additional definitions have been proposed, and this concept has become a well-established tenet in organic chemistry that is routinely taught in introductory chemistry courses.

Antiaromatic molecules are cyclic systems containing alternating single and double bonds, where the π-electron energy of antiaromatic compounds is higher than that of its open-chain counterpart. Therefore, antiaromatic compounds are unstable and highly reactive; often, antiaromatic compounds distort themselves out of planarity to resolve this instability. Antiaromatic compounds fail Hückel's rule of aromaticity, that is, of $(4n+2)$ π-electrons. Compounds that are destabilized relative to conjugated noncyclic polyene models are called antiaromatic.

A compound is said to be antiaromatic if a planar cyclic conjugated system contains an even number of pairs of π-electrons. Antiaromatic molecules possess a negative value of resonance energy and a small energy gap between their highest occupied and lowest unoccupied molecular orbitals. In antiaromatic molecules, an external magnetic field induces a paramagnetic electron current. It has been found that conjugated rings with 2, 6, 10, and 14π-electrons are aromatic, while those with 4, 8, 12, 16, and 20 are not. Thus, it was found that the cyclopropenyl anion (**13**) is less stable than the cyclopropanyl anion (**14**), although the former is an allylic anion. The delocalized square-planar cyclobutadiene (**15**) is less stable than the localized rectangular form (**16**). The antiaromatic molecule will thus be in its ground state, but this will be of higher energy than would be calculated or found for a model system. Antiaromatic compounds can be expected to have properties antithetical to those of aromatic compounds (Figure 7.9).

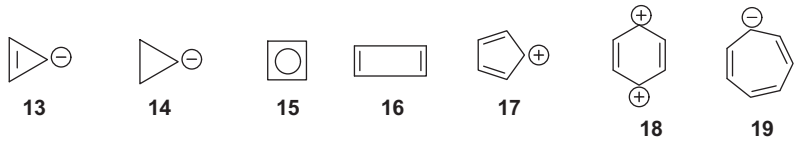


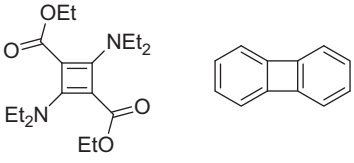
Figure 7.9 Antiaromatic species (**13–19**).

Very recently, it has been shown that on the basis of the energetic criterion of antiaromaticity and the proton affinity of 3-cyclopropenyl anion (**13**) this ion does not merit being differentiated from other allylic anions and is therefore best thought of as non-aromatic. Cyclopropene is the smallest cycloalkene, and its conjugate base at C3 is considered to be a special anion that is destabilized due to the presence of 4π electrons in this fully conjugated monocyclic species. Its acidity, however, follows the same correlation as for cyclobutene, cyclopentene, cyclohexene, and propene. No additional parameter beyond the central C–C–C bond angle is needed to explain or account for the weak acidity of cyclopropene.

The 3-cyclopropenyl anion is more basic than the allyl anion and cyclopropyl anion, its acyclic and saturated counterparts. This can be accounted for by the small central C–C–C bond angle and the resulting electrostatic repulsion in the constrained anion. No additional parameter is needed to account for the weak acidity of cyclopropene at the allylic position. Consequently, on the basis of the thermodynamic definition of antiaromaticity, this concept is not needed to describe the 3-cyclopropenyl anion. Magnetic criteria such as nuclear independent chemical shifts (NICSs) lead to a different conclusion, but in this instance there is no energetic basis for this view. Consequently, the 3-cyclopropenyl anion is best described as non-aromatic despite 50 years of thought to the contrary.

Cyclobutadiene has two bonding electrons, but the other two electrons are unpaired because of the degeneracy of the two nonbonding orbitals. The two electrons in the nonbonding levels do not contribute to the stabilization of the molecule. Furthermore, because these electrons occupy a high-energy orbital they are particularly available for chemical reactions. The experimental evidence indicates that cyclobutadiene is rectangular (**16**) rather than square (**15**) (Figure 7.9). This modifies somewhat the orbital picture from the simple *Hückel* pattern, which assumes a square geometry. The two-nonbonding levels are no longer degenerate, so cyclobutadiene is not predicted to have unpaired electrons. Nevertheless, higher-level MO calculations agree with the *Hückel* concept in predicting cyclobutadiene to be an extremely unstable molecule with a high-energy occupied orbital.

The π-electron energy of cyclobutadiene is higher than that of its open-chain counterpart, 1,3-butadiene, and it is therefore said to be antiaromatic rather than aromatic. Recent studies on cyclobutadiene show that it has a rectangular structure as opposed to a square structure and two different 1,2-dideuterio-1,3-cyclobutadiene stereoisomers. This indicates that the π-electrons are localized and therefore not considered to be aromatic. However, it is far from stable; it is highly reactive, and has a very short lifetime. Cyclobutadiene dimerizes by a Diels–Alder reaction at



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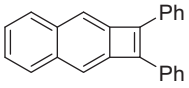


22

Figure 7.10 Some stable antiaromatic species.

35 K. The monomeric form has been studied at higher temperatures by trapping with matrix isolation in a noble gas.

The simplest $4n$ system is cyclobutadiene (in which $n = 1$), which is an extremely unstable compound. It can be stabilized by metal complexation. One method of stabilizing cyclobutadiene is by means of well-chosen substituents, for example, diethyl 2,4-bis(diethylamino)cyclobutadiene-1,3-dicarboxylate (**20**) is reasonably stable, melting at 52 °C, and the ring is square planar. Benzo-annelation has also been used as a method of stabilization. Biphenylene (**21**) has long been known, and 1,2-diphenylnaphtho[*b*]cyclobutadiene (**22**) is now known (Figure 7.10).

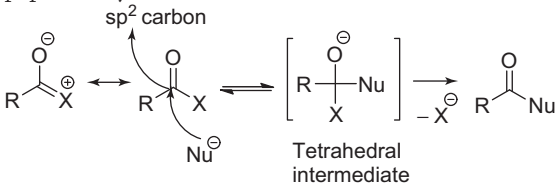
X-Ray diffraction studies indicate that the two bonds connecting the benzo rings in biphenylene are of approximately single bond length, and hence we might expect that the four-membered ring is an antiaromatic singlet. The NMR spectrum has indeed recently been interpreted as lending some support to an antiaromatic structure for the four-membered ring. Cyclooctatetraene is a $4n$ system but is neither aromatic nor antiaromatic because the molecule escapes a planar geometry. Cyclooctatetraene, with 8π electrons, is assumed to be planar. Three orbitals are bonding, three are antibonding, and two are nonbonding, that is, they have the same energy, α, as the original atomic orbitals.

By adding or removing an electron pair via a redox reaction, a π system can become aromatic and therefore more stable than the original non-aromatic or antiaromatic compound, for instance the cyclooctatetraenide dianion. The IUPAC criteria for antiaromaticity of a molecule are that the molecule must have $4n$ π electrons, where n is any integer, it must be cyclic, it must have a conjugated π-electron system, and it must be planar. It is observed that the energy difference between aromatic and antiaromatic compounds diminishes with increasing size. For instance, the 12π system diphenylene is an antiaromatic compound but it is stable and even commercially available. The low energy penalty for antiaromaticity is also demonstrated in certain pyrazine–dihydropyrazine pairs.

7.6 Tetrahedral Intermediates

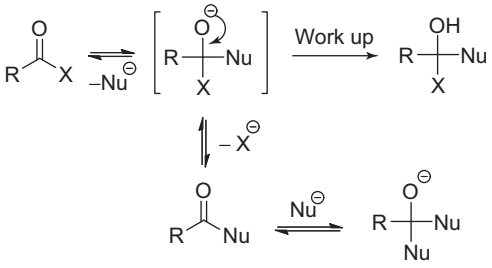
The tetrahedral intermediate is one of those iconic species on which the foundation of reaction mechanisms in organic chemistry is built. It refers to a (normally undetected and hence merely inferred) species formed initially when a nucleophilic reagent attacks a carbonyl compound. A tetrahedral intermediate is a reaction

intermediate in which the bond arrangement around an initially double-bonded carbon atom has been transformed from trigonal into tetrahedral. Tetrahedral intermediates result from nucleophilic addition to a carbonyl group. The stability of a tetrahedral intermediate depends on the ability of the groups attached to the new tetrahedral carbon atom to leave with the negative charge. Most tetrahedral intermediates have a more fleeting existence. Tetrahedral intermediates are very significant in organic syntheses and biological systems as a key intermediate in esterification, transesterification, ester hydrolysis, formation and hydrolysis of amides and peptides, hydride reductions, and other chemical reactions (Scheme 7.67).



Scheme 7.67 Nucleophilic substitution of carbonyl compounds through tetrahedral intermediate.

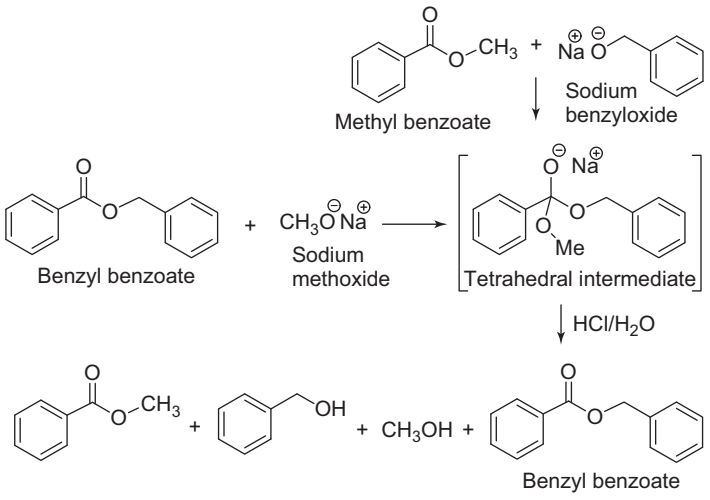
The carbonyl oxygen is basic, and will give electrons to Lewis acids, the carbonyl carbon is electrophilic and accepts electrons from and forms bonds with all sorts of nucleophiles. Addition of a nucleophile to a carbonyl will give a tetrahedral intermediate, and predicting what happens next is the same as predicting the carbonyl's chemistry. There are four possible outcomes for a tetrahedral intermediate. The reaction may reverse, stop there, or collapse to a new carbonyl compound, which may or may not go on to react again (Scheme 7.68). Its importance to understanding the activity of enzymes cannot be overstated.



Scheme 7.68 Fate of a tetrahedral intermediate.

One of the earliest accounts of the tetrahedral intermediate came from Rainer Ludwig Claisen in 1887. In the reaction of benzyl benzoate with sodium methoxide and methyl benzoate with sodium benzyl oxide, he observed a white precipitate which under acidic conditions yields benzyl benzoate, methyl benzoate, methanol, and benzyl alcohol (Scheme 7.69).

Victor Grignard assumed the existence of an unstable tetrahedral intermediate in 1901, while investigating the reaction of esters with organomagnesium reagents. The first evidence for tetrahedral intermediates in the substitution reactions of



Scheme 7.69 Formation of various products through a tetrahedral intermediate.

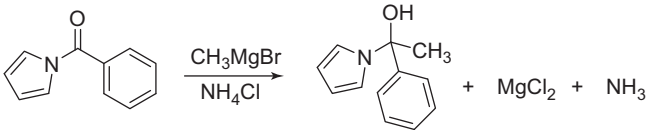
carboxylic derivatives was provided by Myron L. Bender in 1951. He labeled carboxylic acid derivatives with oxygen isotope O^{18} and treated them with water to make labeled carboxylic acids. At the end of the reaction, he found that the remaining starting material had a decreased proportion of labeled oxygen, which is consistent with the existence of the tetrahedral intermediate.

The nucleophilic attack on the carbonyl group proceeds via a Bürgi–Dunitz trajectory. The angle between the line of nucleophilic attack and the C–O bond is greater than 90°. This is due to a better orbital overlap between the HOMO of the nucleophile and the π^* LUMO of the C–O double bond. Although the tetrahedral intermediates are usually transient intermediates, many compounds of this general structure are known. The reactions of aldehydes, ketones, and their derivatives frequently have a detectable tetrahedral intermediate, while for the reactions of derivatives of carboxylic acids this is not the case. At the oxidation level of carboxylic acid derivatives, groups such as OR, OAr, NR_2, or Cl are conjugated with the carbonyl group, which means that addition to the carbonyl group is thermodynamically less favored than addition to corresponding aldehyde or ketone. Stable tetrahedral intermediates of carboxylic acid derivatives do exist and they usually possess at least one of the following four structural features: polycyclic structures (e.g., tetrodotoxin), compounds with a strong electron-withdrawing group attached to the acyl carbon (e.g., *N,N*-dimethyltrifluoroacetamide), compounds with donor groups that are poorly conjugated with the potential carbonyl group (e.g., cyclol), and compounds with sulfur atoms bonded to the anomeric center (e.g., S-acylated-1,8-naphtalenedithiol). These compounds were used to study the kinetics of tetrahedral intermediate decomposition into its respective carbonyl species, and to measure the IR, UV, and NMR spectra of the tetrahedral adduct.

The first X-ray crystal structures of tetrahedral intermediates were obtained from the porcine trypsin crystallized with soybean trypsin inhibitor in 1974, and the

bovine trypsin crystallized with bovine pancreatic trypsin inhibitor in 1973. In both cases the tetrahedral intermediate is stabilized in the active sites of enzymes, which have evolved to stabilize the transition state of peptide hydrolysis.

In 2002, David Evans *et al*. observed a very stable neutral tetrahedral intermediate in the reaction of N-acylpyrroles with organometallic compounds followed by protonation with ammonium chloride producing a carbinol (Scheme 7.70).



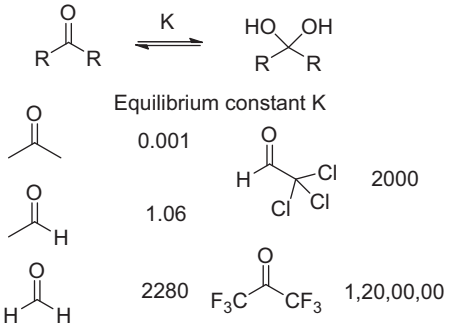
Scheme 7.70 Carbinol formation through a tetrahedral intermediate.

7.6.1 Acetals and Hemiacetals

Hemiacetals and acetals are essentially tetrahedral intermediates, formed by the addition of nucleophiles to a carbonyl group. They are relatively stable and used as protective groups in synthetic chemistry. A very well-known reaction occurs when acetaldehyde is dissolved in methanol to produce a hemiacetal. Most hemiacetals are unstable with respect to their parent aldehydes and alcohols. For example, the equilibrium constant for the reaction of acetaldehyde with simple alcohols is about 0.5, where the equilibrium constant is defined as $K = [\text{hemiacetal}]/[\text{aldehyde}][\text{alcohol}]$. Hemiacetals of ketones (sometimes called *hemiketals*) are even less stable than those of aldehydes. However, cyclic hemiacetals and hemiacetals bearing electron-withdrawing groups are stable. Electron-withdrawing groups attached to the carbonyl atom shift the equilibrium constant toward the hemiacetal. They increase the polarization of the carbonyl group, which already has a positively polarized carbonyl carbon, and make it even more prone to attack by a nucleophile. Scheme 7.71 shows the extent of hydration of some carbonyl compounds. Hexafluoroacetone is probably the most hydrated carbonyl compound possible. Formaldehyde reacts with water so readily because its substituents are very small, a purely steric effect.

Cyclopropanones, three-membered ring ketones, are also hydrated to a significant extent. Since three-membered rings are very strained (bond angles forced to be 60°), sp^3 hybridization is more favorable than sp^2 hybridization. For the sp^3 hybridized hydrate the bonds have to be distorted by about 49°, while for the sp^2 hybridized ketone the bond angle distortion is about 60°. Consequently, addition to the carbonyl group allows some of the strain inherent in the small ring to be released, which is why cyclopropanone and cyclobutanone are very reactive electrophiles (Figure 7.11).

Cyclohexanone hydrate is favored because it relieves a lot of angle strain. Chloral hydrate relieves dipole and steric interactions. Aldehyde hydrates are much more stable than ketone hydrates, presumably because they are both less hindered on the product side and more electron poor on the starting material side. Conjugation



Scheme 7.71 Extent of hydration of some carbonyl compounds.

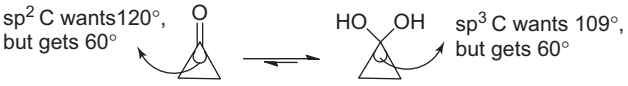


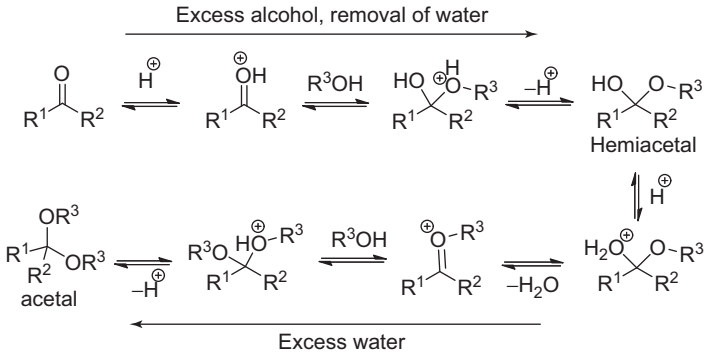
Figure 7.11 Strained three-membered rings.

of a phenyl group to the carbonyl group stabilizes the product side of the reaction, which is why acetophenone hydrate is much less favored than acetone hydrate.

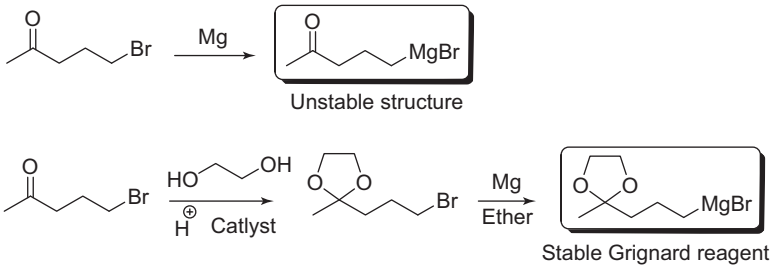
For larger rings, where the bond angles are not as distorted, the stability of the hemiacetals is due to entropy and the proximity of the nucleophile to the carbonyl group. Formation of an acyclic acetal involves a decrease in entropy because two molecules are consumed for every one produced. In contrast, the formation of cyclic hemiacetals involves a single molecule reacting with itself, making the reaction more favorable. Another way to understand the stability of cyclic hemiacetals is to look at the equilibrium constant as the ratio of the forward and backward reaction rate. For a cyclic hemiacetal the reaction is intramolecular so the nucleophile is always held close to the carbonyl group ready to attack, and so the forward rate of reaction is much higher than the backward rate. Many biologically relevant sugars such as glucose are cyclic hemiacetals.

In the presence of acid, hemiacetals can undergo an elimination reaction, losing the oxygen atom that once belonged to the parent aldehyde's carbonyl group. These oxonium ions are powerful electrophiles, and react rapidly with a second molecule of alcohol to from new stable compounds, called *acetals*. Scheme 7.72 shows the mechanism of acetal formation from a hemiacetal.

Acetals, as already pointed out, are stable tetrahedral intermediates and so they can be used as protective groups in organic synthesis. Acetals are stable under basic conditions, so they can be used to protect ketones from a base. An acetal group is hydrolyzed under acidic conditions. Scheme 7.73 gives an example with a dioxolane protecting group.



Scheme 7.72 Mechanism of hemiacetal and acetal formation.



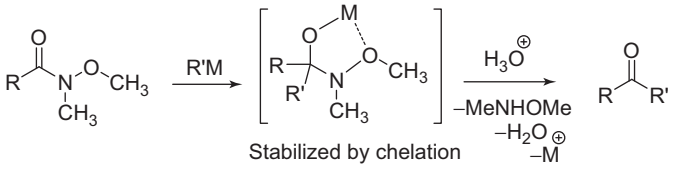
Scheme 7.73 Example of a protecting group.

7.6.2
Weinreb Amides

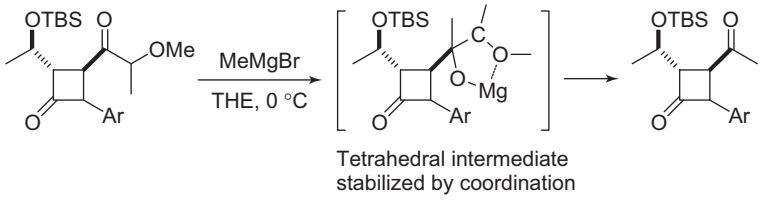
Weinreb amides are N-methoxy-N-methyl-carboxylic acid amides. They react with organometallic compounds to give ketones on protonation (Scheme 7.74). It is generally accepted that the high yields of ketones are due to the high stability of the five-membered ring-chelated intermediate. Quantum mechanical calculations have shown that the tetrahedral adduct is formed easily and it is fairly stable, in agreement with the experimental results. The very facile reaction of Weinreb amides with organolithium and Grignard reagents results from the chelate stabilization in the tetrahedral adduct and more importantly the transition state leading to the adduct (Scheme 7.75). Not only are the tetrahedral intermediates stabilized by chelation, but also (calculations suggest) acceleration arises from preferential chelation of the transition state. This allows the use of normally unreactive amides.

7.6.3
Applications in Biomedicine

A solvated ligand that binds the protein of interest is likely to exist as an equilibrium mixture of several conformers. Likewise the solvated protein also exists as several conformers in equilibrium. Formation of a protein–ligand complex includes



Scheme 7.74 Stable tetrahedral adduct.



Scheme 7.75 Tetrahedral intermediate stabilized by coordination.

displacement of the solvent molecules that occupy the binding site of the ligand, to produce a solvated complex. Because this necessarily means that the interaction is entropically disfavored, highly favorable enthalpy contacts between the protein and the ligand must compensate for the entropic loss. The design of new ligands is usually based on the modification of known ligands for the target proteins. Proteases are enzymes that catalyze hydrolysis of a peptide bond. These proteins have evolved to recognize and bind the transition state, which is a tetrahedral intermediate, of a peptide hydrolysis reaction. Therefore, the main protease inhibitors are tetrahedral intermediate mimics having an alcohol or a phosphate group. Examples are saquinavir, ritonavir, pepstatin, and so on.

7.7 Summary

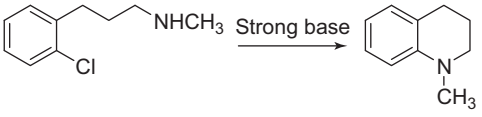
- Arynes and heteroarynes are derived formally by the removal of two adjacent (*ortho*-) substituents from aromatic or heteroaromatic rings, respectively, leaving behind two electrons to be distributed between two orbitals.
- Although in most cases the substituents are *ortho* to one another, this is not a prerequisite and *meta*- and *para*-arynes are also possible intermediates.
- Aryl halides upon treatment with strong base generate arynes.
- The reactions of arynes can be divided into three groups: (i) pericyclic reactions, (ii) nucleophilic additions, and (iii) transition-metal catalyzed reactions.
- The pericyclic reactions can be divided into several categories such as Diels–Alder reactions, [2+2] cycloadditions, 1,3- and 1,4-dipolar cycloadditions, and the ene reactions.
- The major application of arynes in synthesis is in the construction of polycyclic systems using either the Diels–Alder or intramolecular nucleophilic addition reactions.

- Cumulenes are a varied class of compounds, including species such as ketenes, allenes, ketenimines, and isocyanates as well as analogs where carbon is replaced by silicon or germanium, oxygen is replaced by sulfur or selenium, and nitrogen by phosphorus or arsenic.
- Ketenes were first recognized in 1905 when a stable and isolable example of diphenylketene was obtained from the dehalogenation of α-bromodiphenylacetyl bromide.
- The most characteristic reaction of ketenes is cycloaddition.
- QMs (quinone methides) are short-lived, highly reactive powerful intermediates used for the synthesis of complex natural products, modern materials, fine chemicals, and pharmaceuticals.
- The *o*-QM, which is generally formed through the condensation of phenol with aldehyde in the presence of acid or base catalyst, was first suggested by Fries in 1907.
- *o*-QMs are versatile intermediates involving a minimum of seven carbon atoms, which are mainly involved in 1,4-Michael type additions as well as aza-Michael reactions with various nucleophiles.
- A zwitterion (formerly called a *dipolar ion*) is a neutral molecule with a positive and a negative electrical charge, distinct from dipoles at different locations within the molecule.
- The best-known examples of zwitterions are the free amino acids found in cells.
- In addition to the amino acids, many other compounds that contain both acidic and basic centers tautomerize to the zwitterionic form.
- In 1965 Breslow coined the term *antiaromaticity* to describe cyclic compounds that are energetically destabilized by conjugation.
- Antiaromatic molecules are cyclic systems containing alternating single and double bonds, where the π-electron energy of antiaromatic compounds is higher than that of its open-chain counterpart. Therefore, antiaromatic compounds are unstable and highly reactive.
- Antiaromatic compounds fail Hückel's rule of aromaticity, that is, $(4n+2)$ π-electrons. Compounds that are destabilized relative to conjugated noncyclic polyene models are said to be *antiaromatic*.
- A tetrahedral intermediate is a reaction intermediate in which the bond arrangement around an initially double-bonded carbon atom has been transformed from trigonal into tetrahedral.
- Tetrahedral intermediates result from nucleophilic addition to a carbonyl group.
- The stability of a tetrahedral intermediate depends on the ability of the groups attached to the new tetrahedral carbon atom to leave with the negative charge.

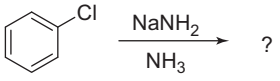
Problems

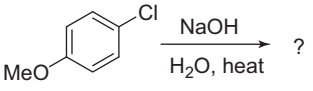
1. Show how benzynes can be used in electrophilic addiction reactions.
2. What is the product of dimerization of benzyne? Show the mechanism.
3. Describe four methods for the preparation of benzynes.

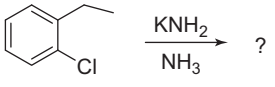
4. Draw all products formed when *m*-chlorotoluene is treated with KNH_2 in NH_3.
5. Explain why 2-chloro-1,3-dimethylbenzene is inert to nucleophilic aromatic substitution by way of an elimination–addition mechanism.
6. Depict the stepwise mechanism for the following reaction.



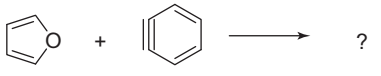
7. Illustrate the products of each reaction with a suitable mechanism.

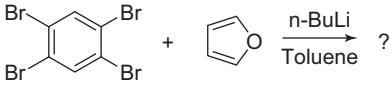
(i) 

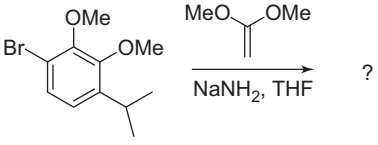
(ii) 

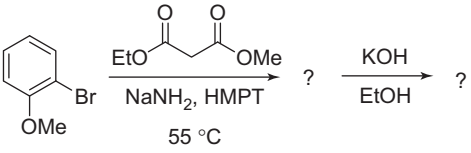
(iii) 

8. Why can't you turn an ester into a ketone with an organometallic reagent directly?
9. Write methods for the preparation of a ketone directly from an acid and an amide.
10. Complete the following reactions with a suitable mechanism.

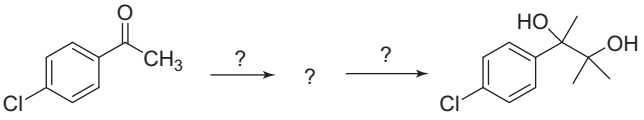
(i) 

(ii) 

(iii) 

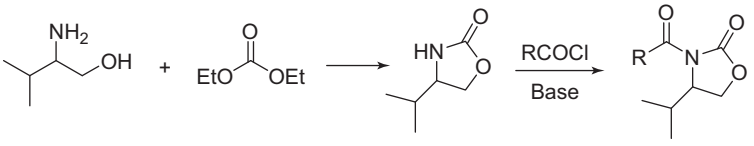
(iv) 

11. Suggest reagents with which to make the drug phenaglycodol by the route shown below.

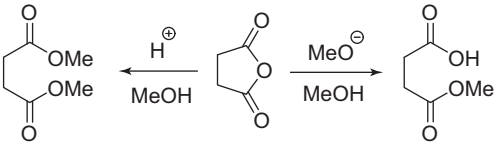


12. Explain why direct ester formation from carboxylic acids and alcohols works in acid solution but not in basic solution. By contrast, ester formation from alcohols and acid anhydrides or chlorides is commonly carried out in basic solution in the presence of bases such as pyridine. Why does this work?

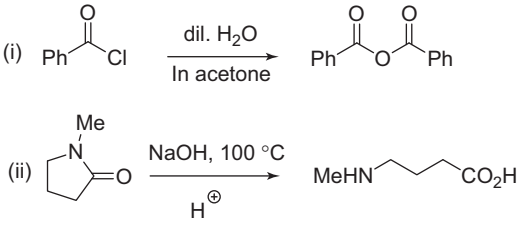
13. Suggest a mechanism for the following reaction.



14. It is possible to make either diester or monoester of butanedioic acid from succinic anhydride as shown below. Why does one method give the diester and the other the monoester?



15. Suggest mechanisms for the following reactions.



Further Reading

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