Chapter 26

Carbanions II

Malonic Ester and Acetoacetic Ester Syntheses

26.1 Carbanions in organic synthesis

We have already seen something of the importance to organic synthesis of the formation of carbon–carbon bonds: it enables us to make big molecules out of little ones. In this process a key role is played by negatively charged carbon. Such *nucleophilic carbon* attacks carbon holding a good leaving group—in alkyl halides or sulfonates, usually—or carbonyl or acyl carbon. Through nucleophilic substitution or nucleophilic addition, a new carbon-carbon bond is formed.

Nucleophilic carbon is of two general kinds. (a) There are the carbanion-like groups in organometallic compounds, usually generated through reaction of an organic halide with a metal: Grignard and organocadmium reagents, for example; the lithium dialkylcopper reagents used in the Corey-House synthesis of hydrocarbons; the organozinc compounds that are intermediates in the Reformatsky reaction. (b) There are the more nearly full-fledged carbanions generated through abstraction of α-hydrogens by base, as in the aldol and Claisen condensations and their relatives.

The difference between these two kinds of carbon is one of degree, not kind. There is interaction--just how much depending on the metal and the solvent—even between electropositive ions like sodium or potassium or lithium and the anion from carbonyl compounds. These intermediates, too, could be called organometallic compounds; the bonding is simply more ionic than that in, say, a Grignard reagent.

In this chapter we shall continue with our study of carbanion chemistry, with emphasis on the attachment of alkyl groups to the α-carbons of carbonyl and acyl compounds. Such *alkylation* reactions owe their great importance to the special nature of the carbonyl group, and in two ways. First, the carbonyl group makes α-hydrogens acidic, so that alkylation can take place. Next, the products

obtained still contain the carbonyl group and hence are highly reactive; they are ideal intermediates for *further* molecule-building.

Of the very many alkylation methods that have been developed, we can look at only a few: first, two classics of organic synthesis, the *malonic ester synthesis* and the *acetoacetic ester synthesis*; and then, several newer methods. In doing this we shall be concerned not only with learning a bit more about how to make new molecules from old ones, but also with seeing the variety of ways in which carbanion chemistry is involved.

26.2 Malonic ester synthesis of carboxylic acids

One of the most valuable methods of preparing carboxylic acids makes use of ethyl malonate (*malonic ester*), $CH_2(COOC_2H_5)_2$, and is called the **malonic ester synthesis**. This synthesis depends upon (a) the high acidity of the α-hydrogens of malonic ester, and (b) the extreme ease with which malonic acid and substituted malonic acids undergo decarboxylation. (As we shall see, this combination of properties is more than a happy accident, and can be traced to a single underlying cause.)

Like acetoacetic ester (Sec. 21.11), and for exactly the same reason, malonic ester contains α-hydrogens that are particularly acidic: they are *alpha* to *two* carbonyl groups. When treated with sodium ethoxide in absolute alcohol, malonic ester is converted largely into its salt, *sodiomalonic ester*:

$$\underset{\text{Stronger acid}}{CH_2(COOC_2H_5)_2} + Na^+{}^-OC_2H_5 \rightleftharpoons \underset{\text{Sodiomalonic ester}}{CH(COOC_2H_5)_2{}^-Na^+} + \underset{\text{Weaker acid}}{HOC_2H_5}$$

Reaction of this salt with an alkyl halide yields a substituted malonic ester, an *ethyl alkylmalonate*, often called an *alkylmalonic ester*:

$$CH(COOC_2H_5)_2{}^-Na^+ + RX \longrightarrow \underset{\substack{\text{Ethyl alkylmalonate}\\ \text{Alkylmalonic ester}}}{RCH(COOC_2H_5)_2} + Na^+X^-$$

This reaction involves nucleophilic attack on the alkyl halide by the carbanion, $CH(COOC_2H_5)_2{}^-$, and, as we might expect, gives highest yields with primary alkyl halides, lower yields with secondary alkyl halides, and is worthless for tertiary alkyl halides and for aryl halides.

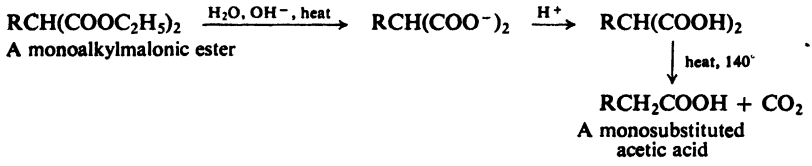
The alkylmalonic ester still contains one ionizable hydrogen, and on treatment with sodium ethoxide it, too, can be converted into its salt; this salt can react with an alkyl halide—which may be the same as, or different from, the first alkyl halide—to yield a dialkylmalonic ester:

$$RCH(COOC_2H_5)_2 + Na^+{}^-OC_2H_5 \rightleftharpoons RC(COOC_2H_5)_2{}^-Na^+ + C_2H_5OH$$

$$\downarrow R'X$$

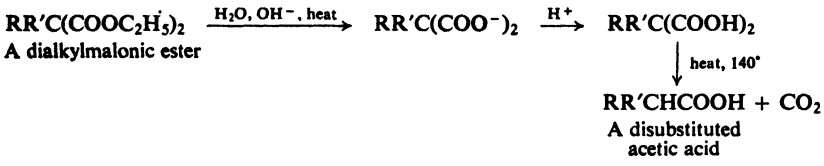
$$\underset{\text{Dialkylmalonic ester}}{RR'C(COOC_2H_5)_2} + Na^+X^-$$

The acidity of malonic ester thus permits the preparation of substituted malonic esters containing one or two alkyl groups. How can these substituted malonic esters be used to make carboxylic acids? When heated above its melting point, malonic acid readily loses carbon dioxide to form acetic acid; in a similar way substituted malonic acids readily lose carbon dioxide to form substituted acetic acids. The monoalkyl- and dialkylmalonic esters we have prepared are readily converted into monocarboxylic acids by hydrolysis, acidification, and heat:



A monoalkylmalonic ester

A monosubstituted acetic acid

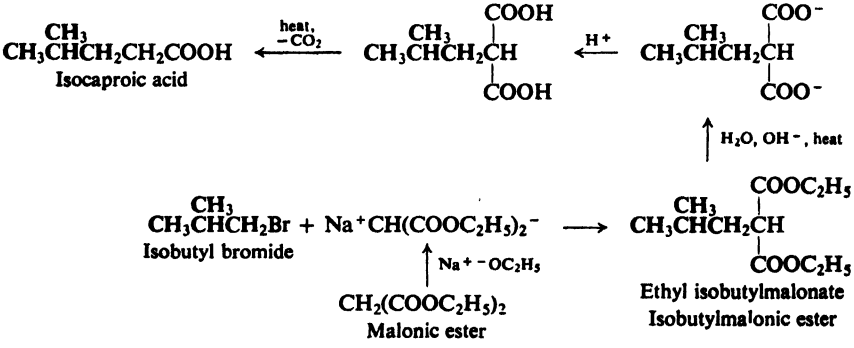


A dialkylmalonic ester

A disubstituted acetic acid

A malonic ester synthesis yields an acetic acid in which one or two hydrogens have been replaced by alkyl groups.

In planning a malonic ester synthesis, our problem is to select the proper alkyl halide or halides; to do this, we have only to look at the structure of the acid we want. Isocaproic acid, for example, $(CH_3)_2CHCH_2CH_2COOH$, can be considered as acetic acid in which one hydrogen has been replaced by an isobutyl group. To prepare this acid by the malonic ester synthesis, we would have to use isobutyl bromide as the alkylating agent:



Isocaproic acid

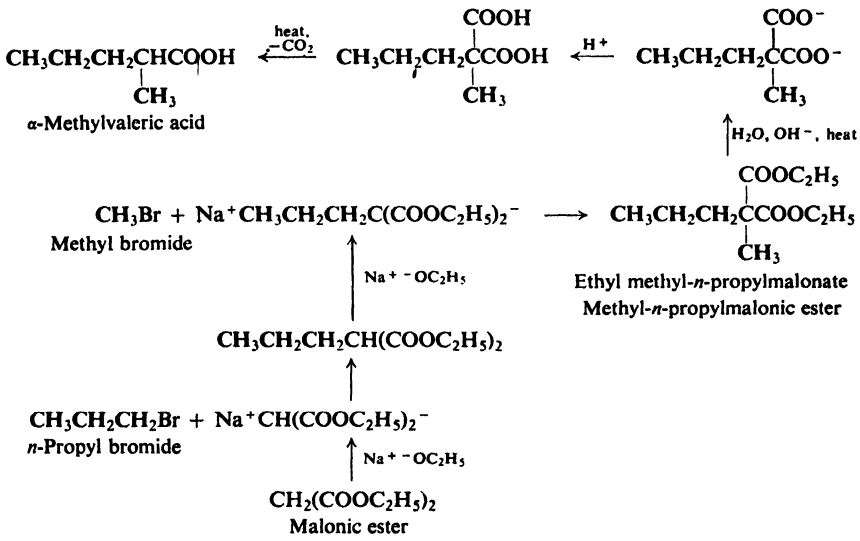
Isobutyl bromide

Malonic ester

Ethyl isobutylmalonate

Isobutylmalonic ester

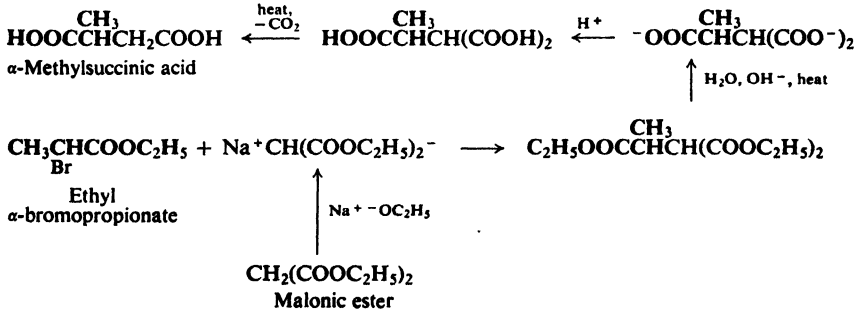
An isomer of isocaproic acid, α-methylvaleric acid, $CH_3CH_2CH_2CH(CH_3)COOH$, can be considered as acetic acid in which one hydrogen has been replaced by a



n-propyl group and a second hydrogen has been replaced by a methyl group; we must therefore use two alkyl halides, *n*-propyl bromide and methyl bromide.

The basic malonic ester synthesis we have outlined can be modified. Often one can advantageously use: different bases as, for example, potassium *tert*-butoxide; alkyl sulfonates instead of halides; polar aprotic solvents like DMSO or DMF (Sec. 1.21).

In place of simple alkyl halides, certain other halogen-containing compounds may be used, in particular the readily available α-bromo esters (why can α-bromo-*acids* not be used?), which yield substituted succinic acids by the malonic ester synthesis. For example:



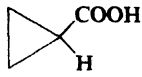
Problem 26.1 Outline the synthesis of the following compounds from malonic ester and alcohols of four carbons or less:

(a) the isomeric acids, *n*-valeric, isovaleric, and α-methylbutyric. (Why can the malonic ester synthesis not be used for the preparation of trimethylacetic acid?)
(b) *leucine* (α-aminoisocaproic acid)
(c) *isoleucine* (α-amino-β-methylvaleric acid)

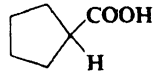
Problem 26.2 *Adipic acid* is obtained from a malonic ester synthesis in which the first step is addition of one mole of ethylene bromide to a large excess of sodiomalonic ester in alcohol. *Cyclopropanecarboxylic acid* is the final product of a malonic ester synthesis in which the first step is addition of one mole of sodiomalonic ester to two moles of ethylene bromide followed by addition of one mole of sodium ethoxide.

$HOOCCH_2CH_2CH_2CH_2COOH$

Adipic acid



Cyclopropane-carboxylic acid



Cyclopentane-carboxylic acid

(a) Account for the difference in the products obtained in the two syntheses. (b) Tell exactly how you would go about synthesizing *cyclopentanecarboxylic acid.*

Problem 26.3 (a) Malonic ester reacts with benzaldehyde in the presence of piperidine (a secondary amine, Sec. 31.12) to yield a product of formula $C_{14}H_{16}O_4$. What is this compound, and how is it formed? (This is an example of the **Knoevenagel reaction.** Check your answer in Problem 21.22 (f), p. 714.) (b) What compound would be obtained if the product of (a) were subjected to the sequence of hydrolysis, acidification, and heating? (c) What is another way to synthesize the product of (b)?

Problem 26.4 (a) Cyclohexanone reacts with cyanoacetic ester (ethyl cyanoacetate, $N{\equiv}CCH_2COOC_2H_5$) in the presence of ammonium acetate to yield a product of formula $C_{11}H_{15}O_2N$. What is this compound, and how is it formed? (This is an example of the **Cope reaction.** Check your answer in Problem 21.22 (g), p. 714.) (b) What compound would be formed from the product of (a) by the sequence of hydrolysis, acidification, and heating?

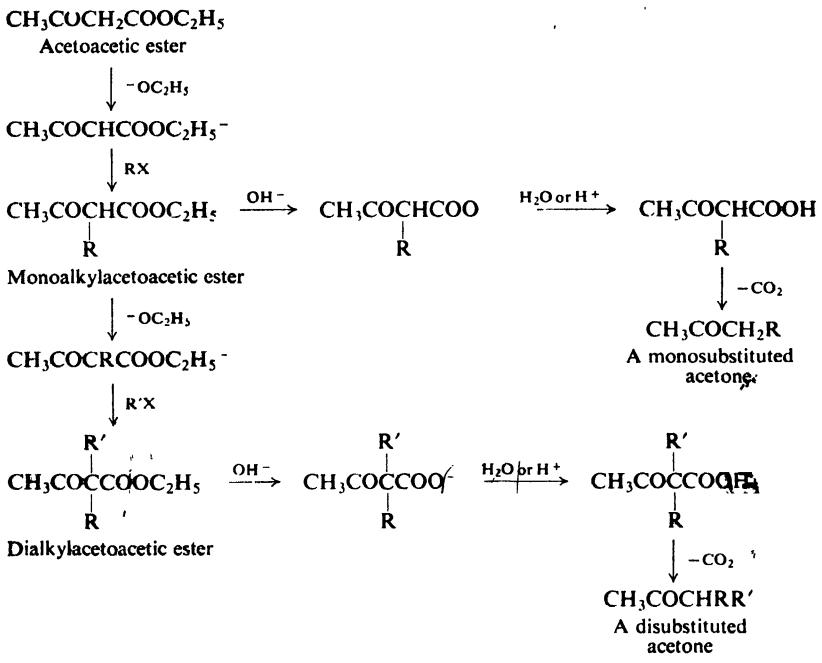
Problem 26.5 In an example of the **Michael condensation,** malonic ester reacts with ethyl 2-butenoate in the presence of sodium ethoxide to yield A, of formula $C_{13}H_{22}O_6$. The sequence of hydrolysis, acidification, and heating converts A into 3-methylpentanedioic acid. What is A, and how is it formed? (*Hint:* See Sec. 8.20. Check your answer in Sec. 27.7.)

26.3 Acetoacetic ester synthesis of ketones

One of the most valuable methods of preparing ketones makes use of ethyl acetoacetate (*acetoacetic ester*), $CH_3COCH_2COOC_2H_5$, and is called the **acetoacetic ester synthesis of ketones.** This synthesis closely parallels the malonic ester synthesis of carboxylic acids.

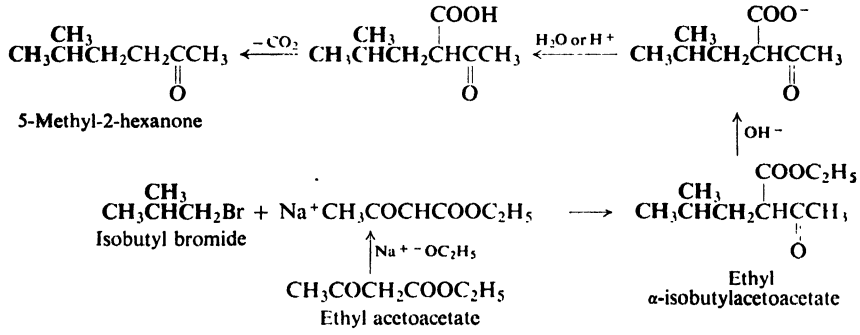
Acetoacetic ester is converted by sodium ethoxide into the sodioacetoacetic ester, which is then allowed to react with an alkyl halide to form an alkylacetoacetic ester (an ethyl alkylacetoacetate), $CH_3COCHRCOOC_2H_5$; if desired, the alkylation can be repeated to yield a dialkylacetoacetic ester, $CH_3COCRR'COOC_2H_5$. All alkylations are conducted in absolute alcohol.

When hydrolyzed by dilute aqueous alkali (or by acid), these monoalkyl- or dialkylacetoacetic esters yield the corresponding acids, $CH_3COCHRCOOH$ or $CH_3COCRR'COOH$, which undergo decarboxylation to form ketones, CH_3COCH_2R or $CH_3COCHRR'$. This loss of carbon dioxide occurs even more readily than from malonic acid, and may even take place before acidification of the hydrolysis mixture.



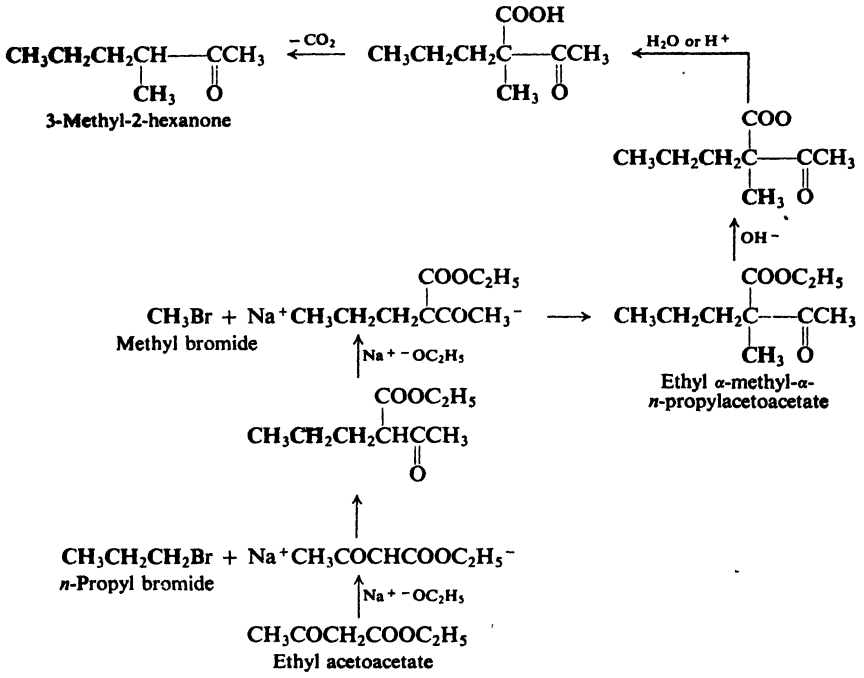
The acetoacetic ester synthesis of ketones yields an acetone molecule in which one or two hydrogens have been replaced by alkyl groups.

In planning an acetoacetic ester synthesis, as in planning a malonic ester synthesis, our problem is to select the proper alkyl halide or halides. To do this, we have only to look at the structure of the ketone we want. For example, 5-methyl-2-hexanone can be considered as acetone in which one hydrogen has been replaced by an isobutyl group. In order to prepare this ketone by the acetoacetic ester synthesis, we would have to use isobutyl bromide as the alkylating agent:



The isomeric ketone 3-methyl-2-hexanone can be considered as acetone in which one hydrogen has been replaced by a *n*-propyl group and a second hydrogen

(on the same carbon) has been replaced by a methyl group; we must therefore use two alkyl halides, *n*-propyl bromide and methyl bromide:



Like the malonic ester synthesis, this synthesis, too, can be modified by changes in the base, solvent, and alkylating agent.

Problem 26.6 To what general class does the reaction between sodioacetoacetic ester and an alkyl halide belong? Predict the relative yields using primary, secondary, and tertiary halides. Can aryl halides be used?

Problem 26.7 (a) Predict the product of the acetoacetic ester synthesis in which ethyl bromoacetate (why not bromoacetic *acid*?) is used as the halide. To what general class of compounds does this product belong? (b) Predict the product of the acetoacetic ester synthesis in which benzoyl chloride is used as the halide; in which chloroacetone is used as the halide. To what general classes of compounds do these products belong?

Problem 26.8 Outline the synthesis of the following compounds from acetoacetic ester, benzene, and alcohols of four carbons or less:

(a)–(c) the isomeric ketones:
methyl *n*-butyl ketone (2-hexanone)
methyl isobutyl ketone (4-methyl-2-pentanone)
methyl *sec*-butyl ketone (3-methyl-2-pentanone)

(d) Why can the acetoacetic ester synthesis not be used for the preparation of methyl *tert*-butyl ketone?

(e) 2,4-pentanedione (*acetylacetone*)

(f) 2,5-hexanedione (*acetonylacetone*)

(g) 1-phenyl-1,4-pentanedione

Problem 26.9 The best general preparation of **α-keto acids** is illustrated by the sequence:

ethyl propionate + ethyl oxalate $\xrightarrow{NaOC_2H_5}$ A ($C_9H_{14}O_5$)

A + dil. H_2SO_4 $\xrightarrow{boil}$ $CO_2 + 2C_2H_5OH + CH_3CH_2\underset{\underset{O}{\|}}{C}COOH$ (α-ketobutyric acid)

What familiar reactions are involved? What is the structure of A?

Problem 26.10 Outline the synthesis from simple esters of:

(a) α-ketoisocaproic acid
(b) α-keto-β-phenylpropionic acid
(c) α-ketoglutaric acid
(d) *leucine* (α-aminoisocaproic acid). (*Hint:* See Sec. 22.11.)
(e) *glutamic acid* (α-aminoglutaric acid)

26.4 Decarboxylation of β-keto acids and malonic acids

The acetoacetic ester synthesis thus depends on (a) the high acidity of the α-hydrogens of β-keto esters, and (b) the extreme ease with which β-keto acids undergo decarboxylation. These properties are exactly parallel to those on which the malonic ester synthesis depends.

We have seen that the higher acidity of the α-hydrogens is due to the ability of the keto group to help accommodate the negative charge of the acetoacetic ester anion. The ease of decarboxylation is, in part, due to *exactly the same factor.* (So, too, is the occurrence of the Claisen condensation, by which the acetoacetic ester is made in the first place.)

Decarboxylation of β-keto acids involves both the free acid and the carboxylate ion. Loss of carbon dioxide from the anion

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-COO^- \longrightarrow CO_2 + CH_3-\underset{O}{C}=CH_2$$

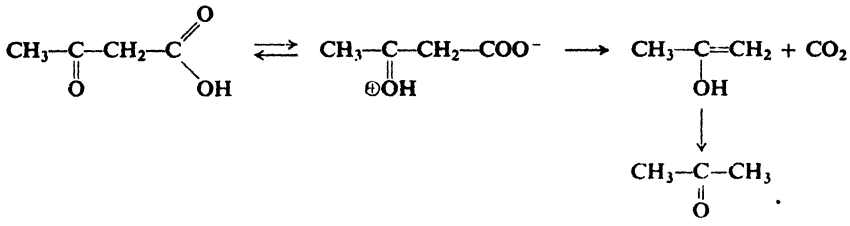
I

yields the carbanion I. This carbanion is formed faster than the simple carbanion ($R:^-$) that would be formed from a simple carboxylate ion ($RCOO^-$) because it is more stable. It is more stable, of course, due to the accommodation of the negative charge by the keto group.

Problem 26.11 Decarboxylation of malonic acid involves both the free acid and the monoanion, but not the doubly-charged anion. (a) Account for the ease of decarboxylation of the monoanion. Which end loses carbon dioxide? (b) How do you account for the lack of reactivity of the doubly-charged anion? (*Hint:* See Sec. 18.20.)

Problem 26.12 In contrast to most carboxylic acids (benzoic acid, say) 2,4,6-trinitrobenzoic acid is decarboxylated extremely easily: by simply boiling it in aqueous acid. How do you account for this?

Decarboxylation of free acetoacetic acid involves transfer of the acidic hydrogen to the keto group, either *prior to* (as shown here) or *simultaneously with*



loss of carbon dioxide. We are quite familiar with the function of protonation to reduce the basicity of a leaving group.

Problem 26.13 When dimethylacetoacetic acid is decarboxylated in the presence of iodine or bromine, there is obtained an iododimethylacetone or a bromodimethylacetone (3-halo-3-methyl-2-butanone), although under these conditions neither iodine nor bromine reacts significantly with the dimethylacetone. What bearing does this experiment have on the mechanism of decarboxylation?

Problem 26.14 Suggest a mechanism for the decarboxylation of free malonic acid.

Problem 26.15 Account for the comparative ease with which phenylpropiolic acid, $C_6H_5C{\equiv}CCOOH$, undergoes decarboxylation in alkaline solution.

26.5 Direct and indirect alkylation of esters and ketones

By the malonic ester and acetoacetic ester we make α-substituted acids and α-substituted ketones. But why not do the job *directly*? Why not convert simple acids (or esters) and ketones into their carbanions, and allow these to react with alkyl halides? There are a number of obstacles: (a) self-condensation—aldol condensation, for example, of ketones; (b) polyalkylation; and (c) for unsymmetrical ketones, alkylation at *both* α-carbons, or at the wrong one. Consider self-condensation. A carbanion can be generated from, say, a simple ketone; but competing with attack on an alkyl halide is attack at the carbonyl carbon of another ketone molecule. What is needed is a base-solvent combination that can convert the ketone *rapidly* and essentially *completely* into the carbanion before appreciable self-condensation can occur. Steps toward solving this problem have been taken, and there are available methods—so far, of limited applicability—for the direct alkylation of acids and ketones.

A tremendous amount of work has gone into the development of alternatives to direct alkylation. Another group is introduced temporarily to do one or more of these things: increase the acidity of the α-hydrogens, prevent self-condensation, and direct alkylation to a specific position. The malonic ester and acetoacetic ester syntheses are, of course, typical of this approach. In the acetoacetic ester synthesis, for example, the carbethoxy group, —COOEt, enhances the acidity of

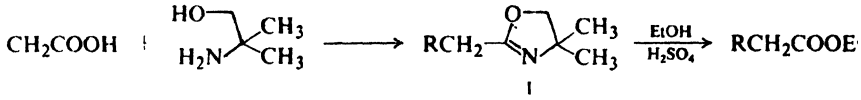
α-hydrogens, but only those on one particular α-carbon, so that alkylation will take place there. Then, when alkylation is over, the carbethoxy group is easily removed by hydrolysis and decarboxylation.

In the biosynthesis of fats (Sec. 37.6), long-chain carboxylic acids are made via a series of what are basically malonic ester syntheses. Although in this case reactions are catalyzed by enzymes, the system still finds it worthwhile to consume carbon dioxide to make a malonyl compound, then form a new carbon–carbon bond, and finally eject the carbon dioxide.

To get some idea of the way problems like these are being approached, let us look at just a few of the other alternatives to direct alkylation.

26.6 Synthesis of acids and esters via 2-oxazolines

Reaction of a carboxylic acid with 2-amino-2-methyl-1-propanol yields a heterocyclic compound called a *2-oxazoline* (I). From this compound the acid can be regenerated, in the form of its ethyl ester, by ethanolysis.

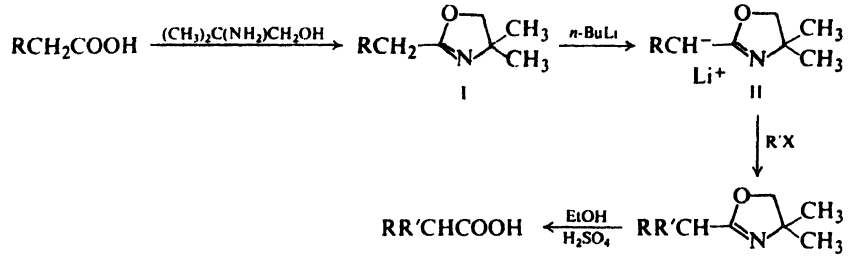


2-Amino-2-methyl-1-propanol

I

A 2-alkyl-4,4-dimethyl-2-oxazoline

Using this way to protect the carboxyl group, A. I. Meyers (Colorado State University) has recently opened an elegant route to alkylated acetic acids—or, by modification along Reformatsky lines, to β-hydroxy esters.



I II

Treatment of the 2-oxazoline with the strong base, *n*-butyllithium, yields the lithio derivative II. This, like sodiomalonic ester, can be alkylated and, if desired, re-alkylated—up to a total of *two* substituents on the α-carbon. Ethanolysis of the new 2-oxazoline yields the substituted ester.

The synthesis depends on: (a) the ease of formation and hydrolysis of 2-oxazolines; (b) the fact that the α-hydrogens retain their acidity in the oxazoline (*Why?*); and (c) the inertness of the 2-oxazoline ring toward the lithio derivative. (The ring is inert toward the Grignard reagent as well, and can be used to protect the carboxyl group in a wide variety of syntheses.)

Problem 26.16 Using the Meyers oxazoline method, outline all steps in the synthesis of: (a) *n*-butyric acid from acetic acid; (b) isobutyric acid from acetic acid; (c) isobutyric acid from propionic acid; (d) β-phenylpropionic acid from acetic acid.

Problem 26.17 (a) Give structural formulas of compounds A and B.

Oxazoline I (R = H) + *n*-BuLi, then $CH_3(CH_2)_5CHO \longrightarrow$ A

A + EtOH, $H_2SO_4 \longrightarrow$ B ($C_{11}H_{22}O_3$)

(b) Outline all steps in the synthesis of ethyl 3-(*n*-propyl)-3-hydroxyhexanoate. (c) Of ethyl 2-ethyl-3-phenyl-3-hydroxypropanoate.

Problem 26.18 (a) Give structural formulas of compounds C–E.

4-hydroxycyclohexanecarboxylic acid + $(CH_3)_2C(NH_2)CH_2OH \longrightarrow$ C ($C_{11}H_{19}O_2N$)

C + CrO_3/pyridine $\longrightarrow$ D ($C_{11}H_{17}O_2N$)

D + C_6H_5MgBr, then C_2H_5OH, $H_2SO_4 \longrightarrow$ E ($C_{15}H_{18}O_2$)

(b) Using benzene, toluene, and any needed aliphatic and inorganic reagents, how would you make $C_6H_5COCH_2CH_2COOH$? (*Hint:* See Sec. 20.10.) (c) Now, how would you make $C_6H_5C(C_2H_5)=CHCH_2COOH$? (d) Outline a possible synthesis of *p*-$CH_3CH_2CHOHC_6H_4COOC_2H_5$. (e) Of $C_6H_5CHOHC_6H_4COOC_2H_5$-*p*.

26.7 Organoborane synthesis of acids and ketones

Hydroboration of alkenes yields alkylboranes, and these, we have seen (Sec. 15.9), can be converted through oxidation into alcohols. But oxidation is only one of many reactions undergone by alkylboranes. Since the discovery of hydroboration in 1957, H. C. Brown and his co-workers (p. 507) have shown that alkylboranes are perhaps the most versatile class of organic reagents known.

In the presence of base, alkylboranes react with bromoacetone to yield alkylacetones, and with ethyl bromoacetate to yield ethyl alkylacetates.

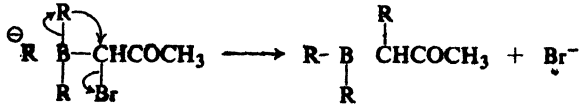
$$R_3B + BrCH_2COCH_3 \xrightarrow{base} RCH_2COCH_3$$
Bromoacetone — An alkylacetone

$$R_3B + BrCH_2COOEt \xrightarrow{base} RCH_2COOEt$$
Ethyl bromoacetate — An ethyl alkylacetate

The following mechanism has been postulated, illustrated for reaction with bromoacetone. Base abstracts (1) a proton—one that is *alpha* both to the carbonyl group and to bromine—to give the carbanion I. Being a strong base, carbanion I

(1) $$\text{Base:} + CH_2BrCOCH_3 \rightleftharpoons {}^-CHBrCOCH_3 + \text{Base:H}$$
I

(2) $$R_3B + {}^-CHBrCOCH_3 \longrightarrow R_3\overset{\ominus}{B}\text{:}CHBrCOCH_3$$
I — II

(3) 
II — III

$$\text{(4)}\qquad R_2B\text{—}\underset{\text{III}}{\overset{R}{\overset{|}{C}}}HCOCH_3 + \text{Base:H} \longrightarrow RCH_2COCH_3 + R_2B\text{:Base}$$

combines (2) with the (Lewis) acidic alkylborane to give II. Intermediate II now rearranges (3) with loss of halide ion to form III. Finally, III undergoes (4) protonolysis (a Lowry-Brønsted acid-base reaction this time) to yield the alkylated ketone.

The key step is (3), in which a new carbon–carbon bond is formed. In II, boron carries a negative charge. Made mobile by this negative charge, and attracted by the adjacent carbon holding a good leaving group, an alkyl group migrates to this carbon—taking its electrons along—and displaces the weakly basic halide ion.

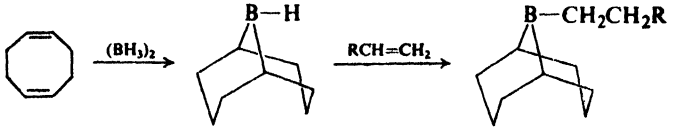
We have, then, three acid-base reactions and a 1,2-alkyl shift: all familiar reaction types. Step (1) involves formation of a carbanion; step (3) involves intramolecular nucleophilic (S_N2) attack by a carbanion-like alkyl group; and step (4) involves attachment of a proton to a carbanion or a carbanion-like moiety.

Protonolysis of alkylboranes is much more difficult than protonolysis of, say, Grignard reagents. The course of reaction (4) is evidently not equilibrium-controlled, but rate-controlled: it is not the stronger base, $R:^-$, that gets the proton, but instead the resonance-stabilized carbanion $[RCHCOCH_3]^-$.

Problem 26.19 Trialkylboranes are inert to water, but are particularly prone to protonolysis by carboxylic acids. (a) Can you suggest a specific mechanism for protonolysis of R_3B by a carboxylic acid? (b) For protonolysis of $R_2BCH(R)COCH_3$ by, say, ArOH?

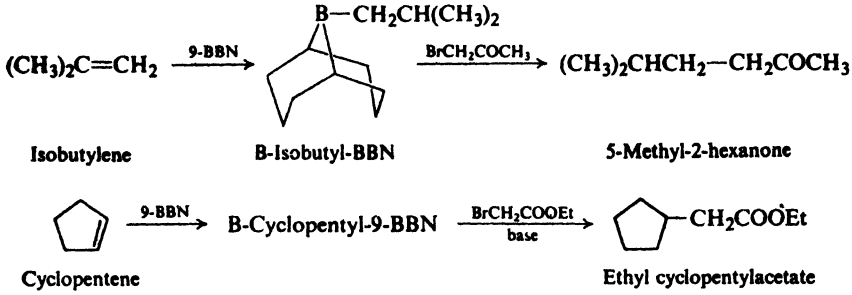
As a synthetic route, this organoborane synthesis parallels the acetoacetic ester and malonic ester syntheses. An acetone unit is furnished by acetoacetic ester or, here, by bromoacetone; an acetic acid unit is furnished by malonic ester or, here, by bromoacetic ester. In these syntheses, bromine plays the same part that the —COOEt group did: by increasing the acidity of certain α-hydrogens, it determines *where* in the molecule reaction will take place; it is easily lost from the molecule when its job is done. Unlike the loss of —COOEt, the departure of —Br is an integral part of the alkylation process.

Consistently high yields depend on the proper selection of reagents. In general, the best base is the bulky potassium 2,6-di-*tert*-butylphenoxide. The best alkylating agent is B-alkyl-9-borabicyclo[3.3.1]nonane, or "B-alkyl-9-BBN," available via successive hydroborations of alkenes:



1,5-Cyclooctadiene — 9-Borabicyclo[3.3.1]nonane (9-BBN) *As dimer* — B-Alkyl-9-borabicyclo[3.3.1]nonane (B-Alkyl-9-BBN)

The overall sequence thus amounts to the conversion of alkenes into ketones and esters. For example:

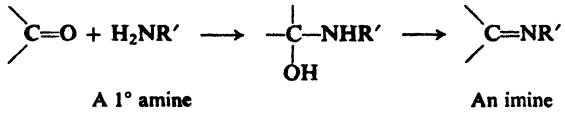


Besides bromoacetone, other bromomethyl ketones ($BrCH_2COR$) can be used if they are available. Bromination is best carried out with cupric bromide as the reagent, and on ketones in which R contains no α-hydrogens to compete with those on methyl: acetophenone, for example, or methyl *tert*-butyl ketone.

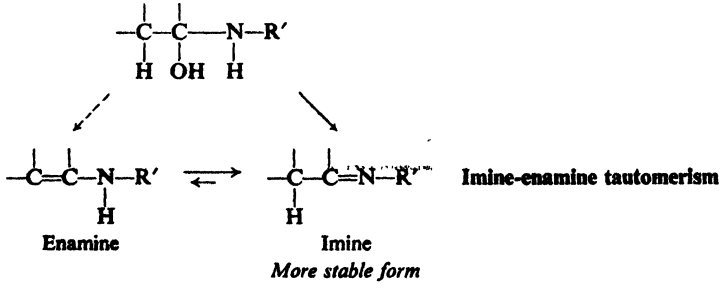
Problem 26.20 Using 9-BBN plus any alkenes and unhalogenated acids or ketones, outline all steps in the synthesis of: (a) 2-heptanone; (b) 4-methylpentanoic acid; (c) 4-methyl-2-hexanone; (d) 1-cyclohexyl-2-propanone; (e) ethyl (*trans*-2-methylcyclopentyl)acetate; (f) 1-phenyl-4-methyl-1-pentanone; (g) 1-cyclopentyl-3,3-dimethyl-2-butanone.

26.8 Alkylation of carbonyl compounds via enamines

As we might expect, amines react with carbonyl compounds by nucleophilic addition. If the amine is *primary*, the initial addition product undergoes dehydration (compare Sec. 19.14) to form a compound containing a carbon–nitrogen



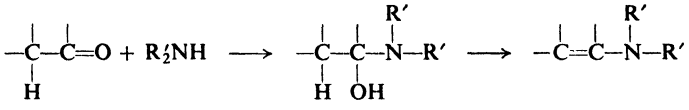
double bond, an *imine*. Elimination occurs with this orientation even if the carbonyl compound contains an α-hydrogen: that is, the preferred product is the



imine rather than the *enamine* (*ene* for the carbon–carbon double bond, *amine* for the amino group). If some enamine should be formed initially it rapidly tautomerizes into the more stable imino form.

The system is strictly analogous to the keto–enol one (Secs. 8.13 and 21.4). The proton is acidic, and therefore separates fairly readily from the hybrid anion; it can return to either carbon or nitrogen, but when it returns to carbon, it tends to stay there. Equilibrium favors formation of the weaker acid.

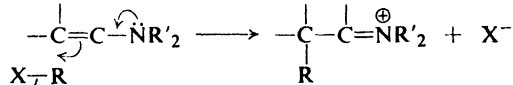
Now, a secondary amine, too, can react with a carbonyl compound, and to yield the same kind of initial product. But here there is no hydrogen left on nitrogen; if dehydration is to occur, it must be in the other direction, to form a carbon–carbon double bond. A stable enamine is the product.



A 2° imine — An enamine

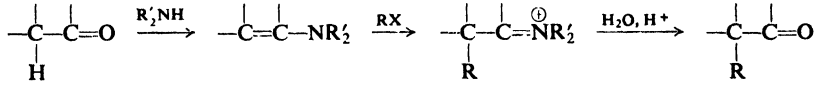
In 1954 Gilbert Stork (of Columbia University) showed how enamines could be used in the alkylation and acylation of aldehydes and ketones, and in the years since then enamines have been intensively studied and used in organic synthesis in a wide variety of ways. All we can do here is to try to understand a little of the basic chemistry underlying the use of enamines.

The usefulness of enamines stems from the fact that they contain *nucleophilic carbon*. The electrons responsible for this nucleophilicity are, in the final analysis, the (formally) unshared pair on nitrogen; but they are available for nucleophilic attack by carbon of the enamine. Thus, in alkylation:



An iminium ion

The product of alkylation is an iminium ion, which is readily hydrolyzed to regenerate the carbonyl group. The overall process, then, is:



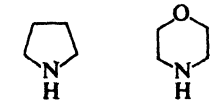
Ketone — Enamine — Iminium ion — Alkylated ketone

(In enamines the nitrogen too is nucleophilic, but attack there, which yields quaternary *ammonium* ions, is generally an unwanted side-reaction. Heating often converts N-alkylated compounds into the desired C-alkylated products.)

Nitrogen in enamines plays the same role it does in the chemistry of aromatic amines—not surprisingly, when we realize that enamines are, after all, *vinyl amines*. (Remember the similarities between vinyl and aryl halides.) For example, bromination

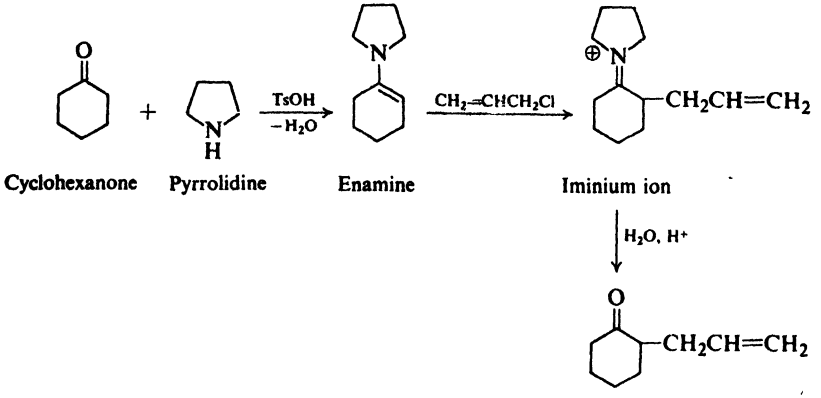
of aniline involves, we say, electrophilic attack by bromine on the aromatic ring; but from the opposite, and equally valid, point of view, it involves nucleophilic attack on bromine by carbons of the ring—with nitrogen furnishing the electrons.

Commonly used secondary amines are the heterocyclic compounds *pyrrolidine* and *morpholine*:

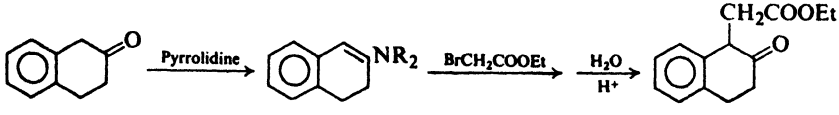


Pyrrolidine Morpholine

Best yields are obtained with reactive halides like benzyl and allyl halides, α-halo esters, and α-halo ketones. For example:



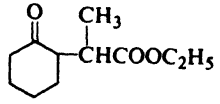
Cyclohexanone Pyrrolidine Enamine Iminium ion

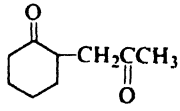


β-Tetralone Enamine

Problem 26.21 Outline all steps in the preparation of each of the following by the enamine synthesis:

(a) 2-benzylcyclohexanone
(b) 2,2-dimethyl-4-pentenal

(c) 

(d) 

(e) 2-(2,4-dinitrophenyl)cyclohexanone
(f) 2,2-dimethyl-3-oxobutanal, $CH_3COC(CH_3)_2CHO$

Problem 26.22 Give structural formulas of compounds A–F.

(a) cyclopentanone + morpholine, then TsOH $\longrightarrow$ A ($C_9H_{15}ON$)
A + C_6H_5CHO, then H_2O, H^+ $\longrightarrow$ B ($C_{12}H_{12}O$)
(b) isobutyraldehyde + *tert*-butylamine $\longrightarrow$ C ($C_8H_{17}N$)
C + C_2H_5MgBr $\longrightarrow$ D ($C_8H_{16}NMgBr$) + E
D + $C_6H_5CH_2Cl$, then H_2O, H^+ $\longrightarrow$ F ($C_{11}H_{14}O$)

PROBLEMS

1. Outline the synthesis of each of the following from malonic ester and any other reagents:

(a) *n*-caproic acid
(b) isobutyric acid
(c) β-methylbutyric acid
(d) α,β-dimethylbutyric acid
(e) 2-ethylbutanoic acid
(f) dibenzylacetic acid
(g) α,β-dimethylsuccinic acid
(h) glutaric acid
(i) cyclobutanecarboxylic acid

2. Outline the synthesis of each of the following from acetoacetic ester and any other needed reagents:

(a) methyl ethyl ketone
(b) 3-ethyl-2-pentanone
(c) 3-ethyl-2-hexanone
(d) 5-methyl-2-heptanone
(e) 3,6-dimethyl-2-heptanone
(f) 4-oxo-2-methylpentanoic acid
(g) γ-hydroxy-*n*-valeric acid
(h) 3-methyl-2-hexanol
(i) 2,5-dimethylheptane
(j) β-methylcaproic acid
(k) β-methylbutyric acid
(l) methylsuccinic acid
(m) 2,5-hexanediol

3. What product would you expect from the hydrolysis by dilute alkali of 2-carbethoxycyclopentanone (see Problem 21.30, p. 718)? Suggest a method of synthesis of 2-methylcyclopentanone.

4. Give structures of compounds A through J:

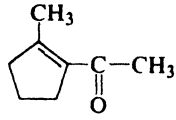
(a) 1,3-dibromopropane + 2 moles sodiomalonic ester $\longrightarrow$ A ($C_{17}H_{28}O_8$)
A + 2 moles sodium ethoxide, then CH_2I_2 $\longrightarrow$ B ($C_{18}H_{28}O_8$)
B + OH^-, heat; then H^+; then heat $\longrightarrow$ C ($C_8H_{12}O_4$)
(b) ethylene bromide + 2 moles sodiomalonic ester $\longrightarrow$ D ($C_{16}H_{26}O_8$)
D + 2 moles sodium ethoxide, then 1 mole ethylene bromide $\longrightarrow$ E ($C_{18}H_{28}O_8$)
E + OH^-, heat; then H^+; then heat $\longrightarrow$ F ($C_8H_{12}O_4$)
(c) 2 moles sodiomalonic ester + I_2 $\longrightarrow$ G ($C_{14}H_{22}O_8$) + 2NaI
G + OH^-, heat; then H^+; then heat $\longrightarrow$ H ($C_4H_6O_4$)
(d) D + 2 moles sodium ethoxide, then I_2 $\longrightarrow$ I ($C_{16}H_{24}O_8$)
I + OH^-, heat; then H^+; then heat $\longrightarrow$ J ($C_6H_8O_4$)
(e) Suggest a possible synthesis for 1,3-cyclopentanedicarboxylic acid; for 1,2-cyclopentanedicarboxylic acid; for 1,1-cyclopentanedicarboxylic acid.

5. Give structures of compounds K through O:

allyl bromide + Mg $\longrightarrow$ K (C_6H_{10})
K + HBr $\longrightarrow$ L ($C_6H_{12}Br_2$)
sodiomalonic ester + excess L $\longrightarrow$ M ($C_{13}H_{23}O_4Br$)
M + sodium ethoxide $\longrightarrow$ N ($C_{13}H_{22}O_4$)
N + OH^-, heat; then H^+; then heat $\longrightarrow$ O ($C_8H_{14}O_2$)

6. When sodium trichloroacetate is heated in diglyme solution with alkenes, there are formed 1,1-dichlorocyclopropanes. How do you account for this?

7. (a) How could you synthesize 2,7-octanedione? (*Hint:* See Problem 26.2, p. 850). (b) Actually, the expected ketone reacts further to give



How does this last reaction occur? To what general types does it belong? (c) How could you synthesize 2,6-heptanedione? (d) What would happen to this ketone under the conditions of (b)?

8. Outline all steps in a possible synthesis of each of the following from simple esters:

(a) 1,2-cyclopentanedione (*Hint:* See Problem 21.33, p. 719–720.)
(b) $CH_3CH_2CH_2COCOOC_2H_5$ (*Hint:* See Problem 26.9, p. 853.)

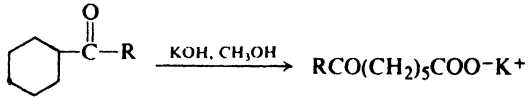
9. Outline the synthesis from readily available compounds of the following hypnotics (see Sec. 20.23):

(a) 5,5-diethylbarbituric acid (Barbital, Veronal; long-acting)
(b) 5-allyl-5-(2-pentyl)barbituric acid (Seconal; short-acting)
(c) 5-ethyl-5-isopentylbarbituric acid (Amytal; intermediate length of action)

10. (a) Contrast the structures of barbituric acid and Veronal (5,5-diethylbarbituric acid). (b) Account for the appreciable acidity ($K_a = 10^{-8}$) of Veronal.

11. When treated with *concentrated* alkali, acetoacetic ester is converted into two moles of sodium acetate. (a) Outline all steps in a likely mechanism for this reaction. (*Hint:* See Sec. 21.11 and Problem 5.8, p. 170.) (b) Substituted acetoacetic esters also undergo this reaction. Outline the steps in a general synthetic route from acetoacetic ester to carboxylic acids. (c) Outline the steps in the synthesis of 2-hexanone via acetoacetic ester. What acids will be formed as by-products? Outline a procedure for purification of the desired ketone. (Remember that the alkylation is carried out in alcohol; that NaBr is formed; that aqueous base is used for hydrolysis; and that ethyl alcohol is a product of the hydrolysis.)

12. (a) Suggest a mechanism for the alkaline cleavage of β-diketones, as, for example:



(b) Starting from cyclohexanone, and using any other needed reagents, outline all steps in a possible synthesis of 7-phenylheptanoic acid. (c) Of pentadecanedioic acid, $HOOC(CH_2)_{13}COOH$.

13. Give structures of compounds P through S:

heptanal (heptaldehyde) + ethyl bromoacetate + Zn, then H_2O $\longrightarrow$ P ($C_{11}H_{22}O_3$)
P + CrO_3 in glacial acetic acid $\longrightarrow$ Q ($C_{11}H_{20}O_3$)
Q + sodium ethoxide, then benzyl chloride $\longrightarrow$ R ($C_{18}H_{26}O_3$)
R + OH^-, heat; then H^+, warm $\longrightarrow$ S ($C_{15}H_{22}O$)

14. Treatment of 1,5-cyclooctadiene with diborane gives a material, T, which is oxidized by alkaline H_2O_2 to a mixture of 72% *cis*-1,5-cyclooctanediol and 28% *cis*-1,4-cyclooctanediol. If T is refluxed for an hour in THF solution (or simply distilled), there is obtained a white crystalline solid, U, which is oxidized to 99%-pure *cis*-1,5-cyclooctanediol.

(a) What is T? What is U? (b) Account for the conversion of T into U.

15. On treatment with concentrated KOH, 2,6-dichlorobenzaldehyde is converted into 1,3-dichlorobenzene and potassium formate. The kinetics shows that the aldehyde and two moles of hydroxide ion are in equilibrium with a reactive intermediate that (ultimately) yields product. (a) Outline a likely mechanism that is consistent with these facts. (*Hint:* See Sec. 19.16.) (b) How do you account for the difference in behavior between this aldehyde and most aromatic aldehydes under these conditions?

16. Give structural formulas of compounds V and W, and tell *exactly* how each is formed:

γ-butyrolactone + CH_3ONa $\longrightarrow$ V ($C_8H_{10}O_3$)
V + conc. HCl $\longrightarrow$ W ($C_7H_{12}OCl_2$)
W + aq. NaOH $\longrightarrow$ dicyclopropyl ketone

17. The structure of *nerolidol*, $C_{15}H_{26}O$, a terpene found in oil of neroli, was established by the following synthesis:

geranyl chloride (RCl) + sodioacetoacetic ester $\longrightarrow$ X ($RC_6H_9O_3$)
X + $Ba(OH)_2$, then H^+, warm $\longrightarrow$ Y (RC_3H_5O)
Y + $NaC{\equiv}CH$, then H_2O $\longrightarrow$ Z (RC_5H_7O)
Z $\xrightarrow{\text{reduction}}$ AA (RC_5H_9O), nerolidol

(a) Give the structure of nerolidol, using R for the geranyl group.
(b) Referring to Problem 27, p. 547, what is the complete structure of nerolidol?

18. The structure of *menthone*, $C_{10}H_{18}O$, a terpene found in peppermint oil, was first established by synthesis in the following way:

ethyl β-methylpimelate + sodium ethoxide, then H_2O $\longrightarrow$ BB ($C_{10}H_{16}O_3$)
BB + sodium ethoxide, then isopropyl iodide $\longrightarrow$ CC ($C_{13}H_{22}O_3$)
CC + OH^-, heat; then H^+; then heat $\longrightarrow$ menthone

(a) What structures for menthone are consistent with this synthesis? (b) On the basis of the isoprene rule (Sec. 8.26) which structure is the more likely? (c) On vigorous reduction menthone yields *p-menthane*, 4-isopropyl-1-methylcyclohexane. Now what structure or structures are most likely for menthone?

19. The structure of *camphoronic acid* (a degradation product of the terpene camphor) was established by the following synthesis:

sodioacetoacetic ester + CH_3I $\longrightarrow$ DD $\xrightarrow{NaOC_2H_5}$ $\xrightarrow{CH_3I}$ EE ($C_8H_{14}O_3$)
EE + ethyl bromoacetate + Zn, then H_2O $\longrightarrow$ FF ($C_{12}H_{22}O_5$)
FF + PCl_5, then KCN $\longrightarrow$ GG ($C_{13}H_{21}O_4N$)
GG + H_2O, H^+, heat $\longrightarrow$ camphoronic acid ($C_9H_{14}O_6$)

What is the structure of camphoronic acid?

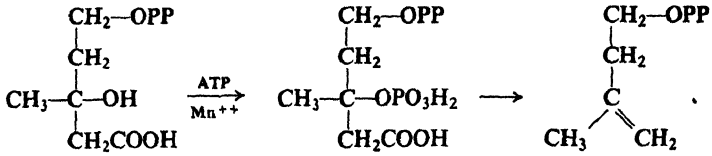
20. Two of the oxidation products of the terpene α-terpineol are *terebic acid* and *terpenylic acid*. Their structures were first established by the following synthesis:

ethyl chloroacetate + sodioacetoacetic ester $\longrightarrow$ HH ($C_{10}H_{16}O_5$)
HH + one mole CH_3MgI, then H_2O $\longrightarrow$ II ($C_{11}H_{20}O_5$)
II + OH^-, H_2O, heat, then H^+ $\longrightarrow$ [JJ ($C_7H_{12}O_5$)] $\longrightarrow$ terebic acid ($C_7H_{10}O_4$)
HH + sodium ethoxide, then ethyl chloroacetate $\longrightarrow$ KK ($C_{14}H_{22}O_7$)
KK + OH^-, then H^+, warm $\longrightarrow$ LL ($C_7H_{10}O_5$)
LL + ethyl alcohol, H^+ $\longrightarrow$ MM ($C_{11}H_{18}O_5$)

MM + one mole CH_3MgI, then H_2O $\longrightarrow$ NN ($C_{12}H_{22}O_5$)
NN + OH^-, H_2O, heat, then H^+ $\longrightarrow$ [OO ($C_8H_{14}O_5$)] $\longrightarrow$
terpenylic acid ($C_8H_{12}O_4$)

What is the structure of terebic acid? Of terpenylic acid?

21. Isopentenyl pyrophosphate, the precursor of isoprene units in nature (Sec. 8.26), is formed enzymatically from the pyrophosphate of *mevalonic acid* by the action of ATP (adenosine triphosphate) and Mn^{++} ion.



Mevalonic acid 5-pyrophosphate

Mevalonic acid 5-pyrophosphate 3-phosphate

Isopentenyl pyrophosphate

It is believed that the function of ATP is to phosphorylate mevalonic acid pyrophosphate at the 3-position.

Just what happens in the last step of this conversion? Why should the 3-phosphate undergo this reaction more easily than the 3-hydroxy compound?

Chapter 27 α,β-Unsaturated Carbonyl Compounds

Conjugate Addition

27.1 Structure and properties

In general, a compound that contains both a carbon–carbon double bond and a carbon–oxygen double bond has properties that are characteristic of both functional groups. At the carbon–carbon double bond an unsaturated ester or unsaturated ketone undergoes electrophilic addition of acids and halogens, hydrogenation, hydroxylation, and cleavage; at the carbonyl group it undergoes the nucleophilic substitution typical of an ester or the nucleophilic addition typical of a ketone.

Problem 27.1 What will be the products of the following reactions?

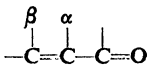
(a) $CH_3CH{=}CHCOOH + H_2 + Pt$
(b) $CH_3CH{=}CHCOOC_2H_5 + OH^- + H_2O$ + heat
(c) $C_6H_5CH{=}CHCOCH_3 + I_2 + OH^-$
(d) $CH_3CH{=}CHCHO + C_6H_5NHNH_2$ + acid catalyst
(e) $CH_3CH{=}CHCHO + Ag(NH_3)_2^+$
(f) $C_6H_5CH{=}CHCOC_6H_5 + O_3$, followed by $Zn + H_2O$
(g) $CH_3CH{=}CHCHO$ + excess H_2 + Ni, heat, pressure
(h) *trans*-$HOOCCH{=}CHCOOH + Br_2/CCl_4$
(i) *trans*-$HOOCCH{=}CHCOOH$ + cold alkaline $KMnO_4$

Problem 27.2 What are A, B, and C, given the following facts?

(a) Cinnamaldehyde ($C_6H_5CH{=}CHCHO$) + H_2 + Ni, at low temperatures and pressures ⟶ A.
(b) Cinnamaldehyde + H_2 + Ni, at high temperatures and pressures ⟶ B.
(c) Cinnamaldehyde + $NaBH_4$, followed by H^+ ⟶ C.

	A	B	C
$KMnO_4$ test	positive	negative	positive
Br_2/CCl_4 test	negative	negative	positive
Tollens' test	positive	negative	negative
$NaHSO_3$ test	positive	negative	negative

In the α,β-unsaturated carbonyl compounds, the carbon–carbon double bond and the carbon–oxygen double bond are separated by just one carbon–carbon single bond; that is, the double bonds are *conjugated.* Because of this conjugation,



α,β-Unsaturated carbonyl compound
Conjugated system

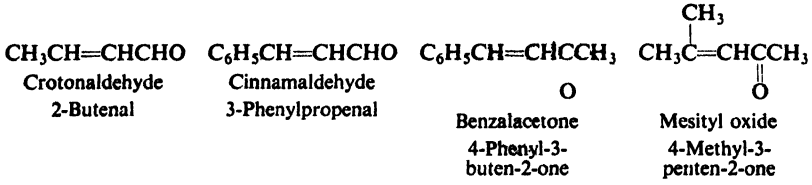
such compounds possess not only the properties of the individual functional groups, but certain other properties besides. In this chapter we shall concentrate on the α,β-unsaturated compounds, and on the special reactions characteristic of the conjugated system.

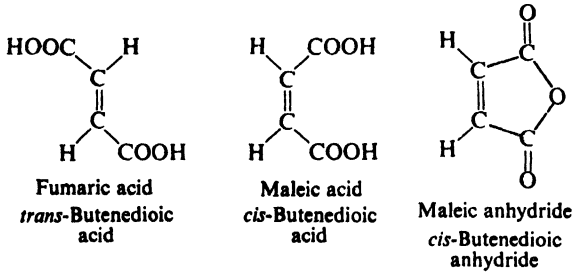
Table 27.1 α,β-UNSATURATED CARBONYL COMPOUNDS

Name	Formula	M.p., °C	B.p., °C
Acrolein	$CH_2{=}CHCHO$	− 88	52
Crotonaldehyde	$CH_3CH{=}CHCHO$	− 69	104
Cinnamaldehyde	$C_6H_5CH{=}CHCHO$	− 7	254
Mesityl oxide	$(CH_3)_2C{=}CHCOCH_3$	42	131
Benzalacetone	$C_6H_5CH{=}CHCOCH_3$	42	261
Dibenzalacetone	$C_6H_5CH{=}CHCOCH{=}CHC_6H_5$	113	
Benzalacetophenone (Chalcone)	$C_6H_5CH{=}CHCOC_6H_5$	62	348
Dypnone	$C_6H_5C(CH_3){=}CHCOC_6H_5$		150–5[1]
Acrylic acid	$CH_2{=}CHCOOH$	12	142
Crotonic acid	*trans*-$CH_3CH{=}CHCOOH$	72	189
Isocrotonic acid	*cis*-$CH_3CH{=}CHCOOH$	16	172*d*
Methacrylic acid	$CH_2{=}C(CH_3)COOH$	16	162
Sorbic acid	$CH_3CH{=}CHCH{=}CHCOOH$	134	
Cinnamic acid	*trans*-$C_6H_5CH{=}CHCOOH$	137	300
Maleic acid	*cis*-$HOOCCH{=}CHCOOH$	130.5	
Fumaric acid	*trans*-$HOOCCH{=}CHCOOH$	302	
Maleic anhydride		60	202
Methyl acrylate	$CH_2{=}CHCOOCH_3$		80
Methyl methacrylate	$CH_2{=}C(CH_3)COOCH_3$		101
Ethyl cinnamate	$C_6H_5CH{=}CHCOOC_2H_5$	12	271
Acrylonitrile	$CH_2{=}CH{-}C{\equiv}N$	− 82	79

Table 27.1 lists some of the more important of these compounds. Many have common names which the student must expect to encounter. For example:

$CH_2{=}CH{-}CHO$	$CH_2{=}CH{-}COOH$	$CH_2{=}CH{-}C{\equiv}N$	$CH_2{=}C(CH_3){-}COOH$
Acrolein	Acrylic acid	Acrylonitrile	Methacrylic acid
Propenal	Propenoic acid	Propenenitrile	2-Methylpropenoic acid





27.2 Preparation

There are several general ways to make compounds of this kind: the **aldol condensation**, to make unsaturated aldehydes and ketones; **dehydrohalogenation of α-halo acids** and the **Perkin condensation**, to make unsaturated acids. Besides these, there are certain methods useful only for making single compounds.

All these methods make use of chemistry with which we are already familiar: the fundamental chemistry of alkenes and carbonyl compounds.

Problem 27.3 Outline a possible synthesis of:

(a) crotonaldehyde from acetylene
(b) cinnamaldehyde from compounds of lower carbon number
(c) cinnamic acid from compounds of lower carbon number
(d) 4-methyl-2-pentenoic acid via a malonic ester synthesis

Problem 27.4 The following compounds are of great industrial importance for the manufacture of polymers: acrylonitrile (for Orlon), methyl acrylate (for Acryloid), methyl methacrylate (for Lucite and Plexiglas). Outline a possible industrial synthesis of: (a) acrylonitrile from ethylene; (b) methyl acrylate from ethylene; (c) methyl methacrylate from acetone and methanol.

(d) Polymerization of these compounds is similar to that of ethylene, vinyl chloride, etc. (Sec. 6.19). Draw a structural formula for each of the polymers.

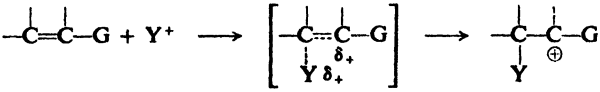
Problem 27.5 Acrolein, $CH_2{=}CHCHO$, is prepared by heating glycerol with sodium hydrogen sulfate, $NaHSO_4$. (a) Outline the likely steps in this synthesis, which involves acid-catalyzed dehydration and keto-enol tautomerization. (*Hint:* Which —OH is easier to eliminate, a primary or a secondary?) (b) How could acrolein be converted into acrylic acid?

27.3 Interaction of functional groups

We have seen (Sec. 6.11) that, with regard to electrophilic addition, a carbon–carbon double bond is activated by an electron-releasing substituent and deactivated

by an electron-withdrawing substituent. The carbon–carbon double bond serves as a source of electrons for the electrophilic reagent; the availability of its electrons is determined by the groups attached to it. More specifically, an electron-releasing substituent stabilizes the transition state leading to the initial carbonium ion by dispersing the developing positive charge; an electron-withdrawing substituent destabilizes the transition state by intensifying the positive charge.

Electrophilic Addition



G releases electrons: activates
G withdraws electrons: deactivates

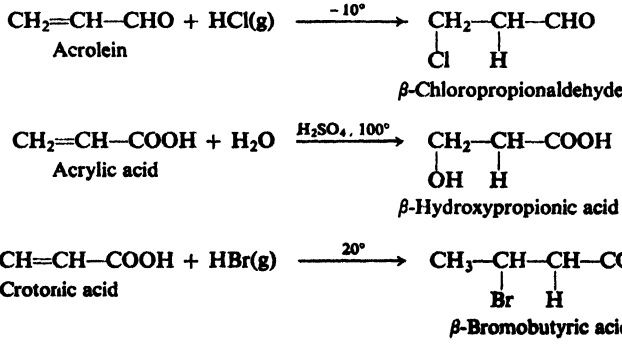
The C=O, —COOH, —COOR, and —CN groups are powerful electron-withdrawing groups, and therefore would be expected to deactivate a carbon–carbon double bond toward electrophilic addition. This is found to be true: α,β-unsaturated ketones, acids, esters, and nitriles are in general less reactive than simple alkenes toward reagents like bromine and the hydrogen halides.

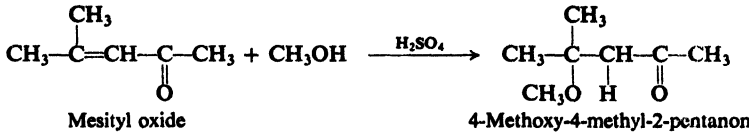
But this powerful electron withdrawal, which deactivates a carbon–carbon double bond toward reagents seeking electrons, at the same time *activates* toward reagents that are electron-rich. As a result, the carbon–carbon double bond of an α,β-unsaturated ketone, acid, ester, or nitrile is susceptible to nucleophilic attack, and undergoes a set of reactions, **nucleophilic addition**, that is uncommon for the simple alkenes.

27.4 Electrophilic addition

The presence of the carbonyl group not only lowers the **reactivity** of the carbon–carbon double bond toward electrophilic addition, but also controls the **orientation** of the addition.

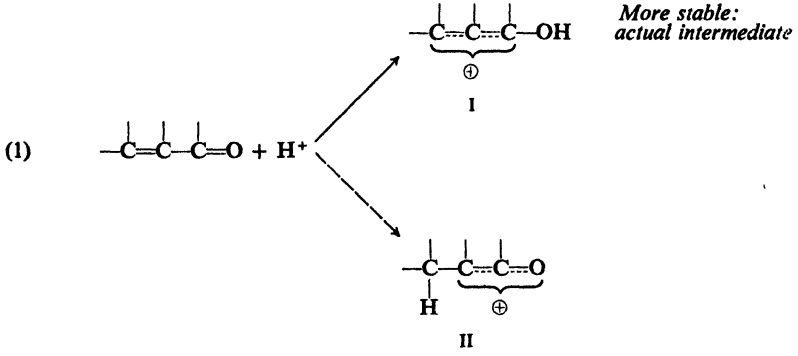
In general, it is observed that addition of an unsymmetrical reagent to an α,β-unsaturated carbonyl compound takes place in such a way that hydrogen becomes attached to the α-carbon and the negative group becomes attached to the β-carbon. For example:





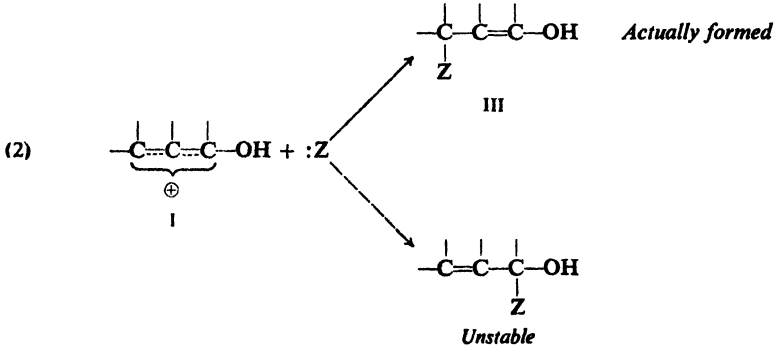
Mesityl oxide 4-Methoxy-4-methyl-2-pentanone

Electrophilic addition to simple alkenes takes place in such a way as to form the most stable intermediate carbonium ion. Addition to α,β-unsaturated carbonyl compounds, too, is consistent with this principle; to see that this is so, however, we must look at the conjugated system as a whole. As in the case of conjugated dienes (Sec. 8.20), addition to an *end* of the conjugated system is preferred, since this yields (step 1) a resonance-stabilized carbonium ion. Addition to the carbonyl oxygen end would yield carbonium ion I; addition to the β-carbon end would yield carbonium ion II.



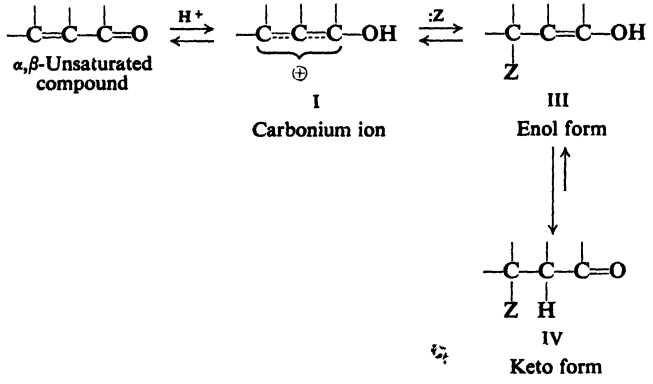
Of the two, I is the more stable, since the positive charge is carried by carbon atoms alone, rather than partly by the highly electronegative oxygen atom.

In the second step of addition, a negative ion or basic molecule attaches itself either to the carbonyl carbon or to the β-carbon of the hybrid ion I.



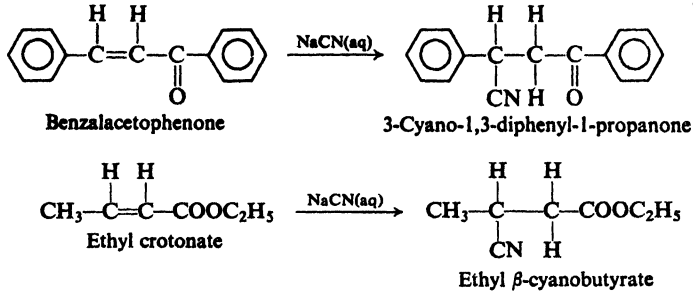
Of the two possibilities, only addition to the β-carbon yields a stable product (III), which is simply the enol form of the saturated carbonyl compound. The

enol form then undergoes tautomerization to the keto form to give the observed product (IV).

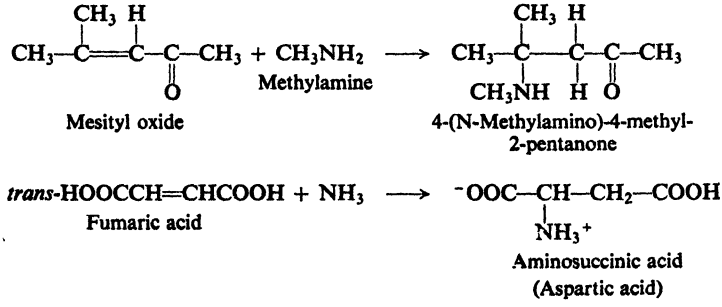


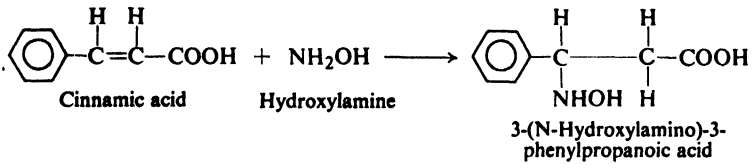
27.5 Nucleophilic addition

Aqueous sodium cyanide converts α,β-unsaturated carbonyl compounds into β-cyano carbonyl compounds. The reaction amounts to addition of the elements of HCN to the carbon–carbon double bond. For example:



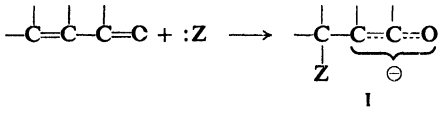
Ammonia or certain derivatives of ammonia (amines, hydroxylamine, phenylhydrazine, etc.) add to α,β-unsaturated carbonyl compounds to yield β-amino carbonyl compounds. For example:





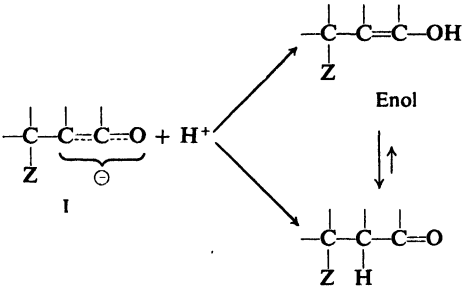
These reactions are believed to take place by the following mechanism:

(1)



I

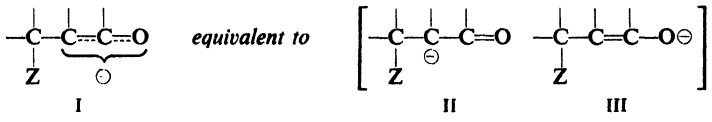
(2)



The nucleophilic reagent adds (step 1) to the carbon–carbon double bond to yield the hybrid anion I, which then accepts (step 2) a hydrogen ion from the solvent to yield the final product. This hydrogen ion can add either to the α-carbon or to oxygen, and thus yield either the keto or the enol form of the product; in either case the same equilibrium mixture, chiefly keto, is finally obtained.

In the examples we have just seen, the nucleophilic reagent, :Z, is either the strongly basic anion, $:CN^-$, or a neutral base like ammonia and its derivatives, $:NH_2-G$. These are the same reagents which, we have seen, add to the carbonyl group of simple aldehydes and ketones. (Indeed, nucleophilic reagents rarely add to the carbon–carbon double bond of α,β-unsaturated *aldehydes*, but rather to the highly reactive carbonyl group.)

These nucleophilic reagents add to the conjugated system in such a way as to form the most stable intermediate anion. The most stable anion is I, which is the hybrid of II and III.

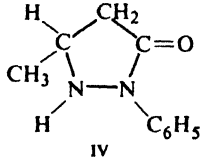


As usual, initial addition occurs to an *end* of the conjugated system, and in this case to the particular end (β-carbon) *that enables the electronegative element oxygen to accommodate the negative charge.*

The tendency for α,β-unsaturated carbonyl compounds to undergo nucleophilic addition is thus due not simply to the electron-withdrawing ability of the carbonyl group, but to the existence of the conjugated system that permits formation of the resonance-stabilized anion I. The importance in synthesis of α,β-unsaturated aldehydes, ketones, acids, esters, and nitriles is due to the fact that they provide such a conjugated system.

Problem 27.6 Draw structures of the anion expected from nucleophilic addition to each of the other positions in the conjugated system, and compare its stability with that of I.

Problem 27.7 Treatment of crotonic acid, $CH_3CH{=}CHCOOH$, with phenylhydrazine yields compound IV.



IV

To what simple class of compounds does IV belong? How can you account for its formation? (*Hint:* See Sec. 20.11.)

Problem 27.8 Treatment of acrylonitrile, $CH_2{=}CHCN$, with ammonia yields a mixture of two products: β-aminopropionitrile, $H_2NCH_2CH_2CN$, and di(β-cyanoethyl)amine, $NCCH_2CH_2NHCH_2CH_2CN$. How do you account for their formation?

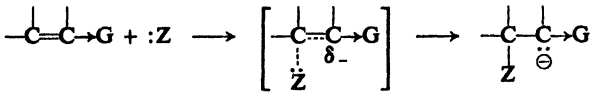
Problem 27.9 Treatment of ethyl acrylate, $CH_2{=}CHCOOC_2H_5$, with methylamine yields $CH_3N(CH_2CH_2COOC_2H_5)_2$. How do you account for its formation?

27.6 Comparison of nucleophilic and electrophilic addition

We can see that nucleophilic addition is closely analogous to electrophilic addition: (a) addition proceeds in two steps; (b) the first and controlling step is the formation of an intermediate ion; (c) both orientation of addition and reactivity are determined by the stability of the intermediate ion, or, more exactly, by the stability of the transition state leading to its formation; (d) this stability depends upon dispersal of the charge.

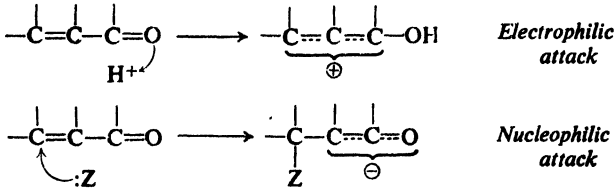
The difference between nucleophilic and electrophilic addition is, of course, that the intermediate ions have opposite charges: negative in nucleophilic addition, positive in electrophilic addition. As a result, the effects of substituents are exactly opposite. Where an electron-withdrawing group deactivates a carbon–carbon double bond toward electrophilic addition, it activates toward nucleophilic addition. An electron-withdrawing group stabilizes the transition state leading to the formation of an intermediate anion in nucleophilic addition by helping to disperse the developing negative charge:

Nucleophilic addition



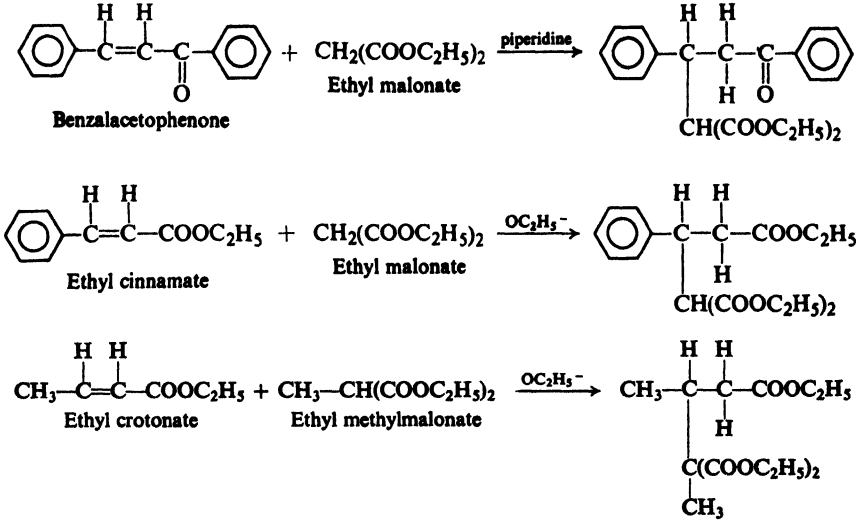
G *withdraws electrons: activates*

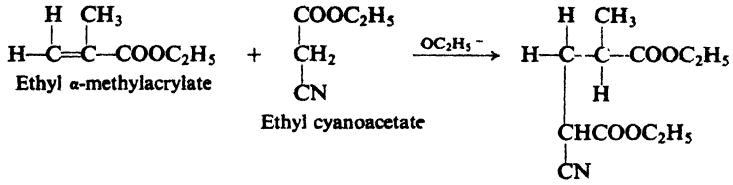
Addition to an α,β-unsaturated carbonyl compound can be understood best in terms of an attack on the entire conjugated system. To yield the most stable intermediate ion, this attack must occur at an end of the conjugated system. A nucleophilic reagent attacks at the β-carbon to form an ion in which the negative charge is partly accommodated by the electronegative atom oxygen; an electrophilic reagent attacks oxygen to form a carbonium ion in which the positive charge is accommodated by carbon.



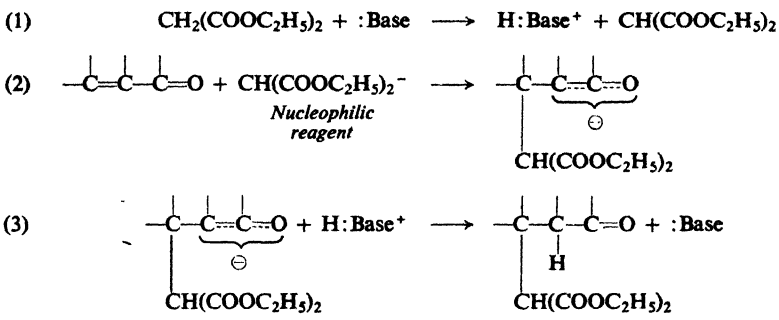
27.7 The Michael addition

Of special importance in synthesis is the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds known as the **Michael addition**. Like the reactions of carbanions that we studied in the previous chapter, it results in formation of carbon–carbon bonds. For example:



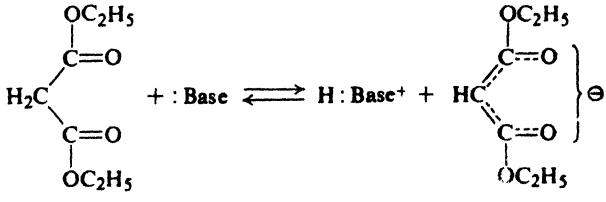


The Michael addition is believed to proceed by the following mechanism (shown for malonic ester):

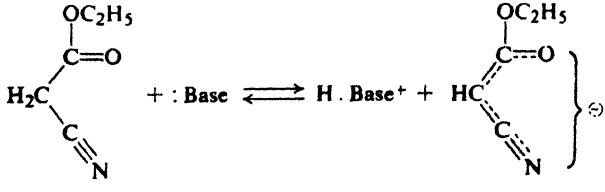


The function of the base is to abstract (step 1) a hydrogen ion from malonic ester and thus generate a carbanion which, acting as a nucleophilic reagent, then attacks (step 2) the conjugated system in the usual manner.

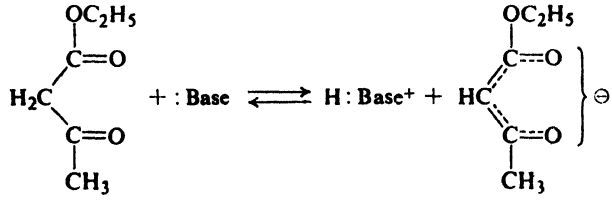
In general, the compound from which the carbanion is generated must be a fairly acidic substance, so that an appreciable concentration of the carbanion can be obtained. Such a compound is usually one that contains a $-CH_2-$ or $-CH-$ group flanked by two electron-withdrawing groups which can help accommodate the negative charge of the anion. In place of ethyl malonate, compounds like ethyl cyanoacetate and ethyl acetoacetate can be used.



Ethyl malonate



Ethyl cyanoacetate



Ethyl acetoacetate

Problem 27.10 Predict the products of the following Michael additions:

(a) ethyl crotonate + malonic ester $\longrightarrow$ A $\xrightarrow{OH^-}$ $\xrightarrow{H^+}$ $\xrightarrow{heat}$ B

(b) ethyl acrylate + ethyl acetoacetate $\longrightarrow$ C $\xrightarrow{H_2O,\ H^+}$ D

(c) methyl vinyl ketone + malonic ester $\longrightarrow$ E

(d) benzalacetophenone + acetophenone $\longrightarrow$ F

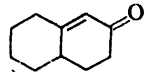
(e) acrylonitrile + allyl cyanide $\longrightarrow$ G $\xrightarrow{H_2O,\ H^+}$ H + $2NH_4^+$

(f) $C_2H_5OOC{-}C\quad C{-}COOC_2H_5$ (1 mole) + ethyl acetoacetate (1 mole) $\longrightarrow$ I

(g) I $\xrightarrow{\text{strong } OH^-,\ H_2O}$ $\xrightarrow{H^+}$ J + CH_3COOH

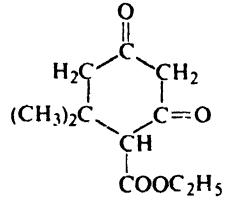
Problem 27.11 Formaldehyde and malonic ester react in the presence of ethoxide ion to give K, $C_8H_{12}O_4$. (a) What is the structure of K? (*Hint:* See Problem 26.3, p. 850.) (b) How can K be converted into L, $(C_2H_5OOC)_2CHCH_2CH(COOC_2H_5)_2$? (c) What would you get if L were subjected to hydrolysis, acidification, and heat?

Problem 27.12 Show how a Michael addition followed by an aldol condensation can transform a mixture of methyl vinyl ketone and cyclohexanone into $\Delta^{1,9}$-octalone.



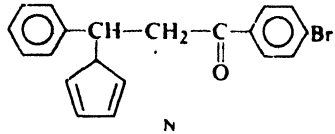
$\Delta^{1,9}$-Octalone

Problem 27.13 When mesityl oxide, $(CH_3)_2C\quad CHCOCH_3$, is treated with ethyl malonate in the presence of sodium ethoxide, compound M is obtained. (a) Outline the steps in its formation. (b) How could M be turned into 5,5-dimethyl-1,3-cyclohexanedione?



M

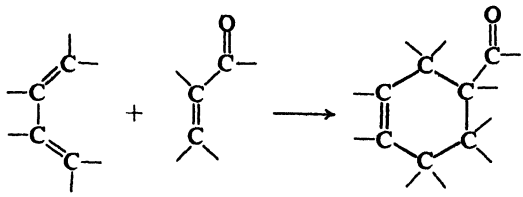
Problem 27.14 In the presence of piperidine (a secondary amine, Sec. 31.12), 1,3-cyclopentadiene and benzal-*p*-bromoacetophenone yield N. Outline the steps in its formation.



N

27.8 The Diels-Alder reaction

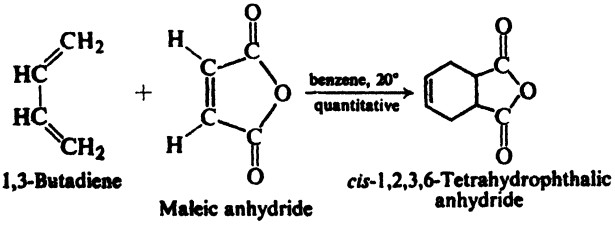
α,β-Unsaturated carbonyl compounds undergo an exceedingly useful reaction with conjugated dienes, known as the **Diels-Alder reaction**. This is an addition reaction in which C–1 and C–4 of the conjugated diene system become attached



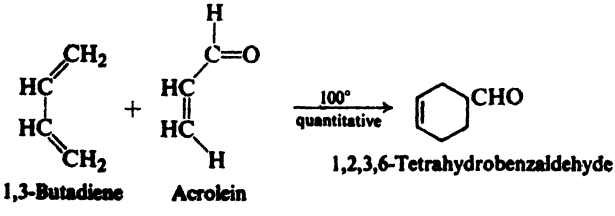
Diene | Dienophile (Greek: diene-loving) | Adduct *Six-membered ring*

to the doubly-bonded carbons of the unsaturated carbonyl compound to form a six-membered ring. A concerted, single-step mechanism is almost certainly involved; both new carbon–carbon bonds are partly formed in the same transition state, although not necessarily to the same extent. The Diels-Alder reaction is the most important example of *cycloaddition*, which is discussed further in Sec. 29.9. Since reaction involves a system of 4 π electrons (the diene) and a system of 2 π electrons (the dienophile), it is known as a [4 + 2] cycloaddition.

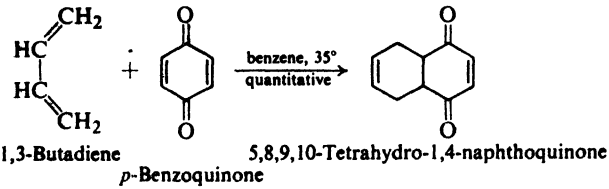
The Diels-Alder reaction is useful not only because a ring is generated, but also because it takes place so readily for a wide variety of reactants. Reaction is favored by electron-withdrawing substituents in the dienophile, but even simple alkenes can react. Reaction often takes place with the evolution of heat when the reactants are simply mixed together. A few examples of the Diels-Alder reaction are:



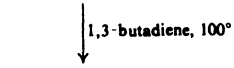
1,3-Butadiene | Maleic anhydride | *cis*-1,2,3,6-Tetrahydrophthalic anhydride

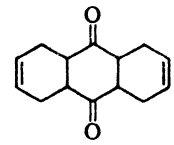


1,3-Butadiene | Acrolein | 1,2,3,6-Tetrahydrobenzaldehyde

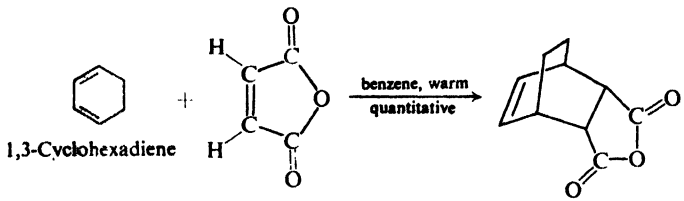


1,3-Butadiene + *p*-Benzoquinone → 5,8,9,10-Tetrahydro-1,4-naphthoquinone



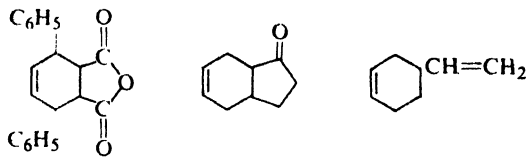


1,4,5,8,11,12,13,14-Octahydro-9,10-anthraquinone

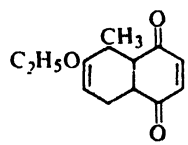


1,3-Cyclohexadiene + Maleic anhydride

Problem 27.15 From what reactants could each of the following compounds be synthesized?



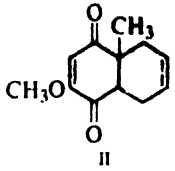
Problem 27.16 (a) In one synthesis of the hormone *cortisone* (by Lewis Sarett of Merck, Sharp and Dohme), the initial step was the formation of I by a Diels-Alder reaction. What were the starting materials?



I

(b) In another synthesis of cortisone (by R. B. Woodward, p. 938), the initial

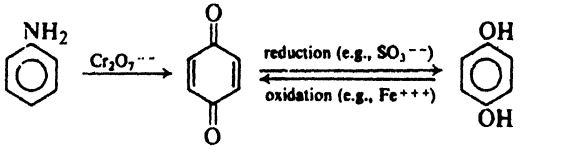
step was the formation of II by a Diels-Alder reaction. What were the starting materials?



II

27.9 Quinones

α,β-Unsaturated ketones of a rather special kind are given the name of **quinones**: these are cyclic diketones of such a structure that they are converted by reduction into hydroquinones, phenols containing two —OH groups. For example:



p-Benzoquinone (Quinone)

Yellow

Hydroquinone

Because they are highly conjugated, quinones are colored; *p*-benzoquinone, for example, is yellow.

Also because they are highly conjugated, quinones are rather closely balanced, energetically, against the corresponding hydroquinones. The ready interconversion provides a convenient oxidation-reduction system that has been studied intensively. Many properties of quinones result from the tendency to form the aromatic hydroquinone system.

Quinones—some related to more complicated aromatic systems (Chap. 30)—have been isolated from biological sources (molds, fungi, higher plants). In many cases they seem to take part in oxidation-reduction cycles essential to the living organism.

Problem 27.17 When *p*-benzoquinone is treated with HCl, there is obtained 2-chlorohydroquinone. It has been suggested that this product arises via an initial 1,4-addition. Show how this might be so.

Problem 27.18 (a) Hydroquinone is used in photographic developers to aid in the conversion of silver ion into free silver. What property of hydroquinone is being taken advantage of here?

(b) *p*-Benzoquinone can be used to convert iodide ion into iodine. What property of the quinone is being taken advantage of here?

Problem 27.19 How do you account for the fact that the treatment of phenol with nitrous acid yields the mono-oxime of *p*-benzoquinone?

PROBLEMS

1. Outline all steps in a possible laboratory synthesis of each of the unsaturated carbonyl compounds in Table 27.1, p. 866, using any readily available monofunctional compounds: simple alcohols, aldehydes, ketones, acids, esters, and hydrocarbons.

2. Give the structures of the organic products expected from the reaction of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, with each of the following:

(a) H_2, Ni
(b) $NaBH_4$
(c) NaOI
(d) O_3, then Zn, H_2O
(e) Br_2
(f) HCl
(g) HBr
(h) H_2O, H^+
(i) CH_3OH, H^+
(j) NaCN (aq)
(k) CH_3NH_2
(l) aniline
(m) NH_3
(n) NH_2OH
(o) benzaldehyde, base
(p) ethyl malonate, base
(q) ethyl cyanoacetate, base
(r) ethyl methylmalonate, base
(s) ethyl acetoacetate, base
(t) 1,3-butadiene
(u) 1,3-cyclohexadiene
(v) 1,3-cyclopentadiene

3. In the presence of base the following pairs of reagents undergo Michael addition. Give the structures of the expected products.

(a) benzalacetophenone + ethyl cyanoacetate
(b) ethyl cinnamate + ethyl cyanoacetate
(c) ethyl fumarate + ethyl malonate
(d) ethyl acetylenedicarboxylate + ethyl malonate
(e) mesityl oxide + ethyl malonate
(f) mesityl oxide + ethyl acetoacetate
(g) ethyl crotonate + ethyl methylmalonate
(h) formaldehyde + 2 moles ethyl malonate
(i) acetaldehyde + 2 moles ethyl acetoacetate
(j) methyl acrylate + nitromethane
(k) 2 moles ethyl crotonate + nitromethane
(l) 3 moles acrylonitrile + nitromethane
(m) 1 mole acrylonitrile + $CHCl_3$

4. Give the structures of the compounds expected from the hydrolysis and decarboxylation of the products obtained in Problem 3, parts (a) through (i).

5. Depending upon reaction conditions, dibenzalacetone and ethyl malonate can be made to yield any of three products by Michael addition.

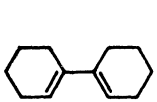
dibenzalacetone + 2 moles ethyl malonate $\longrightarrow$ A (no unsaturation)
dibenzalacetone + 1 mole ethyl malonate $\longrightarrow$ B (one carbon–carbon double bond)
dibenzalacetone + 1 mole ethyl malonate $\longrightarrow$ C (no unsaturation)

What are A, B, and C?

6. Give the structure of the product of the Diels-Alder reaction between:

(a) maleic anhydride and isoprene
(b) maleic anhydride and 1,1′-bicyclohexenyl (I)
(c) maleic anhydride and 1-vinyl-1-cyclohexene
(d) 1,3-butadiene and methyl vinyl ketone
(e) 1,3-butadiene and crotonaldehyde
(f) 2 moles 1,3-butadiene and dibenzalacetone
(g) 1,3-butadiene and β-nitrostyrene ($C_6H_5CH{=}CHNO_2$)
(h) 1,3-butadiene and 1,4-naphthoquinone (II)
(i) *p*-benzoquinone and 1,3-cyclohexadiene
(j) *p*-benzoquinone and 1,1′-bicyclohexenyl (I)
(k) *p*-benzoquinone and 2 moles 1,3-cyclohexadiene

(l) *p*-benzoquinone and 2 moles 1,1′-bicyclohexenyl (I)
(m) 1,3-cyclopentadiene and acrylonitrile
(n) 1,3-cyclohexadiene and acrolein



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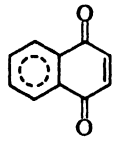
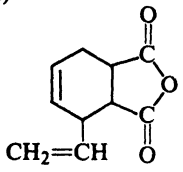


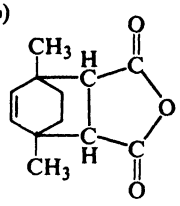
II

7. From what reactants could the following be synthesized by the Diels-Alder reaction?

(a)

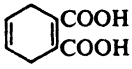


(b)

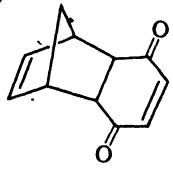


(c)

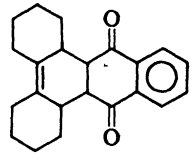
(d)



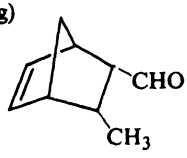
(e)



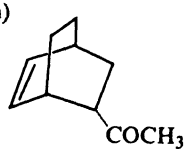
(f)



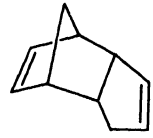
(g)



(h)



(i)



8. The following observations illustrate one aspect of the stereochemistry of the Diels-Alder reaction:

maleic anhydride + 1,3-butadiene $\longrightarrow$ D ($C_8H_8O_3$)
D + H_2O, heat $\longrightarrow$ E ($C_8H_{10}O_4$)
E + H_2, Ni $\longrightarrow$ F ($C_8H_{12}O_4$), m.p. 192°
fumaryl chloride (*trans*-ClOCCH=CHCOCl) + 1,3-butadiene $\longrightarrow$ G ($C_8H_8O_2Cl_2$)
G + H_2O, heat $\longrightarrow$ H ($C_8H_{10}O_4$)
H + H_2, Ni $\longrightarrow$ I ($C_8H_{12}O_4$), m.p. 215°
I can be resolved; F cannot be resolved.

Does the Diels-Alder reaction involve a *syn*-addition or an *anti*-addition?

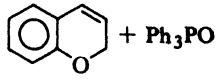
9. On the basis of your answer to Problem 8, give the stereochemical formulas of the products expected from each of the following reactions. Label meso compounds and racemic modifications.

(a) crotonaldehyde (*trans*-2-butenal) + 1,3-butadiene
(b) *p*-benzoquinone + 1,3-butadiene
(c) maleic anhydride + 1,3-butadiene, followed by cold alkaline $KMnO_4$
(d) maleic anhydride + 1,3-butadiene, followed by hot $KMnO_4$ $\longrightarrow$ $C_8H_{10}O_8$

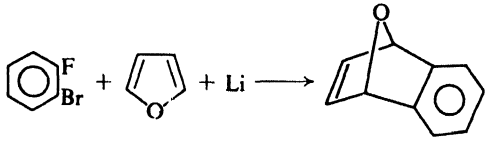
10. Account for the following observations:

(a) Dehydration of 3-hydroxy-2,2-dimethylpropanoic acid yields 2-methyl-2-butenoic acid.

(b) $C_2H_5OOC{-}COOC_2H_5$ (Ethyl oxalate) + $CH_3CH{=}CHCOOC_2H_5$ (Ethyl crotonate) $\xrightarrow{OC_2H_5^-}$ $C_2H_5OOC{-}\underset{\underset{O}{\|}}{C}{-}CH_2CH{=}CHCOOC_2H_5$

(c) $CH_2{=}CH{-}\overset{+}{P}Ph_3\ Br^-$ + salicylaldehyde + a little base $\longrightarrow$  + Ph_3PO

(d) $CH_3CH{=}CHCOOC_2H_5 + Ph_3P{=}CH_2 \longrightarrow CH_3{-}\underset{\underset{CH_2}{/\ \backslash}}{CH}{-}CH{-}COOC_2H_5 + Ph_3P$

(e) 

11. When *citral* (Problem 26, p. 652) is refluxed with aqueous potassium carbonate, acetaldehyde distills from the mixture and 6-methyl-5-hepten-2-one is obtained in high yield. Show all steps in a likely mechanism. (*Hint:* See Sec. 21.5.)

12. In connection with his new research problem, our naïve graduate student (Problem 18, p. 650, and Problem 20, p. 724) needed a quantity of the unsaturated alcohol $C_6H_5CH{=}CHC(OH)(CH_3)(C_2H_5)$. He added a slight excess of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, to a solution of ethylmagnesium bromide, and, by use of a color test, found that the Grignard reagent had been consumed. He worked up the reaction mixture in the usual way with dilute acid. Having learned a little (but not much) from his earlier sad experiences, he tested the product with iodine and sodium hydroxide; when a copious precipitate of iodoform appeared, he concluded that he had simply recovered his starting material.

He threw his product into the waste crock, carefully and methodically destroyed his glassware, burned his laboratory coat, left school, and went into politics, where he did quite well; his career in Washington was marred only, in the opinion of some, by his blind antagonism toward all appropriations for scientific research and his frequent attacks —alternately vitriolic and caustic—on the French.

What had he thrown into the waste crock? How had it been formed?

13. Treatment of $CF_3(C_6H_5)C{=}CF_2$ with EtONa/EtOH yields chiefly $CF_3(C_6H_5)C{=}CF(OEt)$. Similar treatment of $CF_2Cl(C_6H_5)C{=}CF_2$ yields $EtOCF_2(C_6H_5)C{=}CF_2$. The rates of the two reactions are almost identical. It has been suggested that both reactions proceed by the same mechanism.

Show all steps in a mechanism that is consistent with the nature of these reactants, and that accounts for the similarity in rate despite the difference in final product.

14. Give structures of compounds J through QQ:

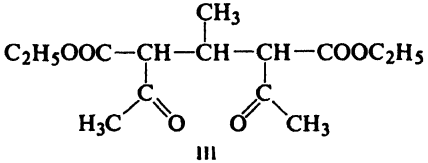
(a) glycerol + $NaHSO_4$, heat $\longrightarrow$ J (C_3H_4O)
J + ethyl alcohol + HCl $\longrightarrow$ K ($C_7H_{15}O_2Cl$)
K + NaOH, heat $\longrightarrow$ L ($C_7H_{14}O_2$)
L + cold neutral $KMnO_4$ $\longrightarrow$ M ($C_7H_{16}O_4$)
M + dilute H_2SO_4 $\longrightarrow$ N ($C_3H_6O_3$) + ethyl alcohol

(b) $C_2H_5OOC{-}C{\equiv}C{-}COOC_2H_5$ + sodiomalonic ester $\longrightarrow$ O ($C_{15}H_{22}O_8$)
O + OH^-, heat; then H^+; then heat $\longrightarrow$ P ($C_6H_6O_6$), *aconitic acid*, found in sugar cane and beetroot
(c) ethyl fumarate + sodiomalonic ester $\longrightarrow$ Q ($C_{15}H_{24}O_8$)
Q + OH^-, heat; then H^+; then heat $\longrightarrow$ R ($C_6H_8O_6$), *tricarballylic acid*
(d) benzil ($C_6H_5COCOC_6H_5$) + benzyl ketone ($C_6H_5CH_2COCH_2C_6H_5$) + base $\longrightarrow$ S ($C_{29}H_{20}O$), "tetracyclone"
S + maleic anhydride $\longrightarrow$ T ($C_{33}H_{22}O_4$)
T + heat $\longrightarrow$ CO + H_2 + U ($C_{32}H_{20}O_3$)
(e) S + $C_6H_5C{\equiv}CH$ $\longrightarrow$ V ($C_{37}H_{26}O$)
V + heat $\longrightarrow$ CO + W ($C_{36}H_{26}$)
(f) acetone + $BrMgC{\equiv}COC_2H_5$, then H_2O $\longrightarrow$ X ($C_7H_{12}O_2$)
X + H_2, $Pd/CaCO_3$ $\longrightarrow$ Y ($C_7H_{14}O_2$)
Y + H^+, warm $\longrightarrow$ Z (C_5H_8O), β-methylcrotonaldehyde
(g) ethyl 3-methyl-2-butenoate + ethyl cyanoacetate + base $\longrightarrow$ AA ($C_{12}H_{19}O_4N$)
AA + OH^-, heat; then H^+; then heat $\longrightarrow$ BB ($C_7H_{12}O_4$)
(h) mesityl oxide + ethyl malonate + base $\longrightarrow$ CC ($C_{13}H_{22}O_5$)
CC + NaOBr, OH^-, heat; then H^+ $\longrightarrow$ $CHBr_3$ + BB ($C_7H_{12}O_4$)
(i) $CH_3C{\equiv}CNa$ + acetaldehyde $\longrightarrow$ DD (C_5H_8O)
DD + $K_2Cr_2O_7$, H_2SO_4 $\longrightarrow$ EE (C_5H_6O)
(j) 3-pentyn-2-one + H_2O, Hg^{++}, H^+ $\longrightarrow$ FF ($C_5H_8O_2$)
(k) mesityl oxide + NaOCl, then H^+ $\longrightarrow$ GG ($C_5H_8O_2$)
(l) methallyl chloride (3-chloro-2-methylpropene) + HOCl $\longrightarrow$ HH ($C_4H_8OCl_2$)
HH + KCN $\longrightarrow$ II ($C_6H_8ON_2$)
II + H_2SO_4, H_2O, heat $\longrightarrow$ JJ ($C_6H_8O_4$)
(m) ethyl adipate + NaOEt $\longrightarrow$ KK ($C_8H_{12}O_3$)
KK + methyl vinyl ketone + base $\xrightarrow{\text{Michael}}$ LL ($C_{12}H_{18}O_4$)
LL + base $\xrightarrow{\text{aldol}}$ MM ($C_{12}H_{16}O_3$)
(n) hexachloro-1,3-cyclopentadiene + CH_3OH + KOH $\longrightarrow$ NN ($C_7H_6Cl_4O_2$)
NN + $CH_2{=}CH_2$, heat, pressure $\longrightarrow$ OO ($C_9H_{10}Cl_4O_2$)
OO + Na + *t*-BuOH $\longrightarrow$ PP ($C_9H_{14}O_2$)
PP + dilute acid $\longrightarrow$ QQ (C_7H_8O), *7-ketonorbornene*

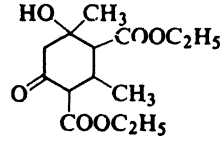
15. *Spermine*, $H_2NCH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$, found in seminal fluid, has been synthesized from acrylonitrile and 1,4-diaminobutane (putrescine). Show how this was probably done.

16. Outline all steps in each of the following syntheses:
(a) $HOOC{-}CH{=}CH{-}CH{=}CH{-}COOH$ from adipic acid
(b) $HC{\equiv}C{-}CHO$ from acrolein (*Hint:* See Problem 14(a) above.)
(c) $CH_3COCH{=}CH_2$ from acetone and formaldehyde
(d) $CH_3COCH{=}CH_2$ from vinylacetylene
(e) β-phenylglutaric acid from benzaldehyde and aliphatic reagents
(f) phenylsuccinic acid from benzaldehyde and aliphatic reagents
(g) 4-phenyl-2,6-heptanedione from benzaldehyde and aliphatic reagents (*Hint:* See Problem 3(f), above.)

17. Treatment of ethyl acetoacetate with acetaldehyde in the presence of the base piperidine was found to give a product of formula $C_{14}H_{22}O_6$. Controversy arose about its structure: did it have open-chain structure III or cyclic structure IV, each formed by combinations of aldol and Michael condensations?



III



IV

(a) Show just how each possible product could have been formed.
(b) Then the nmr spectrum of the compound was found to be the following

a complex, δ 0.95–1.10, 3H
b singlet, δ 1.28, 3H
c triplet, centered at δ 1.28, 3H
d triplet, centered at δ 1.32, 3H
e singlet, δ 2.5, 2H
f broad singlet, δ 3.5, 1H
g complex, δ 2–4, total of 3H
h quartet, δ 4.25, 2H
i quartet, δ 4.30, 2H

Which structure is the correct one? Assign all peaks in the spectrum. Describe the spectrum you would expect from the other possibility.

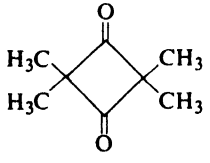
18. Give the likely structures for UU and VV.

1,3-butadiene + propiolic acid ($HC{\equiv}CCOOH$) ⟶ RR ($C_7H_8O_2$)
RR + 1 mole $LiAlH_4$ ⟶ SS ($C_7H_{10}O$)
SS + methyl chlorocarbonate (CH_3OCOCl) ⟶ TT ($C_9H_{12}O_3$)
TT + heat (short time) ⟶ toluene + UU (C_7H_8)
UU + tetracyanoethylene ⟶ VV ($C_{13}H_8N_4$)

Compound UU is not toluene or 1,3,5-cycloheptatriene; on standing at room temperature it is converted fairly rapidly into toluene. Compound UU gives the following spectral data. Ultraviolet: λ_{max} 303 mμ, ϵ_{max} 4400. Infrared: strong bands at 3020, 2900, 1595, 1400, 864, 692, and 645 cm^{-1}; medium bands at 2850, 1152, and 790 cm^{-1}.

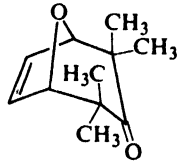
19. Give structures of compounds WW through YY, and account for their formation:
cyclopentanone + pyrrolidine, then acid ⟶ WW ($C_9H_{15}N$)
WW + $CH_2{=}CHCOOCH_3$ ⟶ XX ($C_{13}H_{21}O_2N$)
XX + H_2O, H^+, heat ⟶ YY ($C_9H_{14}O_3$)

20. Irradiation by ultraviolet light of 2,2,4,4-tetramethyl-1,3-cyclobutanedione (V) produces tetramethylethylene and two moles of carbon monoxide. When the irradiation is carried out in furan (VI), there is obtained a product believed to have the structure VII.



V

VI



VII

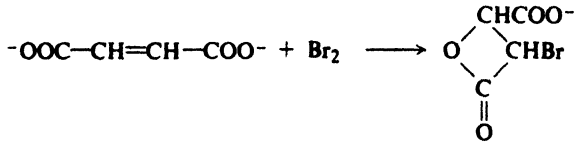
(a) Chief support for structure VII comes from elemental analysis, mol. wt. determination, and nmr data:

a singlet, δ 0.85, 6H
b singlet, δ 1.25, 6H
c singlet, δ 4.32, 2H
d singlet, δ 6.32, 2H

Show how the nmr data support the proposed structure. Why should there be two singlets of 6H each instead of one peak of 12H?

(b) It is proposed that, in the formation of tetramethylethylene, one mole of carbon monoxide is lost at a time. Draw electronic structures to show all steps in such a two-stage mechanism. How does the formation of VII support such a mechanism?

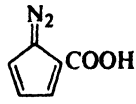
21. β-Lactones cannot be made from β-hydroxyacids. The β-lactone VIII was obtained, however, by treatment of sodium maleate (or sodium fumarate) with bromine water.



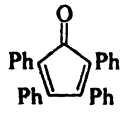
VIII

This experiment, reported in 1937 by P. D. Bartlett and D. S. Tarbell (of Harvard University), was an important step in the establishment of the mechanism of addition of halogens to carbon–carbon double bonds. Why is this so? How do you account for the formation of the β-lactone?

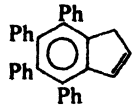
22. When the sodium salt of diazocyclopentadiene-2-carboxylic acid (IX) is heated above 140°, N_2 and CO_2 are involved. If IX is heated in solution with tetracyclone (X),



IX



X



XI

CO is evolved as well, and 4,5,6,7-tetraphenylindene (XI) is obtained. Show all steps in a likely mechanism for the formation of XI. (*Hint*: See Problem 10(e) above.) Of what special theoretical interest are these findings?

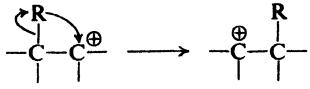
Chapter 28

Rearrangements and Neighboring Group Effects

Nonclassical Ions

28.1 Rearrangements and neighboring group effects: intramolecular nucleophilic attack

Carbonium ions, we know, can rearrange through migration of an organic group or a hydrogen atom, with its pair of electrons, to the electron-deficient

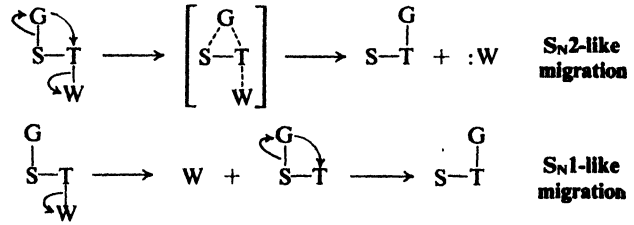


carbon. Indeed, when carbonium ions were first postulated as reactive intermediates (p. 160), it was to account for rearrangements of a particular kind. Such rearrangements still provide the best single clue that we are dealing with a carbonium ion reaction.

The driving force behind all carbonium ion reactions is the need to provide electrons to the electron-deficient carbon. When an electron-deficient carbon is generated, a near-by group may help to relieve this deficiency. It may, of course, remain in place and release electrons through the molecular framework, inductively or by resonance. Or—and this is what we are concerned with here—it may actually *carry the electrons* to where they are needed. Other atoms besides carbon can be electron-deficient—in particular, nitrogen and oxygen—and they, too, can get electrons through rearrangement. The most important class of molecular rearrangements is that involving *1,2-shifts to electron-deficient atoms*. It is the kind of rearrangement that we shall deal with in this chapter.

An electron-deficient carbon is most commonly generated by the departure of a leaving group which takes the bonding electrons with it. The migrating group is, of course, a nucleophile, and so a rearrangement of this sort amounts to *intramolecular nucleophilic substitution*. Now, as we have seen, nucleophilic substitution can be of two kinds, S_N2 and S_N1. Exactly the same possibilities exist for a re-

arrangement: it can be S_N2-like, with the migrating group helping to push out the leaving group in a single-step reaction; or it can be S_N1-like, with the migrating



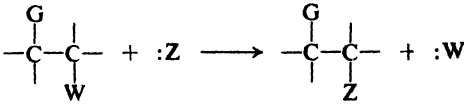
G = migrating group
S = migration source
T = migration terminus

group waiting for the departure of the leaving group before it moves. This matter of *timing* of bond-breaking and bond-making is, as we shall see, of major concern in the study of rearrangements.

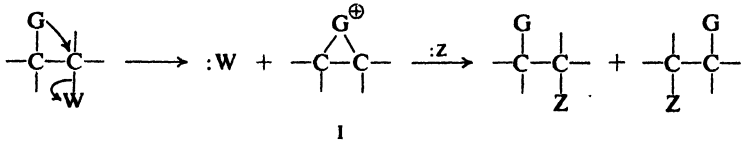
The term *anchimeric assistance* (Gr., *anchi* + *meros*, adjacent parts) is often used to describe the help given by a migrating group in the expelling of a leaving group.

In a rearrangement, a near-by group carries electrons to an electron-deficient atom, and then *stays there.* But sometimes, it happens, a group brings electrons and then *goes back to where it came from.* This gives rise to what are called **neighboring group effects**: intramolecular effects exerted on a reaction through direct participation—that is, through movement to within bonding distance—by a group near the reaction center.

Neighboring group effects involve the same basic process as rearrangement. Indeed, in many cases there *is* rearrangement, but it is *hidden.* What we see on the surface may be this:



But what is actually happening may be this:



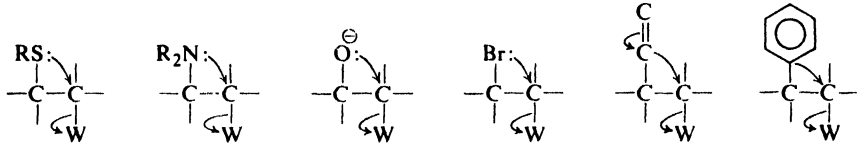
I

The neighboring group, acting as an internal nucleophile, attacks carbon at the reaction center; the leaving group is lost, and there is formed a *bridged intermediate* (I), usually a cation. This undergoes attack by an external nucleophile to yield the product. The overall stereochemistry is determined by the way in which the bridged ion is formed and the way in which it reacts, and typically differs from the

stereochemistry observed for simple attack by an external nucleophile. If a neighboring group helps to push out the leaving group—that is, gives anchimeric assistance—it may accelerate the reaction, sometimes tremendously. Thus, neighboring group participation is most often revealed by a *special kind of stereochemistry* or by an *unusually fast rate of reaction.*

We have, of course, encountered internal nucleophilic attack before. In the preparation of epoxides by action of base on halohydrins (Sec. 17.10), the bridged intermediate—the epoxide—happens to be stable in the reaction medium, persists, and is isolated.

If a neighboring group is to form a bridged cation, it must have electrons to form the extra bond. These may be *unshared pairs* on atoms like sulfur, nitrogen, oxygen, or bromine; *π electrons* of a double bond or aromatic ring; or even, in some cases, *σ electrons.*



In making its nucleophilic attack, a neighboring group competes with outside molecules that are often intrinsically much stronger nucleophiles. Yet the evidence clearly shows that the neighboring group enjoys—for its nucleophilic power—a tremendous advantage over these outside nucleophiles. Why is this? The answer is quite simple: *because it is there.*

The neighboring group is there, in the same molecule, poised in the proper position for attack. It does not have to wait until its path happens to cross that of the substrate; its "effective concentration" is extremely high. It does not have to give up precious freedom of motion (translational entropy) when it becomes locked into a transition state. Between it and the reaction center there are no tightly clinging solvent molecules that must be stripped away as reaction takes place. Finally, the electronic reorganization—changes in overlap—that accompanies reaction undoubtedly happens more easily in this cyclic system.

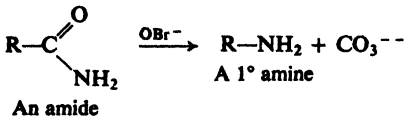
Enzymes function by accelerating, very specifically, rates of the organic reactions involved in life processes. They evidently do this by bringing reactants together into exactly the right positions for reaction to occur. Underlying much enzyme activity, it appears, are what amount to neighboring group effects.

Problem 28.1 Draw the structure of the bridged intermediate (I, above) expected if each of the following were to act as a neighboring group. To what class of compounds does each intermediate belong?

(a) $-N(CH_3)_2$
(b) $-SCH_3$
(c) $-OH$
(d) $-O^-$
(e) $-Br$
(f) $-C_6H_5$
(g) $-C_6H_4OCH_3$-*p*
(h) $-C_6H_4O^-$-*p*
(i) $-CH{=}CHR$

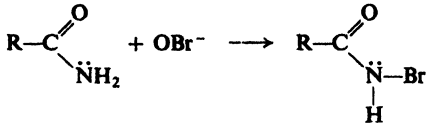
28.2 Hofmann rearrangement. Migration to electron-deficient nitrogen

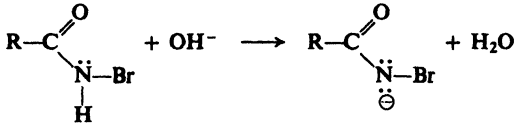
Let us begin with a reaction that we encountered earlier as a method of synthesis of amines: the Hofmann degradation of amides. Whatever the mechanism

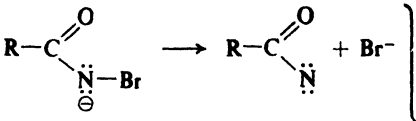


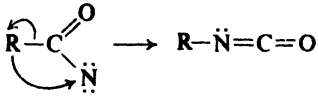
of the reaction, it is clear that rearrangement occurs, since the group joined to carbonyl carbon in the amide is found joined to nitrogen in the product.

The reaction is believed to proceed by the following steps:

(1) 

(2) 

(3) 

(4) 

Simultaneous

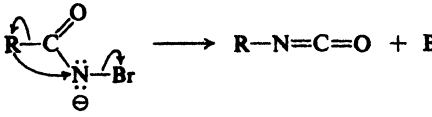
(5)

Step (1) is the halogenation of an amide. This is a known reaction, an N-haloamide being isolated if no base is present. Furthermore, if the N-haloamide isolated in this way is then treated with base, it is converted into the amine.

Step (2) is the abstraction of a hydrogen ion by hydroxide ion. This is reasonable behavior for hydroxide ion, especially since the presence of the electron-withdrawing bromine increases the acidity of the amide. Unstable salts have actually been isolated in certain of these reactions.

Step (3) involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom.

In Step (4) the actual rearrangement occurs. Steps (3) and (4) are generally

(3,4) 

believed to occur simultaneously, the attachment of R to nitrogen helping to push out halide ion. That is, migration is S_N2-like, and provides anchimeric assistance.

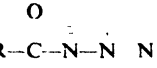
Step (5) is the hydrolysis of an isocyanate (R—N=C=O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

Like the rearrangement of carbonium ions that we have already encountered (Sec. 5.22), the Hofmann rearrangement involves a 1,2-shift. In the rearrangement of carbonium ions a group migrates with its electrons to an electron-deficient carbon; in the present reaction the group migrates with its electrons to an electron-deficient *nitrogen*. We consider nitrogen to be electron-deficient even though it probably loses electrons—to bromide ion—*while* migration takes place, rather than before.

The strongest support for the mechanism just outlined is the fact that many of the proposed intermediates have been isolated, and that these intermediates have been shown to yield the products of the Hofmann degradation. The mechanism is also supported by the fact that analogous mechanisms account satisfactorily for observations made on a large number of related rearrangements. Furthermore, the actual rearrangement step fits the broad pattern of 1,2-shifts to electron-deficient atoms.

In addition to evidence indicating what the various steps in the Hofmann degradation are, there is also evidence that gives us a rather intimate view of just how the rearrangement step takes place. In following sections we shall see what some of that evidence is. We shall be interested in this not just for what it tells us about the Hofmann degradation, but because it will give us an idea of the kind of thing that can be done in studying rearrangements of many kinds.

Problem 28.2 Reaction of acid chlorides with sodium azide, NaN_3, yields *acyl azides*, $RCON_3$. When heated, these undergo the *Curtius rearrangement* to amines, RNH_2, or, in a non-hydroxylic solvent, to isocyanates, RNCO. Using the structure



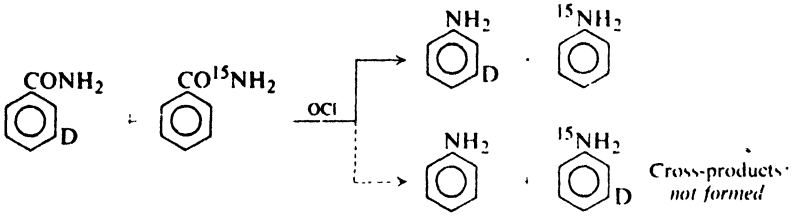
for the azide, suggest a mechanism for the rearrangement. (*Hint:* Write balanced equations.)

28.3 Hofmann rearrangement. Intramolecular or intermolecular?

One of the first questions asked in the study of a rearrangement is this: Is the rearrangement *intra*molecular or *inter*molecular? That is, does the migrating group move from one atom to another atom within the same molecule, or does it move from one molecule to another?

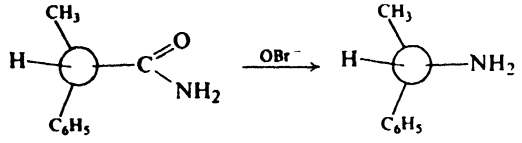
In the mechanism outlined above, the Hofmann rearrangement is shown as intramolecular. How do we know that this is so? To answer this question, T. J. Prosser and E. L. Eliel (of the University of Notre Dame) carried out degradation of a mixture of *m*-deuteriobenzamide and benzamide-^{15}N. When they analyzed the product with the mass spectrometer, they found only *m*-deuterioaniline and

aniline-^{15}N. There was *none* of the mixture of cross-products that would have been formed if a phenyl group from one molecule had become attached to the nitrogen of another. The results of this elegant double labeling experiment thus show beyond doubt that the Hofmann rearrangement is intramolecular.



28.4 Hofmann rearrangement. Stereochemistry at the migrating group

When optically active α-phenylpropionamide undergoes the Hofmann degradation, α-phenylethylamine of the same configuration and of essentially the same optical purity is obtained:



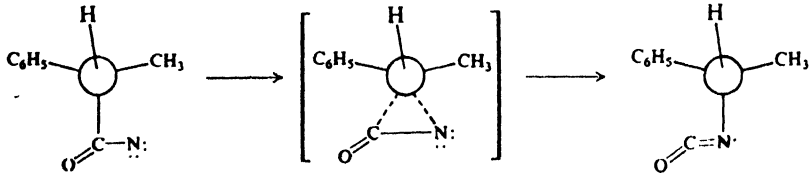
(+)-α-Phenylpropionamide (−)-α-Phenylethylamine

Retention of configuration

Rearrangement proceeds *with complete retention of configuration* about the chiral center of the migrating group.

These results tell us two things. First, nitrogen takes the same relative position on the chiral carbon that was originally occupied by the carbonyl carbon. Second, the chiral carbon does not break away from the carbonyl carbon until it has started to attach itself to nitrogen. If the group were actually to become free during its migration, we would expect considerable loss of configuration and hence a partially racemic product. (If the group were to become free—*really* free—we would expect reaction to be, in part, intermolecular, also contrary to fact.)

We may picture the migrating group as moving from carbon to nitrogen via a transition state, I, in which carbon is pentavalent:

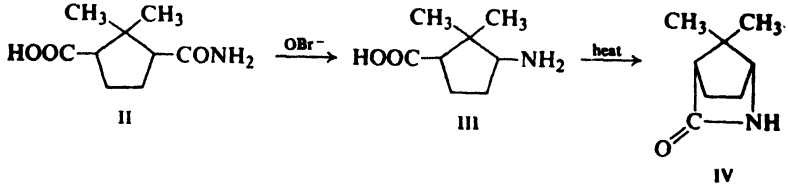


I

The migrating group *steps* from atom to atom; it does *not* jump.

There is much evidence to suggest that the stereochemistry of all 1,2-shifts has this common feature: *complete retention of configuration in the migrating group.*

Problem 28.3 Many years before the Hofmann degradation of optically active α-phenylpropionamide was studied, the following observations were made: when the cyclopentane derivative II, in which the —COOH and —$CONH_2$ groups are *cis* to each other, was treated with hypobromite, compound III was obtained; compound III could be converted by heat into the amide IV (called a *lactam*). What do these results show about the mechanism of the rearrangement? (*Use models.*)

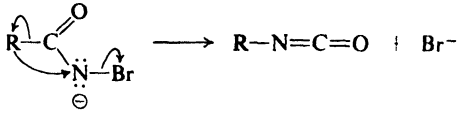


II III IV

28.5 Hofmann rearrangement. Timing of the steps

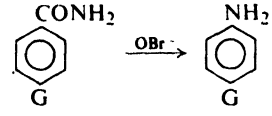
We said that steps (3) and (4) of the mechanism are believed to be simultaneous, that is, that loss of bromide ion and migration occur in the same step:

(3,4)



One reason for believing this is simply the anticipated difficulty of forming a highly unstable intermediate in which an electronegative element like nitrogen has only a sextet of electrons. Such a particle should be even less stable than primary carbocations, and those, we know, are seldom formed; reaction takes the easier, S_N2-like path. Another reason is the effect of structure on rate of reaction. Let us examine this second reason.

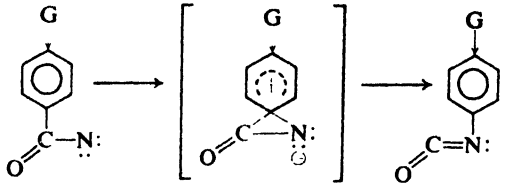
When the migrating group is aryl, the rate of the Hofmann degradation is increased by the presence of electron-releasing substituents in the aromatic ring; thus substituted benzamides show the following order of reactivity:



G: OCH_3 > CH_3 > H > Cl > NO_2

Now, how could electron release speed up Hofmann degradation? One way could be through its effect on the rate of migration. Migration of an alkyl group must involve a transition state containing pentavalent carbon, like I in the preceding section. Migration of an aryl group, on the other hand, takes place via a

structure like V. This structure is a familiar one; from the standpoint of the migrating aryl group, rearrangement is simply electrophilic aromatic substitution, with the electron-deficient atom—nitrogen, in this case—acting as the attacking reagent. In at least some rearrangements, as we shall see, there is evidence that structures



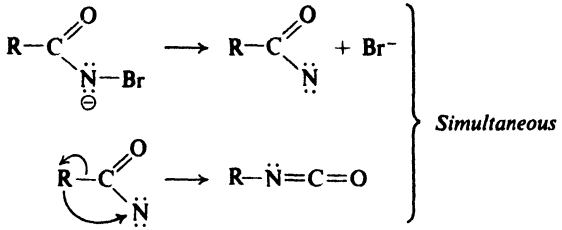
V

like V are actual intermediate compounds, as in the ordinary kind of electrophilic aromatic substitution (Sec. 11.16). Electron-releasing groups disperse the developing charge on the aromatic ring and thus speed up formation of V. Viewed in this way, substituents affect the rate of rearrangement—the *migratory aptitude*—of an aryl group in exactly the same way as they affect the rate of aromatic nitration, halogenation, or sulfonation. (As we shall see, however, conformational effects can sometimes completely outweigh these electronic effects.)

There is another way in which electron release might be speeding up reaction: by speeding up formation of the electron-deficient species in equation (3). But the observed effect is a strong one, and more consistent with the development of the positive charge *in the ring itself*, as during rearrangement.

We should be clear about what the question is here. It is *not* whether some groups migrate faster than others—there is little doubt about that—but whether the rate of rearrangement affects the overall rate—the *measured* rate—of the Hofmann degradation.

It is likely, then, that electron-releasing substituents speed up Hofmann degradation by speeding up rearrangement. Now, under what conditions can this happen? Consider the sequence (3) and (4). Loss of bromide ion (3) could be fast



and reversible, followed by slow rearrangement (4). Rearrangement would be rate-determining, as required, but in that case something else would not fit. The reverse of (3) is combination of the particle ArCON with bromide ion; if this were taking place, so should combination of ArCON with the solvent, water—more abundant and more nucleophilic—to form the *hydroxyamic acid* ArCONHOH. But hydroxamic acids are *not* formed in the Hofmann degradation.

If ArCON were indeed an intermediate, then, it would have to be undergoing

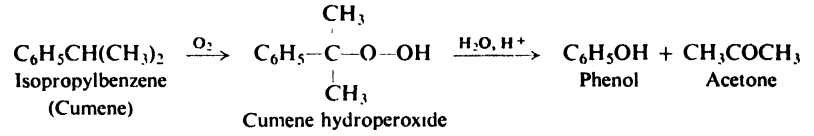
rearrangement as fast as it is formed; that is, (4) would have to be fast compared with (3). But in that case, the overall rate would be independent of the rate of rearrangement, contrary to fact.

We are left with the concerted mechanism (3,4). Attachment of the migrating group helps to push out bromide ion, and overall rate *does* depend on the rate of rearrangement. As the amount of anchimeric assistance varies, so does the observed rate of reaction.

At the migrating group, we said, rearrangement amounts to electrophilic substitution. But at the electron-deficient nitrogen, rearrangement amounts to *nucleophilic* substitution: the migrating group (with its electrons) is a nucleophile, and bromide ion is the leaving group. The sequence (3) and (4) corresponds to an S_N1 mechanism; the concerted reaction (3,4) corresponds to a S_N2 mechanism. Dependence of overall rate on the nature of the nucleophile is consistent with the S_N2-like mechanism, but not with the S_N1-like mechanism.

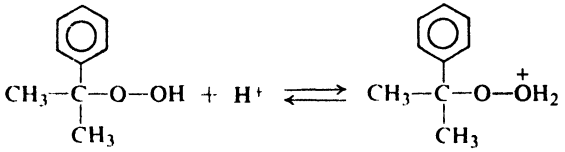
28.6 Rearrangement of hydroperoxides. Migration to electron-deficient oxygen

In Sec. 24.4 we encountered the synthesis of phenol via cumene hydroperoxide:



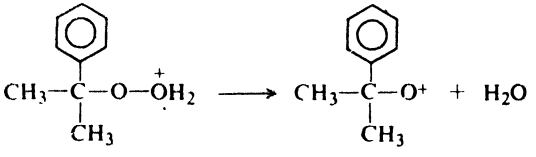
The phenyl group is joined to carbon in the hydroperoxide and to oxygen in phenol: clearly, rearrangement takes place. This time, it involves a 1,2-shift to electron-deficient *oxygen*.

(1)

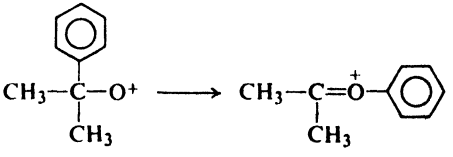


Cumene hydroperoxide
I

(2)



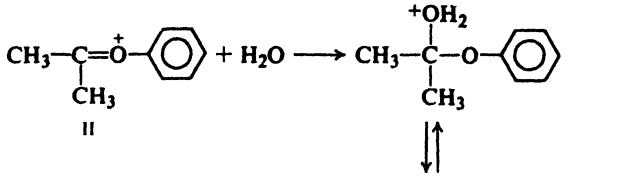
(3)



II

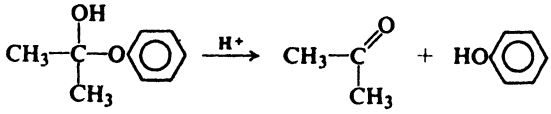
Simultaneous

(4)



II III

(5)



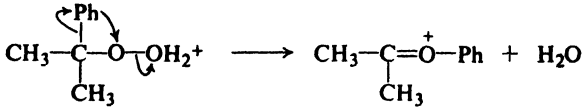
III Acetone Phenol

Acid converts (step 1) the peroxide I into the protonated peroxide, which loses (step 2) a molecule of water to form an intermediate in which oxygen bears only six electrons. A 1,2-shift of the phenyl group from carbon to electron-deficient oxygen yields (step 3) the "carbonium" ion II, which reacts with water to yield (step 4) the hydroxy compound III. Compound III is a hemi-acetal (Sec. 19.15) which breaks down (step 5) to give phenol and acetone.

Every step of the reaction involves chemistry with which we are already quite familiar: protonation of a hydroxy compound with subsequent ionization to leave an electron-deficient particle; a 1,2-shift to an electron-deficient atom; reaction of a carbonium ion with water to yield a hydroxy compound; decomposition of a hemi-acetal. In studying organic chemistry we encounter many new things; but much of what seems new is found to fit into old familiar patterns of behavior.

It is very probable that steps (2) and (3) are simultaneous, the migrating phenyl group helping to push out (2,3) the molecule of water. This concerted

(2,3)

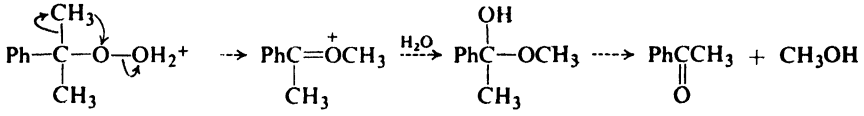


mechanism is supported by the same line of reasoning that we applied to the Hofmann rearrangement. (a) A highly unstable intermediate containing oxygen with only a sextet of electrons should be very difficult to form. (b) There is evidence that, if there *is* such an intermediate, it must undergo rearrangement as fast as it is formed; that is, if (2) and (3) are separate steps, (3) must be fast compared with (2). (c) The rate of overall reaction is speeded up by electron-releasing substituents in migrating aryl groups, and in a way that resembles, *quantitatively*, the effect of these groups on ordinary electrophilic aromatic substitution. Almost certainly, then, substituents affect the overall rate of reaction by affecting the rate of migration, and hence migration must take place in the rate-determining step. This rules out the possibility of a fast (3), and leaves us with the concerted reaction (2,3).

Problem 28.4 When α-phenylethyl hydroperoxide, $C_6H_5CH(CH_3)O{-}OH$, undergoes acid-catalyzed rearrangement in $H_2{}^{18}O$, recovered unrearranged hydroperoxide is found to contain *no* oxygen-18. Taken with the other evidence, what does this finding tell us about the mechanism of reaction?

28.7 Rearrangement of hydroperoxides. Migratory aptitude

The rearrangement of hydroperoxides lets us see something that the Hofmann rearrangement could not: the preferential migration of one group rather than another. That is, we can observe the relative speeds of migration—the relative migratory aptitudes—of two groups, not as a difference in rate of reaction, but as a difference in the product obtained. In cumene hydroperoxide, for example, any one of three groups could migrate: phenyl and two methyls. If, instead of phenyl,

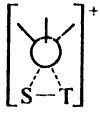


Acetophenone Methanol

Not obtained

methyl were to migrate, reaction would be expected to yield methanol and acetophenone. Actually, phenol and acetone are formed quantitatively, showing that a phenyl group migrates much faster than a methyl.

It is generally true in 1,2-shifts that aryl groups have greater migratory aptitudes than alkyl groups. We can see why this should be so. Migration of an alkyl group must involve a transition state containing pentavalent carbon (IV). Migration



IV

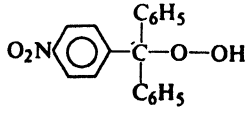
Alkyl migration. *pentavalent carbon*

V

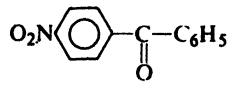
Aryl migration: *benzenonium ion*

of an aryl group, on the other hand, takes place via a structure of the benzenonium ion type (V); transition state or actual intermediate, V clearly offers an easier path for migration than does IV.

The hydroperoxide may contain several aryl groups and, if they are different, we can observe competition in migration between them, too. As was observed in



VI



VII

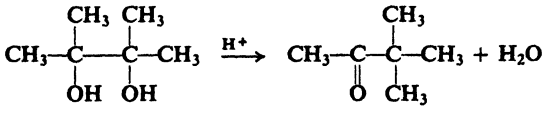
the rate study, the relative migratory aptitude of an aryl group is raised by electron-releasing substituents, and lowered by electron-withdrawing substituents. For example, when *p*-nitrotriphenylmethyl hydroperoxide (VI) is treated with acid, it yields exclusively phenol and *p*-nitrobenzophenone (VII); as we would have expected, phenyl migrates in preference to *p*-nitrophenyl.

Problem 28.5 When *p*-methylbenzyl hydroperoxide, $p\text{-}CH_3C_6H_4CH_2O\text{—}OH$, is treated with acid, there are obtained *p*-methylbenzaldehyde (61%) and *p*-cresol (38%). (a) How do you account for the formation of each of these? What other products must have been formed? (b) What do the relative yields of the aromatic products show?

Problem 28.6 Treatment of aliphatic hydroperoxides, $RCH_2O\text{—}OH$ and $R_2CHO\text{—}OH$, with aqueous acid yields aldehydes and ketones as the only organic products. What conclusion do you draw about migratory aptitudes?

28.8 Pinacol rearrangement. Migration to electron-deficient carbon

Upon treatment with mineral acids, 2,3-dimethyl-2,3-butanediol (often called *pinacol*) is converted into methyl *tert*-butyl ketone (often called *pinacolone*). The

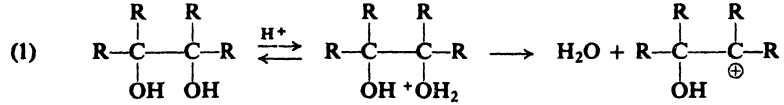


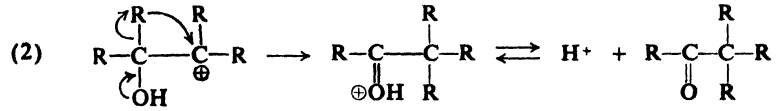
Pinacol
2,3-Dimethyl-2,3-butanediol

Pinacolone
Methyl *tert*-butyl ketone
3,3-Dimethyl-2-butanone

glycol undergoes dehydration, and in such a way that rearrangement of the carbon skeleton occurs. Other glycols undergo analogous reactions, which are known collectively as **pinacol rearrangements.**

The pinacol rearrangement is believed to involve two important steps: (1) loss of water from the protonated glycol to form a carbonium ion; and (2) rearrangement of the carbonium ion by a 1,2-shift to yield the protonated ketone.





Both steps in this reaction are already familiar to us: formation of a carbonium ion from an alcohol under the influence of acid, followed by a 1,2-shift to the electron-deficient atom. The pattern is also familiar: rearrangement of a cation to a more stable cation, in this case to the protonated ketone. The driving force is the

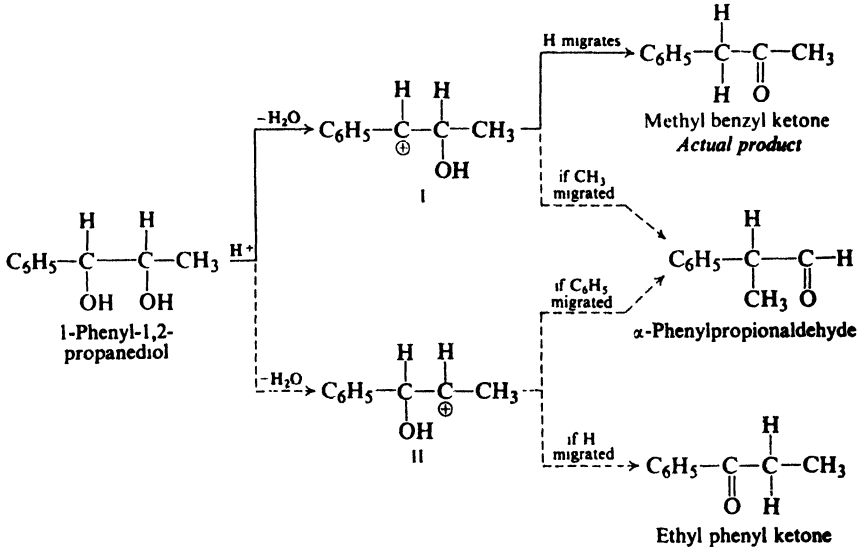
usual one behind carbonium ion reactions: the need to provide the electron-deficient carbon with electrons. The special feature of the pinacol rearrangement is the presence in the molecule of the second oxygen atom; it is this oxygen atom, with its unshared pairs, that ultimately provides the needed electrons.

Problem 28.7 Account for the products of the following reactions:

(a) 1,1,2-triphenyl-2-amino-1-propanol $\xrightarrow{HONO}$ 1,2,2-triphenyl-1-propanone
(*Hint:* See Problem 23.11, p. 763.)

(b) 2-phenyl-1-iodo-2-propanol + Ag^+ $\longrightarrow$ benzyl methyl ketone

When the groups attached to the carbon atoms bearing —OH differ from one another, the pinacol rearrangement can conceivably give rise to more than one compound. The product actually obtained is determined (a) by which —OH group is lost in step (1), and then (b) by which group migrates in step (2) to the electron-deficient carbon thus formed. For example, let us consider the rearrangement of 1-phenyl-1,2-propanediol. The structure of the product actually obtained, methyl benzyl ketone, indicates that the benzyl carbonium ion (I) is formed in preference to the secondary carbonium ion (II), and that —H migrates in preference to $-CH_3$.



Study of a large number of pinacol rearrangements has shown that usually the product is the one expected if, first, ionization occurs to yield the more stable carbonium ion, and then, once the preferred ionization has taken place, migration takes place according to the sequence —Ar > —R. (We have already seen how it is that an aryl group migrates faster than an alkyl.) Hydrogen can migrate, too, but we cannot predict its relative migratory aptitude. Hydrogen may migrate in preference to —R or —Ar, but this is not always the case; indeed, it sometimes happens that with a given pinacol either —H or —R can migrate, depending upon experimental conditions.

Among aryl groups, relative migratory aptitude depends—other things being equal—on the ability of the ring to accommodate a positive charge. However, as we shall see in the next section, strong stereochemical factors can be involved, and may outweigh these electronic factors.

Problem 28.8 For the rearrangement of each of the following glycols show which carbonium ion you would expect to be the more stable, and then the rearrangement that this carbonium ion would most likely undergo:

(a) 1,2-propanediol
(b) 2-methyl-1,2-propanediol
(c) 1-phenyl-1,2-ethanediol
(d) 1,1-diphenyl-1,2-ethanediol
(e) 1-phenyl-1,2-propanediol
(f) 1,1-diphenyl-2,2-dimethyl-1,2-ethanediol
(g) 1,1,2-triphenyl-2-methyl-1,2-ethanediol
(h) 2-methyl-3-ethyl-2,3-pentanediol
(i) 1,1-bis(*p*-methoxyphenyl)-2,2-diphenyl-1,2-ethanediol

We have depicted the pinacol rearrangement as a two-step process with an actual carbonium ion as intermediate. There is good evidence that this is so, at least when a tertiary or benzylic cation can be formed. Evidently the stability of the incipient cation in the transition state permits (S_N1-like) loss of water without anchimeric assistance from the migrating group. This is, we note, in contrast to what happens in migration to electron-deficient nitrogen or oxygen.

Problem 28.9 The following reactions have all been found to yield a mixture of pinacol and pinacolone, and *in the same proportions*: treatment of 3-amino-2,3-dimethyl-2-butanol with nitrous acid; treatment of 3-chloro-2,3-dimethyl-2-butanol with aqueous silver ion; and acid-catalyzed hydrolysis of the epoxide of 2,3-dimethyl-2-butene. What does this finding indicate about the mechanism of the pinacol rearrangement?

Problem 28.10 When pinacol was treated with acid in $H_2{}^{18}O$ solution, recovered unrearranged pinacol was found to contain oxygen-18. Studies showed that oxygen exchange took place two to three times as fast as rearrangement. What bearing does this fact have on the mechanism of rearrangement?

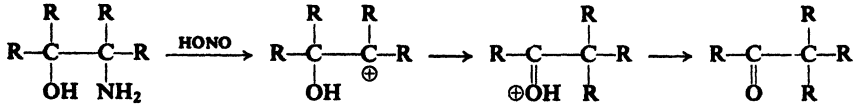
28.9 Pinacolic deamination. Conformational effects

Primary aliphatic amines react with nitrous acid to form diazonium salts (Sec. 23.10).

$$\underset{\text{1° aliphatic amine}}{RNH_2} + NaNO_2 + HX \longrightarrow RN_2{}^+X^- \longrightarrow R^+X^- + N_2 \qquad R^+X^- \longrightarrow \text{products}$$

Unlike their aromatic counterparts, however, these diazonium ions are extremely unstable, and lose nitrogen rapidly to give products that strongly suggest intermediate formation of carbonium ions (Problem 23.11, p. 763).

If such an amino group is located *alpha* to a hydroxyl group, then treatment with nitrous acid causes a reaction closely related to the pinacol rearrangement, *pinacolic deamination*:



This system permits many studies not possible with pinacols, since here the electron-deficiency is generated at a pre-determined position: at the carbon that held the amino group.

Problem 28.11 Give the structure of the carbonium ion generated: (a) by action of acid on 1,1-diphenyl-1,2-propanediol; (b) by action of nitrous acid on 1,1-diphenyl-2-amino-1-propanol.

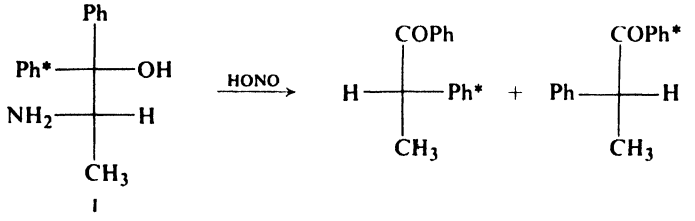
Let us examine the stereochemistry of pinacolic deamination in some detail. In this we shall see the operation of a factor we have not yet encountered in rearrangements: *conformational effects.* More important, we shall get some idea of the methods used to attack problems like this.

When optically active 2-amino-1,1-diphenyl-1-propanol is treated with nitrous acid, there is obtained 1,2-diphenyl-1-propanone of inverted configuration but lower optical purity than the starting material. Reaction has taken place with

Inversion (77%) plus racemization (23%)
equivalent to
inversion (88.5%) plus retention (11.5%)

racemization plus inversion: stereochemistry typical of S_N1 reactions, and consistent with the idea of an open carbonium ion as intermediate.

In a series of elegant experiments, Clair Collins (of Oak Ridge National Laboratory) has given us intimate details about the reaction: the intermediacy of open carbonium ions, their approximate life-time, and the conformational factors that affect their chemistry. Collins, too, carried out deamination of optically active 2-amino-1,1-diphenyl-1-propanol, but his starting material was labeled stereospecifically (I) with carbon-14 in one of the phenyl groups. He resolved



1,1-Diphenyl-2-amino-1-propanol (I)

Inversion: *migration of Ph** (88%)

Retention: *migration of Ph* (12%)

the products and, by degradation studies, determined the location of the radioactive label in each. The inverted product had been formed exclusively by migration of the labeled group, Ph*; the product of retained configuration was formed exclusively by migration of the unlabeled group, Ph. (The 12% of retention observed by Collins agrees, of course, quite well with the results of the earlier simple stereochemical study.)

On the basis of these results, Collins pictured the reaction as taking place as shown in Fig. 28.1. Three conclusions were drawn. (a) *An open carbonium ion is formed.* If, instead, migration of phenyl were concerted with loss of N_2, attack

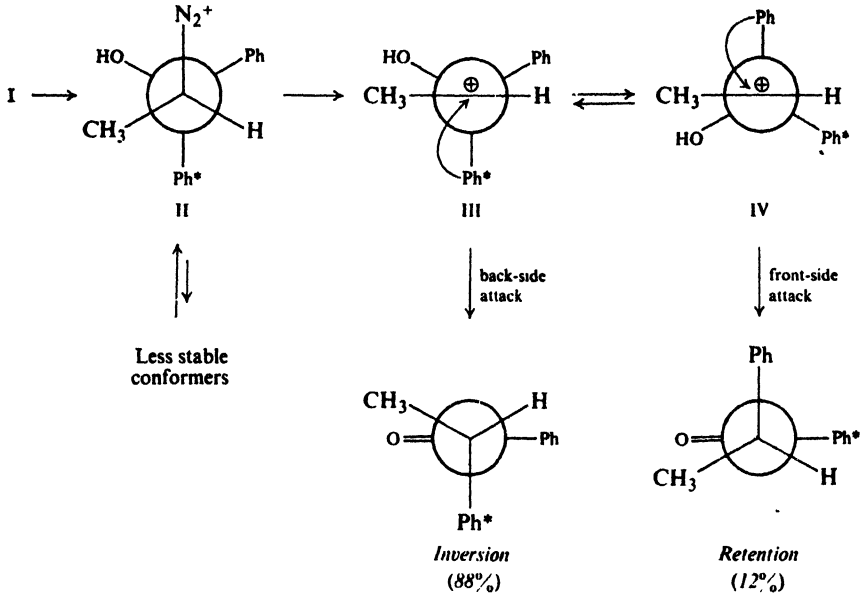
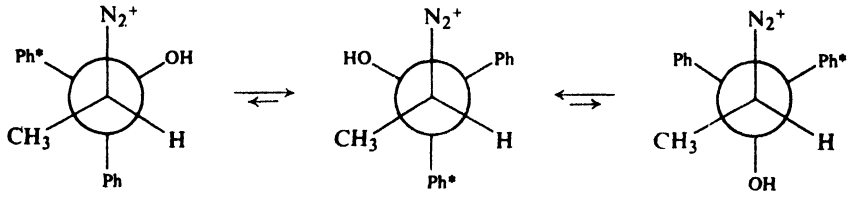


Figure 28.1. Pinacolic deamination of optically active labeled 2-amino-1,1-diphenyl-1-propanol.The most abundant conformer, II, of the diazonium ion yields cation III. Cation III does two things: (a) rearranges by back-side migration of Ph*, and (b) rotates, in the easiest way possible, to form cation IV, which rearranges by front-side migration of Ph.

would have been exclusively back-side, with complete inversion. (b) *The carbonium ion does not last long enough for very much rotation to occur about the central carbon–carbon bond.* If, instead, the carbonium ion were long-lived, there would have been equilibration between the equally stable conformations III and IV, leading to complete racemization and equal migration of Ph and Ph*. (c) *Conformational effects largely determine the course of rearrangement.* The most stable and hence most abundant conformation of the diazonium ion is II, in which the bulky phenyl groups flank tiny hydrogen. Nitrogen is lost to yield carbonium ion III. This first-formed cation is the species that undergoes most of the rearrangement, and in the way consistent with its conformation: back-side migration of Ph*. Some cations last long enough for partial rotation (involving eclipsing only of the small groups $-CH_3$ and $-OH$) to conformation IV, which rearranges by front-side migration of Ph.

The course of rearrangement is thus determined largely by the conformation of the first-formed ion and, to a lesser extent, of the ion most easily formed from

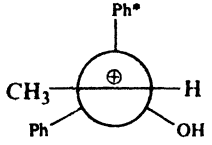
it by limited rotation. These conformations reflect, in turn, the most stable conformation of the parent diazonium ion.



II

Most abundant conformer

Furthermore, we can see that rearrangement of either cation III or cation IV involves a transition state in which the bulky non-migrating groups—methyl and one phenyl—are on opposite sides of the molecule: a so-called *trans* transition state. In contrast, front-side migration of Ph* would require, first, formation of the less stable cation V (either from a less abundant conformation of the diazonium



V

CH_3 and Ph crowded together: *cation slow to form, slow to rearrange*

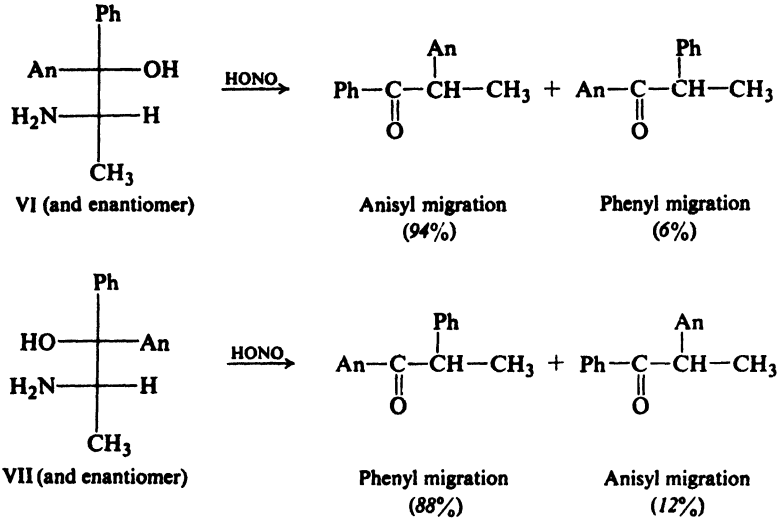
ion or, by rotation, from cation III); and then, its reaction via a crowded *cis* transition state. Both these processes are slow, and their combination does not happen to a measurable extent.

The fine print on page 235 described two extreme situations for the reaction of different conformers. (a) If reaction of the conformers is much faster than the rotation that interconverts them, then the ratio of products obtained reflects the relative populations of the conformers. (b) If reaction of the conformers is much slower than their interconversion, then the ratio of products reflects the relative stabilities of the transition states involved. It was pointed out that, whichever situation exists, we will in general make the same rough prediction about products, since a particular spacial relationship will affect conformer stabilities and transition state stabilities in much the same way.

In pinacolic deamination we have a rather special situation, where reaction and rotation are of roughly comparable speeds, and hence both the populations and the reactivities of conformers affect the product ratio. Most interesting of all, perhaps, is the ingenuity that Collins used to show that this is so.

Conformational factors can determine more than the stereochemistry of rearrangement. In light of Collins' findings, let us examine work done earlier by D. Y. Curtin (of the University of Illinois) with 2-amino-1-anisyl-1-phenyl-1-propanol. This resembles Collins' labeled compound (p. 899), except that an anisyl group (*p*-methoxyphenyl group) takes the place of one of the phenyls. Here, the competition in migration is between a phenyl and an anisyl, instead of between labeled and unlabeled phenyl groups.

Curtin prepared both diastereomeric forms, VI and VII, each as a racemic



modification. In the deamination of VI, migration of anisyl was found to exceed that of phenyl, 94:6. This, we might say, is to be expected: with its electron-releasing methoxyl group, anisyl migrates much faster than phenyl. But in the deamination of the diastereomer VII, *phenyl migration was found to exceed that of anisyl, 88:12.* Clearly, migratory aptitude is *not* the controlling factor in the reaction of VII—nor then, most probably, in the reaction of VI, either.

The most reasonable interpretation of Curtin's work is outlined in Fig. 28.2. This assumes a situation exactly analogous to that indicated by Collins' work, a reasonable assumption since anisyl and phenyl are of the same bulk. Whether phenyl or anisyl migrates predominantly depends on which group is in the proper location in the first-formed carbonium ion, and this again depends on the most stable conformation of the parent diazonium ion. The minor product in each case is due to front-side migration of the aryl group brought into position by the easiest rotation of the carbonium ion.

In the case of diastereomer VII, for example, phenyl is in position to migrate in cation VII*b*, and does so. Competing with this migration is rotation about the single bond to form cation VII*c*, which reacts by anisyl migration. We notice that the percentage of back-side attack by phenyl is the same (88%) as in the original stereochemical study of 2-amino-1,1-diphenyl-1-propanol (p. 899). This *should* be so, since the same competition is involved in both cases: phenyl migration *vs.* rotation about a bond that is sterically the same. (Indeed, it was the quantitative similarity of results in the two studies that gave Collins his first clue as to what might be involved in such reactions, and led to his labeling experiment.)

In these particular reactions, then, just which group migrates is controlled, not electronically by intrinsic migratory aptitude, but sterically by conformational factors. This does *not* negate the idea of migratory aptitude. Groups *do* differ in their tendencies to migrate, and in some cases the effects of such differences can be very great. What we see here is simply that conformational factors can, sometimes, outweigh migratory aptitudes.

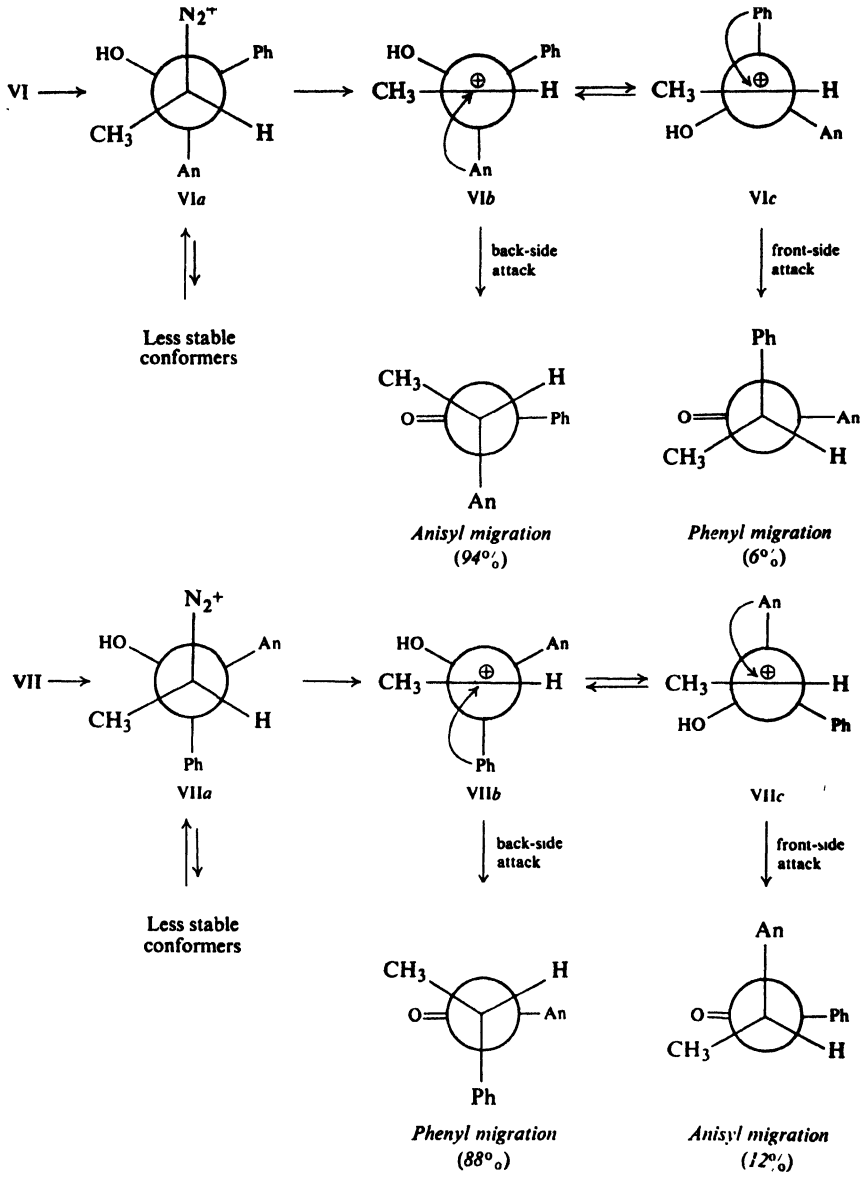
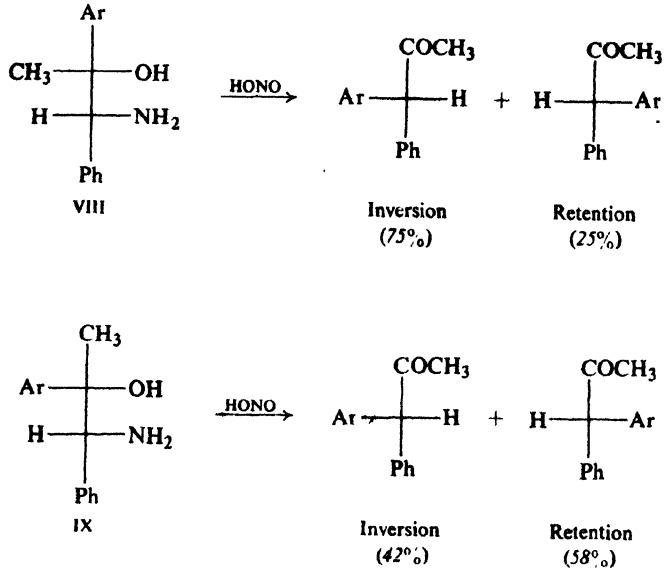


Figure 28.2. Pinacolic deamination of diastereomeric 2-amino-1-anisyl-1-phenyl-1-propanols. In each case the most abundant conformer, VI*a* or VII*a*, of the diazonium ion yields a cation in which an aryl group is in position for back-side migration via a *trans* transition state: anisyl in VI*b*, phenyl in VII*b*. Such rearrangement predominates. Some of each first-formed cation is converted through rotation into another cation, in which the other aryl group is in position for front-side migration via a *trans* transition state: phenyl in VI*c*, anisyl in VII*c*. Such rearrangement gives the minor product.

Another point: here we have reactions not only where steric factors are powerful, but where electronic factors are weak. From the standpoint of the migrating aryl group, remember, rearrangement is electrophilic aromatic substitution with the migration terminus as electrophilic reagent. The reagent, a full-fledged carbonium ion in this case, is highly reactive and hence not very selective; it prefers to attack anisyl rather than phenyl and, other things being equal, would do so. But the preference is not a strong one, and here is less important than the steric factors.

The strength of these electronic factors depends on how badly they are needed. In S_N2-like rearrangements, where the migrating group is needed to help push out the leaving group, differences in migratory tendencies are very great. (That is, the migration terminus is an unreactive reagent and hence is highly selective.) Indeed, as we shall see in Sec. 28.12, the strength of the effects of substituents in migrating aryl groups can be used to measure the relative importance of S_N1-like and S_N2-like rearrangements.

Problem 28.12 When Collins (p. 899) prepared, in optically active form, diastereomers of 1-amino-1-phenyl-2-*p*-tolyl-2-propanol (VIII and IX, Ar = *p*-tolyl) and

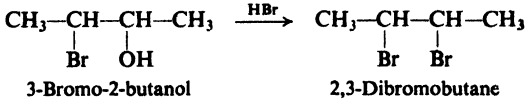


treated them with nitrous acid, he observed the product distribution shown. Note that IX rearranges with *predominant retention*. When Ar = *p*-methoxyphenyl, essentially the same results were obtained. Account in detail for these findings.

28.10 Neighboring group effects: stereochemistry

When treated with concentrated hydrobromic acid, the bromohydrin 3-bromo-2-butanol is converted into 2,3-dibromobutane. This, we say, involves nothing out of the ordinary; it is simply nucleophilic attack (S_N1 or S_N2) by

bromide ion on the protonated alcohol. But in 1939 Saul Winstein (p. 474) and Howard J. Lucas (of the California Institute of Technology) described the stereochemistry of this reaction and, in doing this, opened the door to a whole new concept in organic chemistry: the *neighboring group effect.*



3-Bromo-2-butanol 2,3-Dibromobutane

First, Winstein and Lucas found (Fig. 28.3) that (racemic) *erythro* bromohydrin yields only the *meso* dibromide, and (racemic) *threo* bromohydrin yields

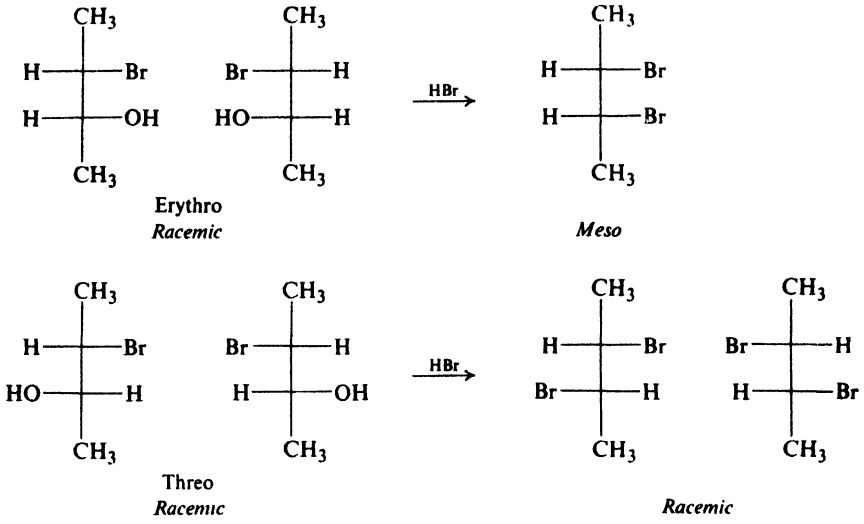


Figure 28.3. Conversion of racemic 3-bromo-2-butanols into 2,3-dibromobutanes.

only the *racemic* dibromide. Apparently, then, reaction proceeds with complete retention of configuration—unusual for nucleophilic substitution. But something even more unusual was still to come.

They carried out the same reaction again but this time used *optically active* starting materials (Fig. 28.4). From optically active *erythro* bromohydrin they obtained, of course, optically inactive product: the *meso* dibromide. But *optically active erythro bromohydrin also yielded optically inactive product: the racemic dibromide.*

In one of the products (I) from the *erythro* bromohydrin, there is retention of configuration. But in the other product (II), there is inversion, not only at the carbon that held the hydroxyl group, but also at the carbon that held bromine—a carbon that, on the surface, is not even involved in the reaction. How is one to account for the fact that exactly half the molecules react with complete retention, and the other half with this strange double inversion?

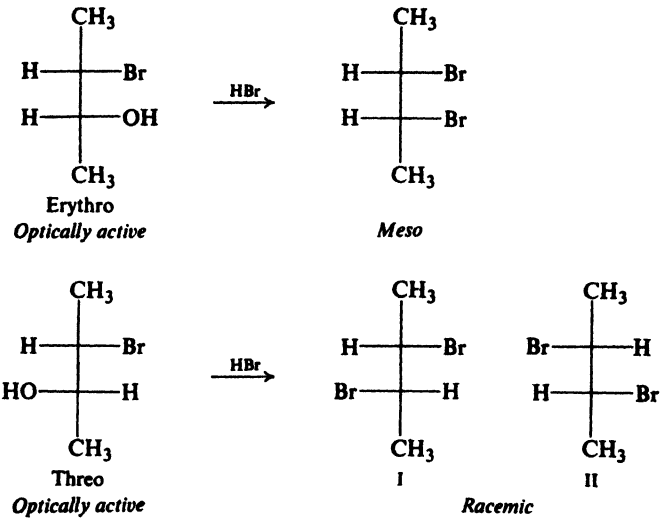
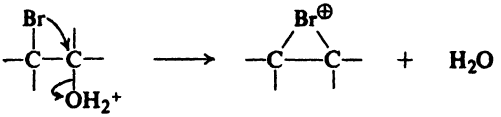


Figure 28.4. Conversion of optically active 3-bromo-2-butanols into 2,3-dibromobutanes.

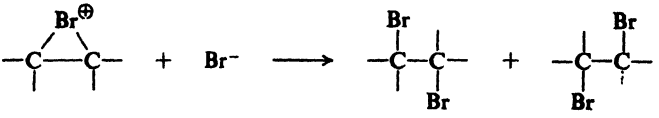
Winstein and Lucas gave the only reasonable interpretation of these facts. In step (1) the protonated bromohydrin loses water to yield, not the open carbonium ion, but a bridged bromonium ion. In step (2) bromide ion attacks this

(1)



A bromonium ion

(2)



bromonium ion to give the dibromide. But it can attack the bromonium ion *at either of two carbon atoms*: attack at one gives the product with retention at both chiral centers; attack at the other gives the product with inversion about both centers. Figure 28.5 depicts the reaction of the optically active *threo* bromohydrin.

The bromonium ion has the same structure as that proposed two years earlier by Roberts and Kimball (Sec. 7.12) as an intermediate in the addition of bromine to alkenes. Here it is formed in a different way, but its reaction is the same, and so is the final product.

Reaction consists of two successive nucleophilic substitutions. In the first one the nucleophile is the neighboring bromine; in the second, it is bromide ion from outside the molecule. Both substitutions are pictured as being S_N2-like;

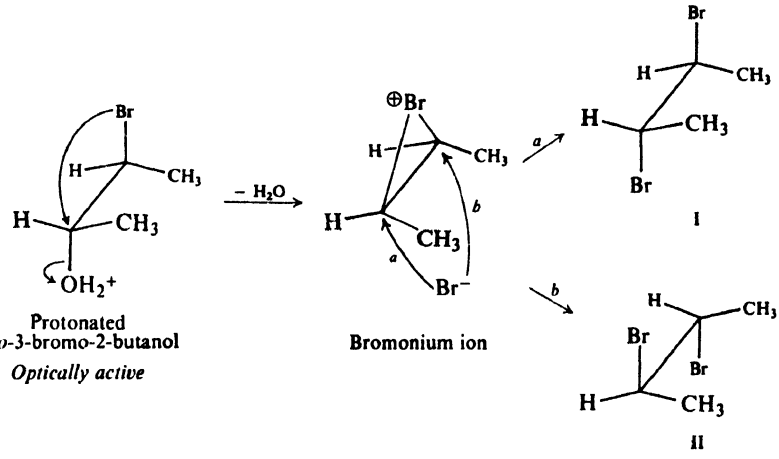


Figure 28.5. Conversion of optically active *threo*-3-bromo-2-butanol into racemic 2,3-dibromobutane via cyclic bromonium ion. Opposite-side attacks *a* and *b* equally likely, give enantiomers in equal amounts.

that is, single-step processes with attachment of the nucleophile and loss of the leaving group taking place in the same transition state. This is consistent with the complete stereospecificity: an open carbonium ion in either (1) or (2) might be expected to result in the formation of a mixture of diastereomers. (As we shall see, there is additional evidence indicating that a neighboring bromine is likely to provide assistance in step (1).)

The basic process is, we see, the same as in rearrangements: intramolecular (1,2) nucleophilic attack. Indeed, there *is* rearrangement here; in half the molecules formed, the bromine has migrated from one carbon to the next.

Problem 28.13 Drawing structures like those in Fig. 28.5, show the stereochemical course of reaction of optically active *erythro*-3-bromo-2-butanol with hydrogen bromide.

Problem 28.14 Actually, the door opened by Winstein and Lucas (Sec. 28.10) was already ajar. In 1937, E. D. Hughes, Ingold (p. 460), and their co-workers reported that, in contrast to the neutral acid or its ester, sodium α-bromopropionate undergoes hydrolysis with *retention* of configuration.

$$\underset{\text{Sodium α-bromopropionate}}{CH_3CHBrCOO^-Na^+} \xrightarrow[H_2O]{OH^-} \underset{\text{Sodium lactate}}{CH_3CHOHCOO^-Na^+}$$

Give a likely interpretation of these findings.

28.11 Neighboring group effects: rate of reaction. Anchimeric assistance

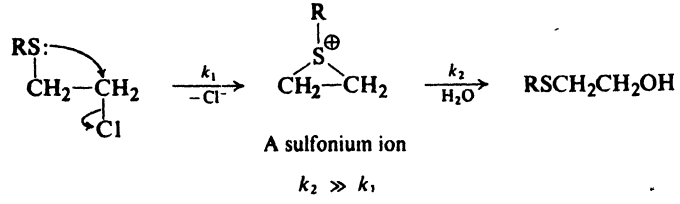
Like other alkyl halides, mustard gas (β,β′-dichlorodiethyl sulfide) undergoes hydrolysis. But this hydrolysis is unusual in several ways: (a) the kinetics is first-

order, with the rate independent of added base; and (b) it is *enormously* faster than hydrolysis of ordinary primary alkyl chlorides.

$$ClCH_2CH_2—S—CH_2CH_2Cl \xrightarrow{H_2O} ClCH_2CH_2—S—CH_2CH_2OH$$

We have encountered this kind of kinetics before in S_N1 reactions and know, in a general way, what it must mean: in the rate-determining step, the substrate is reacting unimolecularly to form an intermediate, which then reacts rapidly with solvent or other nucleophile. But what is this intermediate? It can hardly be the carbonium ion. A primary cation is highly unstable and hard to form, so that primary alkyl chlorides ordinarily react by S_N2 reactions instead; and here we have electron-withdrawing sulfur further to destabilize a carbonium ion.

This is another example of a neighboring group effect, one that shows itself not in stereochemistry but in *rate of reaction*. Sulfur helps to push out chloride ion, forming a cyclic *sulfonium ion* in the process. As fast as it is formed, this intermediate reacts with water to yield the product.



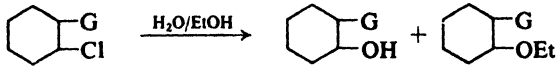
A sulfonium ion

$k_2 \gg k_1$

Reaction thus involves formation of a cation, but not a highly unstable carbonium ion with its electron-deficient carbon; instead, it is a cation in which every atom has an octet of electrons. Open-chain sulfonium ions, R_3S^+, are well-known, stable molecules; here, because of angle strain, the sulfonium ion is less stable and highly reactive—but still enormously more stable and easier to form than a carbonium ion.

The first, rate-determining step is unimolecular, but it is S_N2-like. As with other primary halides, a nucleophile is needed to help push out the leaving group. Here the nucleophile happens to be part of the same molecule. Sulfur has unshared electrons it is willing to share, and hence is highly nucleophilic. Most important, *it is there*: poised in just the right position for attack. The result is an enormous increase in rate.

There is much additional evidence to support the postulate that the effect of neighboring sulfur is due to anchimeric assistance. Cyclohexyl chloride undergoes solvolysis in ethanol-water to yield a mixture of alcohol and ether. As usual for secondary alkyl substrates, reaction is S_N1 with nucleophilic assistance from the solvent (see Sec. 14.17). A C_6H_5S— group on the adjacent carbon can speed



Relative rates of reaction

G:	*trans*-C_6H_5S	»	H	>	*cis*-C_6H_5S
	70,000		1.00		0.16

up reaction powerfully—*but only if it is trans to chlorine.* The *cis* substituted chloride actually reacts more slowly than the unsubstituted compound.

The *trans* sulfide group evidently gives strong anchimeric assistance. Why cannot the *cis* sulfide? The answer is found in the examination of molecular models. Like other nucleophiles, a neighboring group attacks carbon at the side away from the leaving group. In an open-chain compound like mustard gas—or like either diastereomer of 3-bromo-2-butanol—rotation about a carbon–carbon bond can bring the neighboring group into the proper position for back-side attack: *anti* to the leaving group (Fig. 28.6*a*). But in cyclohexane derivatives, 1,2-substituents are *anti* to each other only when they both occupy axial positions—possible only for *trans* substituents (Fig. 28.6*b*). Hence, only the *trans* chloride shows the

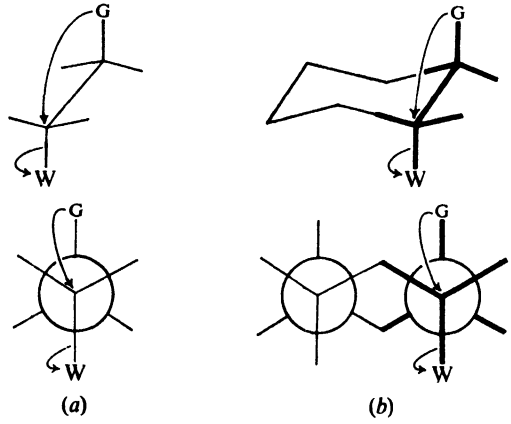


Figure 28.6. Anchimeric assistance. (*a*) *Anti* relationship between neighboring group and leaving group required for back-side attack. (*b*) In cyclohexane derivatives, only *trans*-1,2-substituents can assume *anti* relationship.

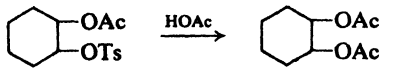
neighboring group effect, anchimeric assistance from sulfur. The *cis* isomer reacts without anchimeric assistance; through its electron-withdrawing inductive effect, sulfur slows down formation of the carbonium ion, and thus the rate of reaction.

Let us look at another example of solvolysis. A very commonly studied system is one in which the solvent is acetic acid (HOAc) and the substrates are alkyl esters of sulfonic acids: ROTs, alkyl tosylates (alkyl *p*-toluenesulfonates); ROBs, alkyl

$$\underset{\text{Alkyl tosylate}}{\text{R—OTs}} \xrightarrow[\text{NaOAc}]{\text{HOAc}} \underset{\text{Alkyl acetate}}{\text{R—OAc}}$$

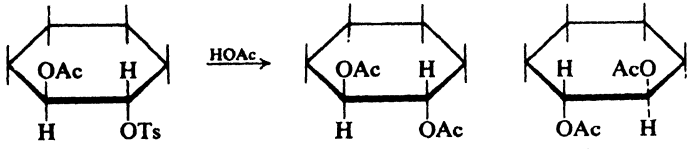
brosylates (alkyl *p*-bromobenzenesulfonates); etc. Loss of the weakly basic sulfonate anion, with more or less nucleophilic assistance from the solvent, generates a cation—as part of an ion pair—which combines with the solvent to yield the acetate.

When 2-acetoxycyclohexyl tosylate is heated in acetic acid there is obtained, as expected, the diacetate of 1,2-cyclohexanediol. The reactant exists as diastereomers, and just what happens—and how fast it happens—depends upon which



2-Acetoxycyclohexyl tosylate — 1,2-Cyclohexanediol diacetate

diastereomer we start with. The *cis* tosylate yields chiefly the *trans* diacetate. Reaction takes the usual course for nucleophilic substitution, predominant inversion. But the *trans* tosylate also yields *trans* diacetate. Here, apparently, reaction takes place with *retention*, unusual for nucleophilic substitution, and in contrast to what is observed for the *cis* isomer. Two pieces of evidence show us clearly



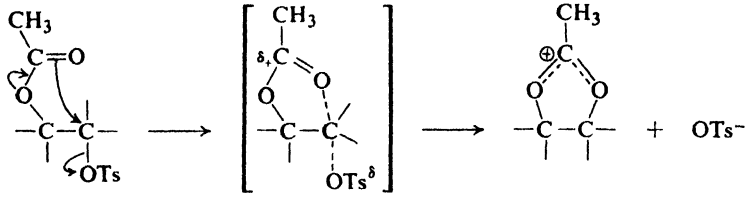
(+)-*trans*-2-Acetoxycyclohexyl tosylate — *Optically active*

trans-1,2-Cyclohexanediol diacetate — *Racemic*

what is happening here: (a) optically active *trans* tosylate yields *optically inactive trans* diacetate; and (b) the *trans* tosylate reacts *800 times as fast as the cis isomer.*

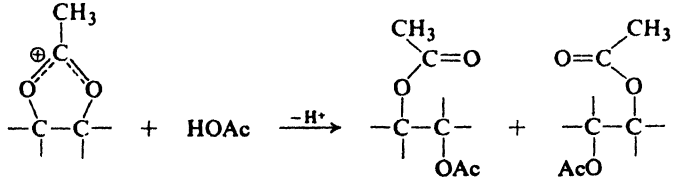
The apparent retention of configuration in the reaction of the *trans* tosylate is a neighboring group effect. The neighboring group is acetoxy, containing oxygen with unshared electrons. Through back-side nucleophilic attack, acetoxy helps to push out the tosylate anion (1) and, in doing this, inverts the configuration at the

(1)



An acetoxonium ion

(2)



carbon under attack. There is formed an *acetoxonium ion.* This symmetrical intermediate undergoes nucleophilic attack (2) by the solvent at either of two carbons—

again with inversion—and yields the product. The result: in half the molecules, retention at both carbons; in the other half, inversion at both carbons.

The *cis* tosylate cannot assume the diaxial conformation needed for back-side attack by acetoxy, and there is no neighboring group effect. Stereochemistry is normal, and reaction is much slower than for the *trans* tosylate.

Compared with unsubstituted cyclohexyl tosylate, the 2-acetoxycyclohexyl tosylates show the following relative reactivities toward acetolysis:

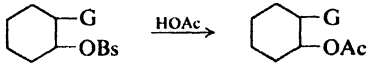
Cyclohexyl tosylate	>	*trans*-2-Acetoxycyclohexyl tosylate	>	*cis*-2-Acetoxycyclohexyl tosylate
1.00		0.30		0.00045

Reaction of the *cis* tosylate is much slower than that of cyclohexyl tosylate, and this we can readily understand: powerful electron-withdrawal by acetoxy slows down formation of the carbonium ion in the S_N1 process. Reaction of the *trans* tosylate, although much faster than that of its diastereomer, is still somewhat slower than that of cyclohexyl tosylate. But should not the anchimerically assisted reaction be much *faster* than the unassisted reaction of the unsubstituted tosylate? The answer is, *not necessarily*. We must not forget the electronic effect of the acetoxy substituent. Although S_N2-like, attack by acetoxy has considerable S_N1 character (see Sec. 17.15); deactivation by electron withdrawal tends to offset activation by anchimeric assistance. The *cis* tosylate is electronically similar to the *trans*, and is a much better standard by which to measure anchimeric assistance. (This point will be discussed further in the next section.)

In Sec. 17.15 we said that the orientation of opening of strained rings like halonium ions and protonated epoxides indicates considerable S_N1 character in the transition state. But if ring-*opening* has S_N1 character so, according to the principle of microscopic reversibility, must ring-*closing*.

Problem 28.15 Of what structures is the acetoxonium ion a hybrid? To what does it owe its stability, relative to a carbonium ion?

Problem 28.16 How do you account for the following relative rates of acetolysis of 2-substituted cyclohexyl brosylates? In which cases is there evidence of a neighboring group effect?



Relative rates

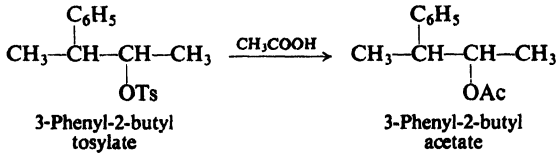
G	*cis*	*trans*
Cl	1.6	5.9
Br	1.5	1250
I		2.2×10^8
H		1.2×10^4

28.12 Neighboring group effects. Neighboring aryl

In 1949, at the University of California at Los Angeles, Donald J. Cram published the first of a series of papers on the effects of neighboring aryl groups, and

set off a controversy that only recently, after twenty years, shows signs of being resolved. Let us look at just one example of the kind of thing he discovered.

Solvolysis of 3-phenyl-2-butyl tosylate in acetic acid yields the acetate. The tosylate contains two chiral centers, and exists as two racemic modifications; so,



3-Phenyl-2-butyl tosylate — 3-Phenyl-2-butyl acetate

too, does the acetate. Solvolysis is completely stereospecific and proceeds, it at first appears, with *retention* of configuration: racemic *erythro* tosylate gives only racemic *erythro* acetate, and racemic *threo* tosylate gives only racemic *threo* acetate (Fig. 28.7). When, however, optically active *threo* tosylate is used, it is found to yield

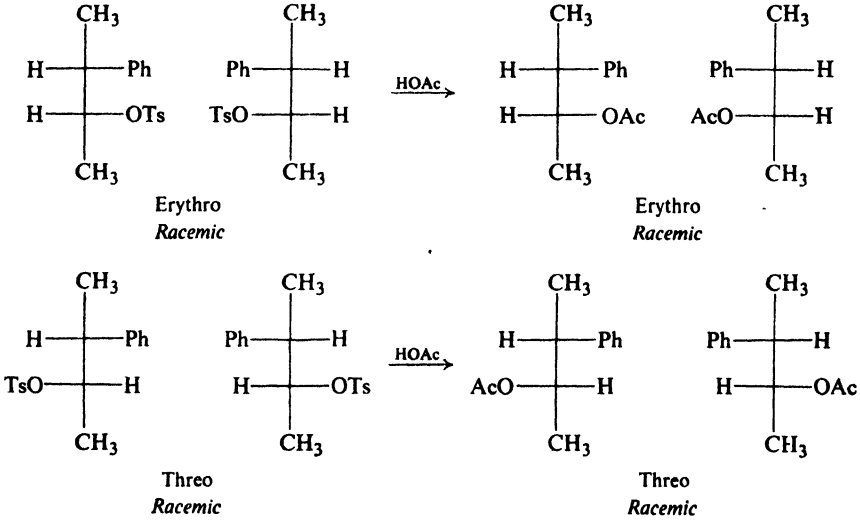
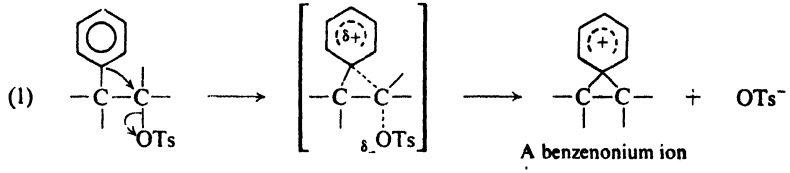


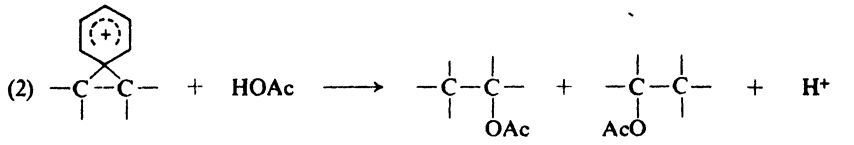
Figure 28.7. Acetolysis of racemic 3-phenyl-2-butyl tosylates.

optically *inactive* product, racemic *threo* acetate. We see here the same pattern as in Sec. 28.10: retention at both carbons in half the molecules of the product, inversion at both carbons in the other half (Fig. 28.8).

Cram interpreted these results in the following way. The neighboring phenyl group, with its π electrons, helps to push out (1) the tosylate anion. There is formed



A benzenonium ion



an intermediate *bridged* ion—a benzenonium ion. This undergoes nucleophilic attack (2) by acetic acid at either of the two equivalent carbons to yield the product.

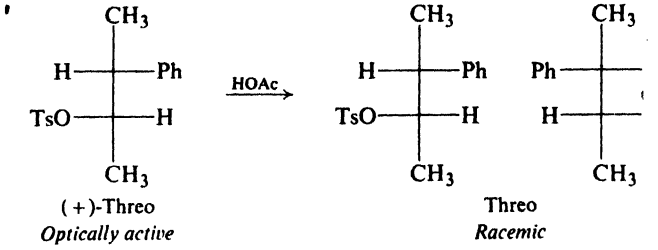


Figure 28.8. Acetolysis of optically active *threo*-3-phenyl-2-butyl tosylate.

Problem 28.17 (a) Drawing structures of the kind in Fig. 28.5 (p. 907), show how Cram's mechanism accounts for the conversion of optically active *threo*-3-phenyl-2-butyl tosylate into racemic acetate. (b) In contrast, optically active *erythro* tosylate yields optically *active erythro* acetate. Show that this, too, fits Cram's interpretation of the reaction.

In the controversy that developed, the point under attack was not so much the existence of the intermediate bridged ion—although this was questioned, too—as its mode of formation. The 3-phenyl-2-butyl tosylates undergo solvolysis at much the same rate as does unsubstituted *sec*-butyl tosylate: formolysis a little faster, acetolysis a little slower. Yet, as depicted by Cram, phenyl gives anchimeric assistance to the reaction. Why, then, is there no rate acceleration?

Several alternatives were proposed: one, that participation by phenyl in expulsion of tosylate occurs, but is weak; another, that bridging occurs, not in the rate-determining step, but rapidly, following formation of an open cation. H. C. Brown (p. 507) suggested that—for unsubstituted phenyl, at least—the intermediate is not a bridged ion at all, but a pair of rapidly equilibrating open carbonium ions; phenyl, now on one carbon and now on the other, blocks back-side attack by the solvent and thus gives rise to the observed stereochemistry.

By 1971, a generally accepted picture of these reactions had begun to emerge, based on work by a number of investigators, prominent among them Paul Schleyer at Princeton University. The big stumbling-block had been the widely held idea that secondary cations are formed, like tertiary cations, with little assistance from the solvent (Sec. 14.17). Using as standards certain special secondary substrates whose structure *prevents* solvent assistance, Schleyer showed that ordinary secondary substrates do indeed react with much solvent assistance.

Cram's original proposal seems to be essentially correct: aryl *can* give anchimeric assistance through formation of bridged ions. Competition is *not* between

aryl-assisted solvolysis and unassisted solvolysis; competition is between aryl-assisted solvolysis and solvent-assisted solvolysis. Anchimeric assistance need not cause anchimeric acceleration. Formation of a bridged cation and an open cation may proceed at much the same rate, one with aryl assistance, the other with equally strong solvent assistance.

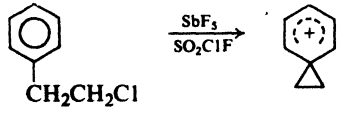
On the assumption of these two competing processes, successful quantitative correlations have been made among data of various kinds: rate of reaction, stereochemistry, scrambling of isotopic labels, and Hammett constants (Sec. 18.11) to represent the relative electronic effects of various substituents in aromatic rings. If neighboring aryl contains strongly electron-withdrawing substituents, reaction products are normal—chiefly alkenes plus inverted ester—and the rate of solvolysis is what one would expect for formation of an open cation slowed down by electron-withdrawing inductive effects. As substituents become increasingly electron-releasing (*p*-Cl, *m*-CH_3, *p*-CH_3, *p*-CH_3O) the rate increases *more* than expected if only inductive effects were operating; the amount of "extra" speed matches the amount of abnormal stereochemistry. Consider, for example, acetolysis of 3-aryl-2-butyl brosylates. One calculates from the rate data that *m*-tolyl assists in 73% of reaction; 68% of the product is found to have retained configuration. For *p*-methyl, calculated 87%, found 88%; for *p*-methoxyphenyl, calculated 99%, found 100%.

How much anchimeric assistance there is, then, depends on how nucleophilic the neighboring group is. It also depends on how badly anchimeric assistance is *needed.* The more nucleophilic the solvent, the more assistance *it* gives, and the less the neighboring group participates. Or, if the open cation is a relatively stable one—tertiary or benzylic—it may need little assistance of any kind, either from the solvent or from the neighboring group.

In summary, an incipient cation can get electrons in three different ways: (a) from a substituent, through an inductive effect or resonance; (b) from the solvent; (c) from a neighboring group.

In all this, H. C. Brown played a role familiar to him: that of gad-fly—the organic chemist's conscience—forcing careful examination of ideas that had been accepted perhaps too readily because of their neatness. The turning point in this part of the great debate was marked by the joint publication of a paper by Brown and Schleyer setting forth essentially the interpretation we have just given.

In 1970, Olah (p. 160) prepared a molecule whose carbon-13 nmr spectrum (cmr) was consistent with a bridged benzenonium ion, and *not* with a pair of equilibrating open cations.

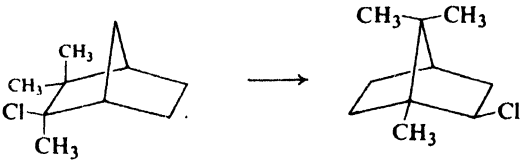


β-Phenylethyl chloride — Bridged benzenonium ion

Problem 28.18 Quenching of Olah's solution with water gave a 3:1 mixture of β-phenylethyl alcohol and α-phenylethyl alcohol. The spectrum showed the presence not only of the bridged cation but, in lesser amounts, of an open cation. What is a likely structure for the open cation, and how is it formed?

28.13 Neighboring group effects: nonclassical ions

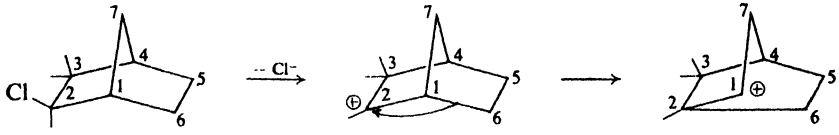
The rearrangement of carbonium ions was first postulated, by Meerwein (p. 160) in 1922, to account for the conversion of camphene hydrochloride into isobornyl chloride. Oddly enough, this chemical landmark is the most poorly



Camphene hydrochloride Isobornyl chloride

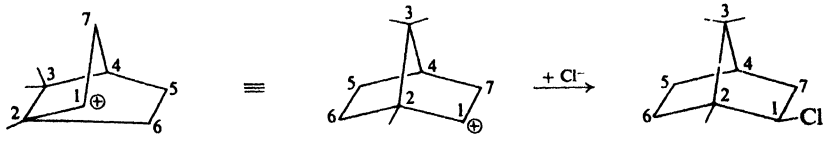
understood of all such rearrangements. With various modifications in structure, this bicyclic system has been for over 20 years the object of closer scrutiny than any other in organic chemistry.

We can see, in a general way, how this particular rearrangement could take place. Camphene hydrochloride loses chloride ion to form cation I, which rearranges by a 1,2-alkyl shift to form cation II. Using models, and keeping careful



Camphene hydrochloride I II

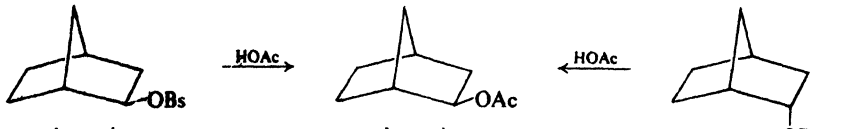
track of the various carbon atoms, we find that cation II need only combine with a chloride ion to yield isobornyl chloride.



II II Isobornyl chloride

We have accounted for the observed change in carbon skeleton, but we have not answered two questions that have plagued the organic chemist for a generation. Why is only the *exo* chloride, isobornyl chloride, obtained, and none of its *endo* isomer, bornyl chloride? Why does camphene hydrochloride undergo solvolysis thousands of times as fast as, say, *tert*-butyl chloride? To see the kind of answers that have been given, let us turn to a simpler but basically similar system.

In 1949 Winstein reported these findings. On acetolysis, the diastereomeric *exo*- and *endo*-norbornyl brosylates both yield *exo*-norbornyl acetate:



and enantiomer — and enantiomer — and enantiomer

exo-Norbornyl brosylate — *exo*-Norbornyl acetate — *endo*-Norbornyl brosylate

If the starting brosylate is optically active the product is still the optically inactive racemic modification. For example:

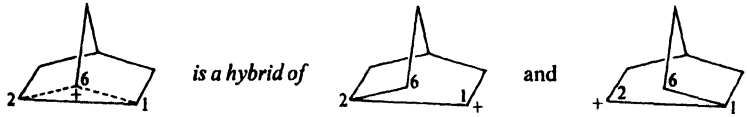
exo-Norbornyl brosylate — *exo*-Norbornyl acetate

Optically active — *Racemic*

Finally, *exo*-norbornyl brosylate reacts 350 times as fast as the *endo* brosylate.

Winstein interpreted the behavior of these compounds in the following way (Fig. 28.9). Loss of brosylate anion yields (1) the bridged cation III, which undergoes nucleophilic attack by solvent (2) at either C–2 or C–1 to yield the product.

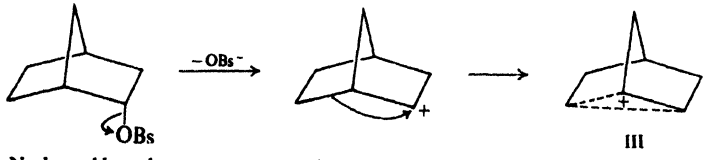
Cation III is stabilized by resonance between two equivalent structures, IV



III — IV — V

and V, each corresponding to an open cation. The charge is divided between two carbons (C–1 and C–2) each of which—held in the proper position by the particular ring system—is bonded to C–6 by a half-bond. The bridging carbon (C–6) is thus pentavalent.

Reaction of the *exo* brosylate is S_N2-like, as shown in Fig. 28.9: back-side attack by C–6 on C–1 helps to push out brosylate, and yields the bridged ion in a single step. The geometry of the *endo* brosylate does not permit such back-side attack, and consequently it undergoes an S_N1-like reaction: slow formation of the open cation followed by rapid conversion into the bridged ion.



endo-Norbornyl brosylate — Open cation — III Bridged cation

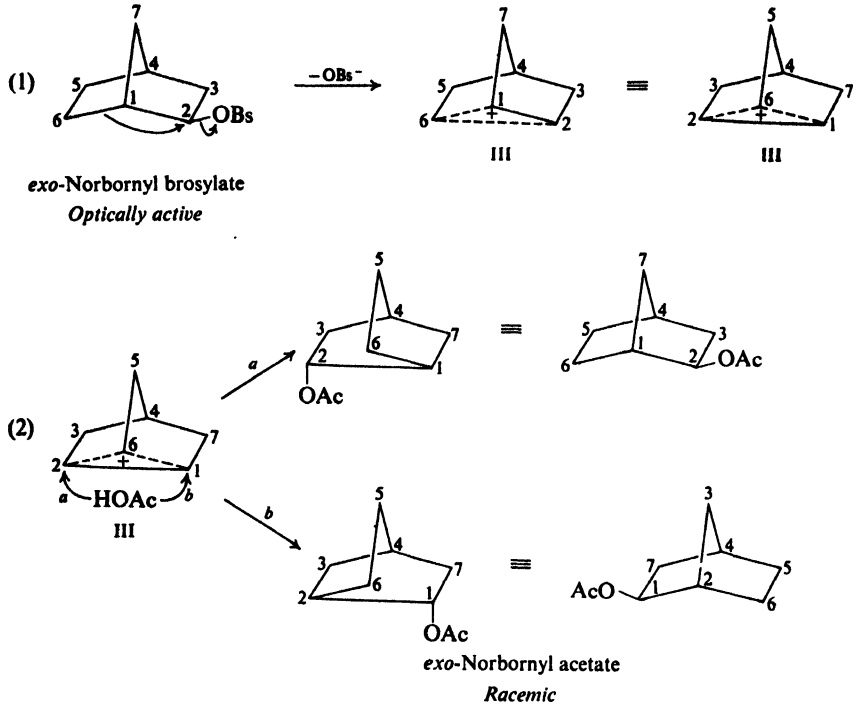
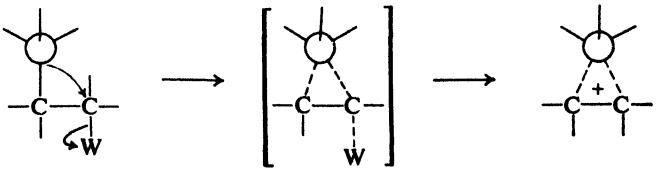


Figure 28.9. Conversion of optically active *exo*-norbornyl brosylate into racemic *exo*-norbornyl acetate via nonclassical ion. Brosylate anion is lost with anchimeric assistance from C–6, to give bridged cation III. Cation III undergoes back-side attack at either C–2 (path *a*) or C–1 (path *b*). Attacks *a* and *b* are equally likely, and give racemic product.

The two diastereomers yield the same product, racemic *exo* acetate, because they react via the same intermediate. But only the *exo* brosylate reacts with anchimeric assistance, and hence it reacts at the faster rate.

What Winstein was proposing was that *saturated* carbon using σ electrons could act as a neighboring group, to give anchimeric assistance to the expulsion of a leaving group, and to form an intermediate bridged cation containing pentavalent carbon. Bridged ions of this kind, with delocalized bonding σ electrons, have become known as ***nonclassical ions.***



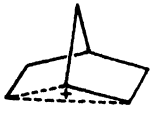
A nonclassical bridged ion

Interpretation of the behavior of the norbornyl and many related systems on the basis of nonclassical ions seemed to be generally accepted until 1962, when H. C. Brown declared, "But the Emperor is naked!" Brown's point was not that the idea of nonclassical ions was necessarily wrong, but that it was *not necessarily right*. It had been accepted too readily, he thought, on the basis of too little evidence, and needed closer examination.

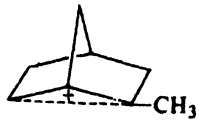
Brown suggested alternative interpretations. The norbornyl cation, for example, might not be a bridged ion but a pair of equilibrating open carbonium ions. That is to say, IV and V are not contributing structures to a resonance hybrid, but two distinct compounds in equilibrium with each other. Each ion can combine with solvent: IV at C-1, V at C-2. Substitution is exclusively *exo* because the *endo* face of each cation lies in a fold of the molecule, and is screened from attack. Differences in rate, too, are attributed to steric factors. It is not that the *exo* substrate reacts unusually fast, but that the *endo* substrate reacts unusually *slowly*, due to steric hindrance to the departure of the leaving group with its cluster of solvent molecules.

To test these alternative hypotheses, a tremendous amount of work has been done, by Brown and by others. For example, camphene hydrochloride is known to undergo ethanolysis 6000 times as fast as *tert*-butyl chloride, and this had been attributed to anchimeric assistance with formation of a bridged ion. Brown pointed out that the wrong standard for comparison had been chosen. He showed that a number of substituted (3°) cyclopentyl chlorides (examine the structure of camphene hydrochloride closely) *also* react much faster than *tert*-butyl chloride. He attributed these fast reactions—including that of camphene hydrochloride—to *relief of steric strain*. On ionization, chloride ion is lost and the methyl group on the sp^2-hybridized carbon moves into the plane of the ring: four non-bonded interactions thus disappear, two for chlorine and two for methyl. For certain systems at least, it became clear that one need not invoke a nonclassical ion to account for the facts.

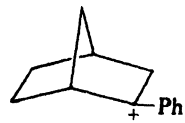
In 1970, Olah reported that he had prepared a stable norbornyl cation in SbF_5–SO_2. From its pmr, cmr, and Raman spectra, he concluded that it has, indeed, the nonclassical structure with delocalization of σ electrons. The 2-phenylnorbornyl cation, on the other hand, has the classical structure; this benzylic



Norbornyl cation
Bridged ion



2-Methylnorbornyl cation
Some bridging



2-Phenylnorbornyl cation
Open ion

cation, stabilized by electrons from the benzene ring, has no need of bridging. The tertiary 2-methylnorbornyl cation is intermediate in character: there is *partial* σ delocalization and hence bridging, but weaker than in the unsubstituted cation. (Interestingly enough, delocalization in the 2-methyl cation seems to come, not from the C_6—C_7 bond, but from the C_6—H bond; Olah pictures the back lobe of the carbon-hydrogen bond overlapping the *p* orbital of C_2.)

Thus, it seems, there *are* such things as nonclassical cations. What is still to be settled is just how much they are involved in the chemistry of ordinary solvolytic reactions.

Problem 28.19 (a) Show how a nonclassical ion intermediate could account for both the stereospecificity and the unusually fast rate (if it *is* unusually fast) of rearrangement of camphene hydrochloride into isobornyl chloride. (b) How do you account for the fact that optically active product is formed here, in contrast to what is obtained from solvolysis of norbornyl compounds?

PROBLEMS

1. Give detailed interpretation of each of the following observations.

(a) $CH_3CH_2CH_2CD_2NH_2 \xrightarrow[H_2O]{HONO}$ 1-butanol + 2-butanol

The 2-butanol is $CH_3CH_2CHOHCHD_2$ (*76.8%*) + $CH_3CHOHCH_2CHD_2$ (*23.2%*)

(b) $CH_3CH_2CD_2CH_2NH_2 \xrightarrow[H_2O]{HONO}$ $CH_3CH_2CD_2CH_2OH$ (*68%*) + $CH_3CH_2CDOHCH_2D$ (*23.9%*)

+ $CH_3CHOHCHDCH_2D$ (*7.7%*) + ($CH_3CHDCHOHCH_2D$ + $CH_3CDOHCH_2CH_2D$) (*0.4%*)

2. Treatment of 1-methyl-1-cyclohexyl hydroperoxide with acid gives a product of formula $C_7H_{14}O_2$, which gives positive tests with CrO_3/H_2SO_4, 2,4-dinitrophenylhydrazine, and NaOI. What is a likely structure for this compound, and how is it formed?

3. (a) Describe simple chemical tests that would serve to distinguish among the possible products of rearrangement of 1-phenyl-1,2-propanediol shown on page 897. Tell exactly what you would do and see. (b) Alternatively, you could use the nmr spectrum. Tell exactly what you would expect to see in the spectrum of each possible product.

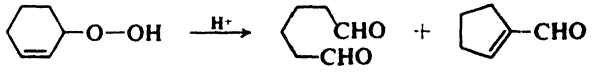
4. In the presence of base, acyl derivatives of hydroxamic acids undergo the **Lossen rearrangement** to yield isocyanates or amines.

$$R{-}\overset{O}{\overset{\|}{C}}{-}\underset{H}{N}{-}O{-}\overset{O}{\overset{\|}{C}}{-}R' \xrightarrow{base} RNCO \xrightarrow{H_2O} RNH_2$$

(a) Write a detailed mechanism for the rearrangement.

(b) Study of a series of compounds in which R and R′ were *m*- and *p*-substituted phenyl groups showed that reaction is speeded up by electron-releasing substituents in R and by electron-withdrawing substituents in R′. How do you account for these effects?

5. (a) Show all steps in the mechanisms probably involved in the following transformation. (*Hint:* Don't forget Sec. 21.5.)



3-Hydroperoxycyclohexene — Adipaldehyde (*6%*) + Cyclopentene-1-carboxaldehyde (*39%*)

(b) An important difference in migratory aptitude is illustrated here. What is it?

6. Benzophenone oxime, $C_{13}H_{11}ON$, m.p. 141°, like other oximes, is soluble in aqueous NaOH and gives a color with ferric chloride. When heated with acids it is transformed into a solid A, $C_{13}H_{11}ON$, m.p. 163°, which is insoluble in aqueous NaOH and in aqueous HCl.

After prolonged heating of A with aqueous NaOH, a liquid B separates and is collected by steam distillation. Acidification of the aqueous residue causes precipitation of a white solid C, m.p. 120–1°.

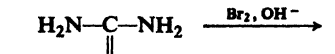
Compound B, b.p. 184°, is soluble in dilute HCl. When this acidic solution is chilled and then treated successively with $NaNO_2$ and β-naphthol, a red solid is formed. B reacts with acetic anhydride to give a compound that melts at 112.5–114°.

(a) What is the structure of A? (b) The transformation of benzophenone oxime into A illustrates a reaction to which the name **Beckmann** is attached. To what general class of reactions must this transformation belong? (c) Suggest a likely series of steps, each one basically familiar, for this transformation? (*Hint:* See Secs. 16.5, 6.10, and 8.13.)

(d) Besides acids like sulfuric, other compounds "catalyze" this reaction. How might PCl_5 do the job? Tosyl chloride?

(e) What product or products corresponding to A would you expect from a similar transformation of acetone oxime; of acetophenone oxime; of *p*-nitrobenzophenone oxime; of methyl *n*-propyl ketoxime? (f) How would you go about identifying each of the products in (e)?

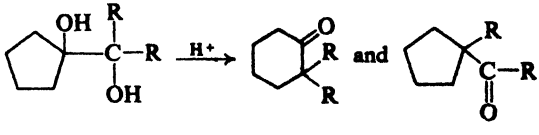
7. Urea is converted by hypohalites into nitrogen and carbonate. Given the fact



that hydrazine, $H_2N{-}NH_2$, is oxidized to nitrogen by hypohalite, show that this reaction of urea is simply an example of the Hofmann degradation of amides.

8. Treatment of triarylcarbinols, Ar_3COH, with acidic hydrogen peroxide yields a 50:50 mixture of ketone, ArCOAr, and phenol, ArOH. (a) Show all steps in a likely mechanism for this reaction. (b) Predict the major products obtained from *p*-methoxytriphenylcarbinol, $p\text{-}CH_3OC_6H_4(C_6H_5)_2COH$. From *p*-chlorotriphenylcarbinol.

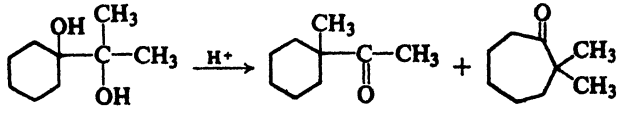
9. (a) Upon treatment with acid I (R = C_2H_5) yields II and III. Show all steps in these transformations.



I II III

(b) Account for the fact that when R = C_6H_5, I yields only II.

(c) Show the most likely steps in the following transformation:



(d) Predict the products of the pinacol rearrangement of 2,3-diphenyl-2,3-butanediol; of 3-phenyl-1,2-propanediol. Describe a simple chemical test that would show whether your prediction was correct or incorrect.

10. When dissolved in HSO_3F–SbF_5–SO_2, the glycol 1,3-propanediol is rapidly converted into propionaldehyde. Write all steps in a likely mechanism for this reaction.

11. In the oxidation stage of hydroboration-oxidation, alkylboranes are converted into alkyl borates, which are hydrolyzed to alcohols. It has been suggested that the formation of the borates involves the reagent HOO^-.

$$H_2O_2 + OH^- \overset{(1)}{\rightleftharpoons} HOO^- + H_2O$$

$$\underset{\text{Trialkylborane}}{R_3B} + 3HOO^- \xrightarrow{(2)} \underset{\text{Alkyl borate}}{(RO)_3B} \xrightarrow{(3)} 3ROH$$

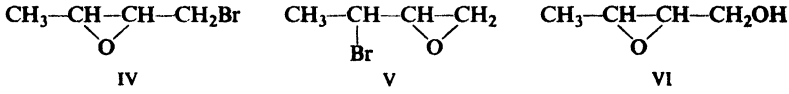
(a) Show all steps in a possible mechanism for step (2), the formation of the borate.

(b) What did you conclude (Problem 15.10, p. 507) was the likely stereochemistry of the oxidation stage of hydroboration-oxidation? Is your mechanism in (a) consistent with this stereochemistry?

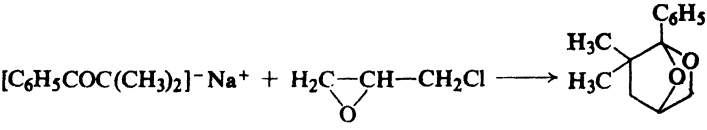
12. Account in detail for each of the following sets of observations:

(a) On treatment with aqueous HBr, both *cis*- and *trans*-2-bromocyclohexanol are converted into *trans*-1,2-dibromocyclohexane.

(b) Treatment of *either* epoxide IV *or* epoxide V with aqueous OH^- gives the same product VI.



IV V VI

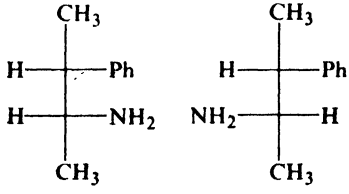
(c) 

(d) The relative rates of formolysis of *p*-$GC_6H_4CH_2CH_2OTs$ for various G's are: H 2.1, OCH_3 160, O^- 10^8.

(e) $CH_3CHClCH_2NEt_2 \xrightarrow{OH^-} CH_3CH(NEt_2)CH_2OH$

(f) *Either* $CH_3CHOHCH_2SEt$ *or* $CH_3CH(SEt)CH_2OH \xrightarrow{HCl} CH_3CHClCH_2SEt$

13. (a) In acetic acid solution nitrous acid converts 3-phenyl-2-butylamine into a mixture of acetates. Examination of these products shows that in the reaction of the



(+)-Erythro (+)-Threo

3-Phenyl-2-butylamine

(+)-*erythro* amine phenyl migration exceeds methyl migration 8:1, whereas in the reaction of the (+)-*threo* amine methyl migration exceeds phenyl migration 1.5:1. Suggest a likely explanation.

(b) In contrast, solvolysis of the corresponding tosylates (Sec. 28.12) gives acetates indicating *no* methyl migration for either diastereomer. How do you account for this difference between the two systems?

14. Spectroscopic and thin layer chromatographic analysis has shown that, even when not found in the final product, epoxides are present during the reaction of such pinacols as 1,1,2,2-tetraphenyl-1,2-ethanediol. It seems most likely that epoxides represent a blind alley down which many molecules stray before pinacolone is finally formed. (a) How are these epoxides probably formed? (b) What probably happens to them in the reaction medium?

15. Labeled $ArCH_2{}^{14}CH_2NH_2$ was treated with HONO, and the $ArCH_2CH_2OH$ obtained was oxidized to ArCOOH. The fraction of the original radioactivity found in the ArCOOH depended on the nature of Ar: *p*-$NO_2C_6H_4$ 8%, C_6H_5 27%, *p*-$CH_3OC_6H_4$ 45%. How do you account for these findings?

16. Collins (p. 899) prepared 1,1,2-triphenylethyl acetate triply labeled with ^{14}C (indicated as C*) and studied reactions (1)–(3) in ordinary acetic acid. The equilibrium

(1) $Ph_2CH{-}\underset{\displaystyle OAc}{\underset{|}{C^*HPh}} \xrightarrow{HOAc} Ph_2CH{-}\underset{\displaystyle OAc}{\underset{|}{C^*HPh}} + Ph_2C^*H{-}\underset{\displaystyle OAc}{\underset{|}{CHPh}}$ (50% / 50%)

(2) $Ph_2CH{-}\underset{\displaystyle OAc}{\underset{|}{CHPh^*}} \xrightarrow{HOAc} Ph_2CH{-}\underset{\displaystyle OAc}{\underset{|}{CHPh^*}} + Ph^*PhCH{-}\underset{\displaystyle OAc}{\underset{|}{CHPh}}$ (33% / 67%)

(3) $Ph_2CH{-}\underset{\displaystyle OAc^*}{\underset{|}{CHPh}} \xrightarrow{HOAc} Ph_2CH{-}\underset{\displaystyle OAc}{\underset{|}{CHPh}}$

product of (1) and (2) had the indicated distribution of labels. The rate of acetate exchange (3) was found to be *identical* with the rates of (1) and (2).

Collins concluded that bridged ions are *not* involved in this particular system.

(a) Explain in detail how his conclusion is justified. Show just what probably *does* happen. (Among other things: what results would be expected if a bridged ion *were* involved?)

(b) Why might this system be expected to differ from, say, the 3-phenyl-2-butyl one?

17. Account in detail for each of the following sets of observations.

(a) Compound VII reacts with acetic acid 1200 times as fast as does ethyl tosylate,

$\underset{\text{VII}}{(CH_3)_2C{=}CHCH_2CH_2OTs} \xrightarrow{HOAc}$

$\underset{\text{VIII}}{(CH_3)_2C{=}CHCH_2CH_2OAc} +$  $CHC(CH_3){=}CH_2$

IX

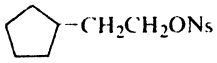
and yields not only VIII but also IX. When the labeled compound VIIa is used, product VIII consists of equal amounts of VIIIa and VIIIb.

$\underset{\text{VIIa}}{(CH_3)_2C{=}CHCH_2CD_2OTs}$ $\underset{\text{VIIIa}}{(CH_3)_2C{=}CHCH_2CD_2OAc}$

$\underset{\text{VIIIb}}{(CH_3)_2C{=}CHCD_2CH_2OAc}$

(b) The cyclopentene derivative X (ONs = *p*-nitrobenzenesulfonate) undergoes solvolysis in acetic acid 95 times as fast as the analogous saturated compound (XI), and gives *exo*-norbornyl acetate (XII).

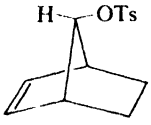
X



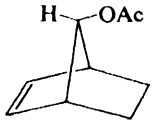
XI

XII

(c) *anti*-7-Norbornylene tosylate (XIII) reacts with acetic acid 10^{11} times as fast



XIII



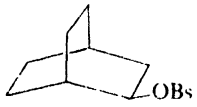
XIV

XV

XVI

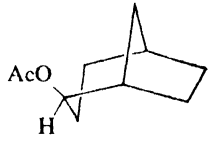
as the saturated analog, and yields *anti*-7-norbornylene acetate (XIV) with *retention* of configuration. Solvolysis of XIII in the presence of $NaBH_4$ gives XV and XVI.

18. (a) We saw (Sec. 28.13) that optically active *exo*-norbornyl brosylate reacts with acetic acid to give optically inactive *exo*-norbornyl acetate. The related brosylate XVII similarly reacts to give XVIII; yet in this case optically active brosylate yields optically

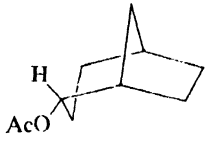


XVII

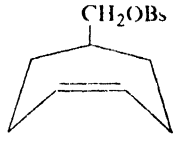
XVIII



XIX



XX



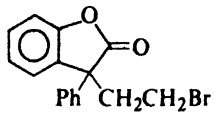
XXI

active acetate. Oddly enough, the complete racemization in the norbornyl reaction and the complete retention here are taken as evidence of the same fundamental behavior. On what common basis can you account for all of the above observations? (*Hint:* See also part (b).)

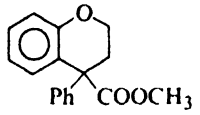
(b) Brosylate XVII also yields XIX, but no XX. When XVII is optically active, so is the XIX that is obtained. How do these facts fit into your answer to (a)?

(c) Brosylate XXI reacts with acetic acid 30 times as fast as the corresponding saturated compound does, and yields (optically inactive) XX, but no XIX. How do you account for these observations?

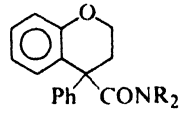
19. (a) Treatment of XXII with $NaOCH_3$ gives product XXIII; treatment of XXII with R_2NH gives the corresponding product XXIV. Show all steps in the most likely mechanism for these rearrangements.



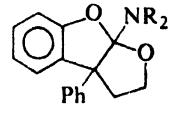
XXII



XXIII



XXIV



XXV

(b) From the reaction of XXII with R_2NH, there is also obtained XXV. How is XXV probably formed? Of what general significance is its isolation?

Chapter 29 Molecular Orbitals. Orbital Symmetry

29.1 Molecular orbital theory

The structure of molecules is best understood through quantum mechanics. Exact quantum mechanical calculations are enormously complicated, and so various methods of approximation have been worked out to simplify the mathematics. The method that is often the most useful for the organic chemist is based on the concept of *molecular orbitals*: orbitals that are centered, not about individual nuclei, but about all the nuclei in the molecule.

What are the various molecular orbitals of a molecule like? What is their order of stability? How are electrons distributed among them? These are things we must know if we are to understand the relative stability of molecules: why certain molecules are aromatic, for example. These are things we must know if we are to understand the course of many chemical reactions: their stereochemistry, for example, and how easy or difficult they are to bring about; indeed, whether or not they will occur at all.

We cannot learn here how to make quantum mechanical calculations, but we can see what the results of some of these calculations are, and learn a little about how to use them.

In this chapter, then, we shall learn what is meant by the *phase* of an orbital, and what *bonding* and *antibonding* orbitals are. We shall see, in a non-mathematical way, what lies behind the Hückel $4n + 2$ rule for aromaticity. And finally, we shall take a brief look at a recent—and absolutely fundamental—development in chemical theory: the application of the concept of *orbital symmetry* to the understanding of organic reactions.

29.2 Wave equations. Phase

In our first description of atomic and molecular structure, we said that electrons show properties not only of particles but also of waves. We must examine a

little more closely the wave character of electrons, and see how this is involved in chemical bonding. First, let us look at some properties of waves in general.

Let us consider the *standing waves* (or *stationary waves*) generated by the vibration of a string secured at both ends: the wave generated by, say, the plucking of a guitar string (Fig. 29.1). As we proceed horizontally along the string from

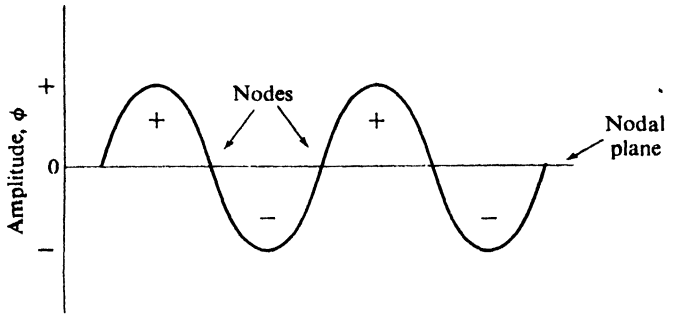


Figure 29.1. Standing waves. Plus and minus signs show relative phases.

left to right, we find that the vertical displacement—the *amplitude* of the wave—increases in one direction, passes through a maximum, decreases to zero, and then increases in the opposite direction. The places where the amplitude is zero are called *nodes*. In Fig. 29.1 they lie in a plane—the *nodal plane*—perpendicular to the plane of the paper. Displacement upward and displacement downward correspond to opposite *phases* of the wave. To distinguish between phases, we arbitrarily assign algebraic signs to the amplitude: plus for, say, displacement upward, and minus for displacement downward. If we were to superimpose similar waves on one another exactly *out of phase*—that is, with the crests of one lined up with the troughs of the other—they would cancel each other; that is to say, the sum of their amplitudes, + and −, would be zero.

The differential equation that describes the wave is a *wave equation*. Solution of this equation gives the amplitude, ϕ, as a function, $f(x)$, of the distance, x, along the wave. Such a function is a *wave function*.

Now, electron waves are described by a wave equation of the same general form as that for string waves. The wave functions that are acceptable solutions to this equation again give the amplitude, ϕ, this time as a function, not of a single coordinate, but of the three coordinates necessary to describe motion in three dimensions. It is these electron wave functions that we call *orbitals*.

Any wave equation has a *set* of solutions—an infinity of them, actually—each corresponding to a different energy level. The *quantum* thus comes naturally out of the mathematics.

Like a string wave, an electron wave can have nodes, where the amplitude is zero. On opposite sides of a node the amplitude has opposite signs, that is, the wave is of opposite phases. Of special interest to us is the fact that between the two lobes of a *p* orbital lies a nodal plane, perpendicular to the axis of the orbital

(Fig. 29.2). The two lobes are of opposite phase, and this is often indicated by + and − signs.

As used here, the signs do not have anything to do with charge. They simply indicate that the amplitude is of opposite algebraic sign in the two lobes. To avoid

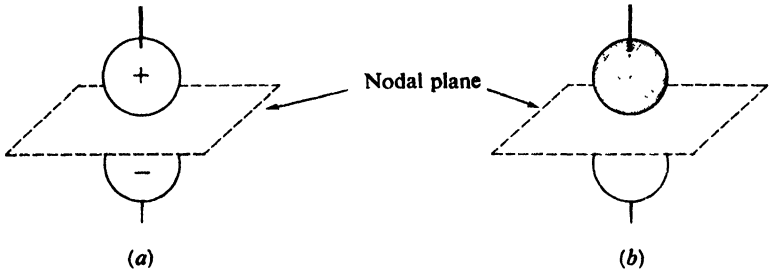


Figure 29.2. The *p* orbital. The two lobes are of opposite phase, indicated either (*a*) by plus and minus signs or (*b*) by shading.

confusion, we shall show lobes as shaded and unshaded. Two shaded lobes are of the same phase, both plus or both minus—it does not matter which. Similarly, two unshaded lobes are of the same phase; a shaded lobe and an unshaded lobe are of opposite phase.

The amplitude or wave function, ϕ, *is* the orbital. As is generally true for waves, however, it is the square of the amplitude, ϕ^2, that has physical meaning. For electron waves, ϕ^2 represents the probability of finding an electron at any particular place. The fuzzy balls or simple spheres we draw to show the "shapes" of orbitals are crude representations of the space within which ϕ^2 has a particular value—the space within which the electron spends, say, 95% of its time. Whether ϕ is positive or negative, ϕ^2 is of course positive; this makes sense, since probability cannot be negative. The usual practice is to draw the lobes of a *p* orbital to represent ϕ^2; if + or − signs are added, or one lobe is shaded and the other unshaded, this is to show the relative signs of ϕ.

29.3 Molecular orbitals. LCAO method

As chemists, we picture molecules as collections of atoms held together by bonds. We consider the bonds to arise from the overlap of an atomic orbital of one atom with an atomic orbital of another atom. A new orbital is formed, which is occupied by a pair of electrons of opposite spin. Each electron is attracted by both positive nuclei, and the increase in electrostatic attraction gives the bond its strength, that is, stabilizes the molecule relative to the isolated atoms.

This highly successful qualitative model parallels the most convenient quantum mechanical approach to molecular orbitals: **the method of linear combination of atomic orbitals (LCAO).** We have assumed that the shapes and dispositions of bond orbitals are related in a simple way to the shapes and dispositions of atomic orbitals. The LCAO method makes the same assumption *mathematically*: to

calculate an approximate molecular orbital, ψ, one uses a *linear combination* (that is, a combination through addition or subtraction) of atomic orbitals.

$$\psi = \phi_A + \phi_B$$

where

ψ is the molecular orbital
ϕ_A is atomic orbital A
ϕ_B is atomic orbital B

The rationale for this assumption is simple: when the electron is near atom A, ψ resembles ϕ_A; when the electron is near atom B, ψ resembles ϕ_B.

Now this combination is *effective*—that is, the molecular orbital is appreciably more stable than the atomic orbitals—only if the atomic orbitals ϕ_A and ϕ_B:

(a) overlap to a considerable extent;
(b) are of comparable energy; and
(c) have the same symmetry about the bond axis.

These requirements can be justified mathematically. Qualitatively, we can say this: if there is not considerable overlap, the energy of ψ is equal to either that of ϕ_A or that of ϕ_B; if the energy of ϕ_A and ϕ_B are quite different, the energy of ψ is essentially that of the more stable atomic orbital. In either case, there is no significant stabilization, and no bond formation.

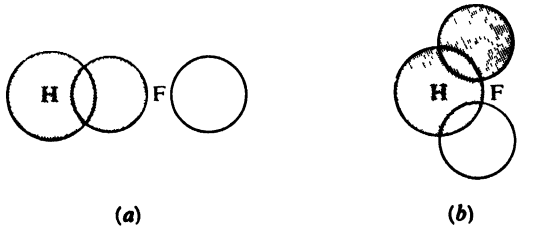


Figure 29.3. The hydrogen fluoride molecule: dependence of overlap on orbital symmetry. (*a*) Overlap of lobes of same phase leads to bonding. (*b*) Positive overlap and negative overlap cancel each other.

When we speak of the symmetry of orbitals, we are referring to the relative phases of lobes, and their disposition in space. To see what is meant by requirement (c), that the overlapping orbitals have the same symmetry, let us look at one example: hydrogen fluoride. This molecule can be pictured as resulting from overlap of the *s* orbital of hydrogen with a *p* orbital of fluorine. In Fig. 29.3*a*, we use the $2p_x$ orbital, where the *x* coordinate is taken as the H—F axis. The shaded *s* orbital overlaps the shaded lobe of the *p* orbital, and a bond forms. If, however, we were to use the $2p_z$ (or $2p_y$) orbital as in Fig. 29.3*b*, overlap of *both* lobes—plus and minus—would occur and cancel each other. That is, the positive overlap integral would be exactly canceled by the negative overlap integral; the net effect would be *no overlap*, and no bond formation. The dependence of overlap on phase is fundamental to chemical bonding.

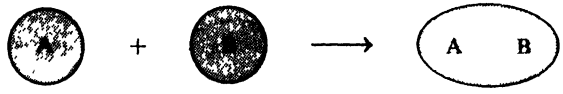
29.4 Bonding and antibonding orbitals

Quantum mechanics shows that linear combination of two functions gives, not one, but *two* combinations and hence *two* molecular orbitals: a *bonding* orbital, more stable than the component atomic orbitals; and an *antibonding* orbital, less stable than the component orbitals.

$\psi_+ = \phi_A + \phi_B$ Bonding orbital: *stabilizes molecule*

$\psi_- = \phi_A - \phi_B$ Antibonding orbital: *destabilizes molecule*

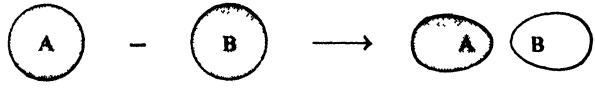
Two *s* orbitals, for example, can be added,



s *s* σ orbital

Bonding

or subtracted.



s *s* σ^* orbital

Antibonding

We can see, in a general way, why there must be two combinations. There can be as many as two electrons in each component atomic orbital, making a total of four electrons; two molecular orbitals are required to accommodate them.

Figure 29.4 shows schematically the shapes of the molecular orbitals, bonding and antibonding, that result from overlap of various kinds of atomic orbitals. We recognize the bonding orbitals, σ and π, although until now we have not shown the two lobes of a π orbital as being of opposite phase. An antibonding orbital, we see, has a nodal plane perpendicular to the bond axis, and cutting between the atomic nuclei. The antibonding sigma orbital, σ^*, thus consists of two lobes, of opposite phase. The antibonding pi orbital, π^*, consists of four lobes.

In a bonding orbital, electrons are concentrated in the region between the nuclei, where they can be attracted by both nuclei. The increase in electrostatic attraction lowers the energy of the system. In an antibonding orbital, by contrast, electrons are *not* concentrated between the nuclei; electron charge is zero in the nodal plane. Electrons spend most of their time farther from a nucleus than in the separated atoms. There is a decrease in electrostatic attraction, and an increase in repulsion between the nuclei. The energy of the system is higher than that of the separated atoms. *Where electrons in a bonding orbital tend to hold the atoms together, electrons in an antibonding orbital tend to force the atoms apart.*

It may at first seem strange that electrons in certain orbitals can actually weaken the bonding. Should not *any* electrostatic attraction, even if less than optimum, be better than none? We must remember that it is the bond dissociation energy we are concerned with. We are not comparing the electrostatic attraction in an antibonding orbital with no electrostatic attraction; we are comparing it with the stronger electrostatic attraction in the separated atoms.

There are, in addition, orbitals of a third kind, *non-bonding orbitals.* As the name indicates, electrons in these orbitals—unshared pairs, for example—neither strengthen nor weaken the bonding between atoms.

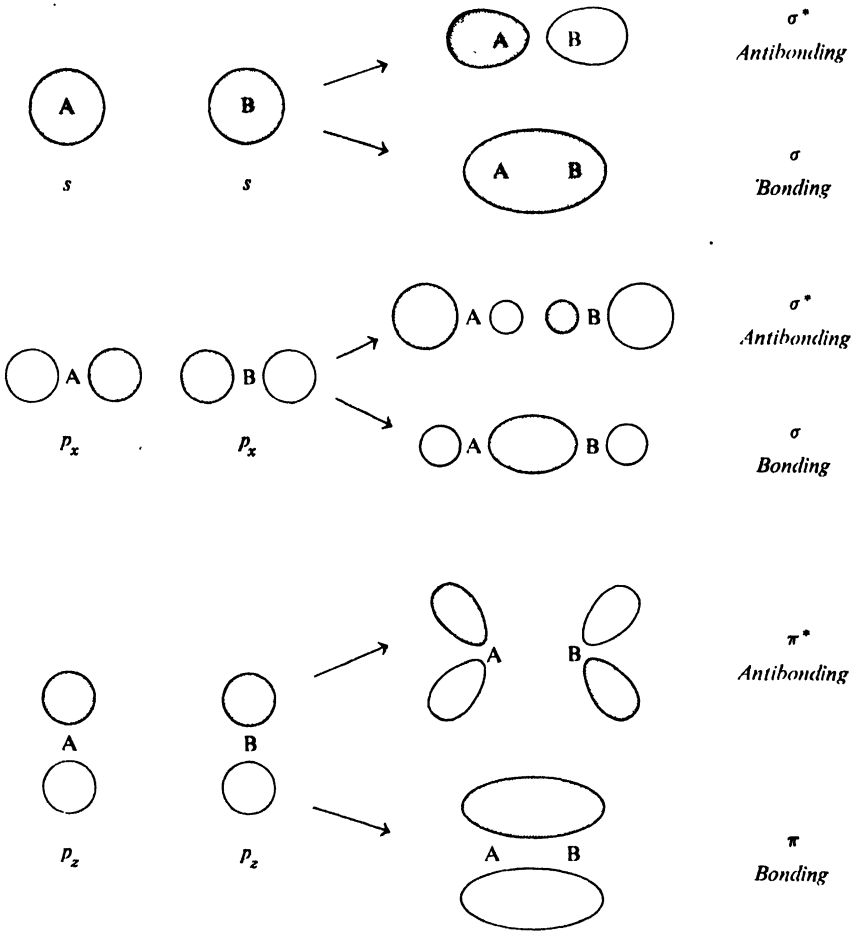


Figure 29.4. Bonding and antibonding orbitals.

29.5 Electronic configurations of some molecules

Let us look at the electronic configurations of some familiar molecules. The shapes and relative stabilities of the various molecular orbitals are calculated by quantum mechanics, and we shall simply use the results of these calculations. We picture the nuclei in place, with the molecular orbitals mapped out about them, and we feed electrons into the orbitals. In doing this we follow the same rules that we followed in arriving at the electronic configurations of atoms. There can be only two electrons—and of opposite spin—in each orbital, with orbitals of lower energy being filled up first. If there are orbitals of equal energy, each gets an electron before any one of them gets a pair of electrons. We shall limit our attention to orbitals containing π electrons, since these electrons will be the ones of chief interest to us.

For the π electrons of ethylene (Fig. 29.5), there are two molecular orbitals since there are two linear combinations of the two component p orbitals. The broken line in the figure indicates the non-bonding energy level; below it lies the bonding orbital, π, and above it lies the antibonding orbital, π^*.

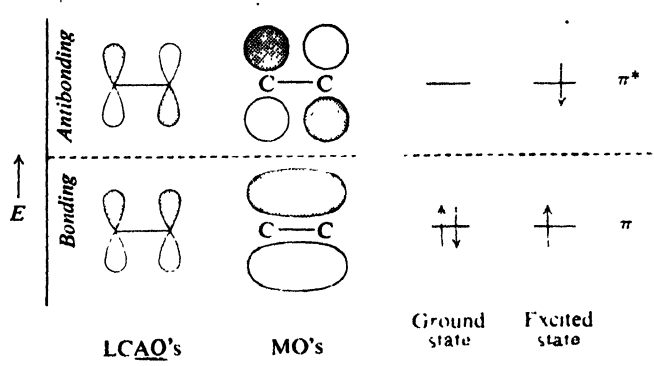


Figure 29.5. Ethylene. Configuration of π electrons in ground state and excited state.

Normally, a molecule exists in the state of lowest energy, the *ground state.* But, as we have seen (Sec. 13.5), absorption of light of the right frequency (in the ultraviolet region) raises a molecule to an *excited state*, a state of higher energy. In the ground state of ethylene, we see, both π electrons are in the π orbital; this configuration is specified as π^2, where the superscript tells the number of electrons in that orbital. In the excited state one electron is in the π orbital and the other—still of opposite spin—is in the π^* orbital; this configuration, $\pi\pi^*$, is naturally the less stable since only one electron helps to hold the atoms together, while the other tends to force them apart.

For 1,3-butadiene, with four component p orbitals, there are four molecular orbitals for π electrons (Fig. 29.6). The ground state has the configuration $\psi_1^2\psi_2^2$; that is, there are two electrons in each of the bonding orbitals, ψ_1 and ψ_2. The higher of these, ψ_2, resembles two isolated π orbitals, although it is of somewhat lower

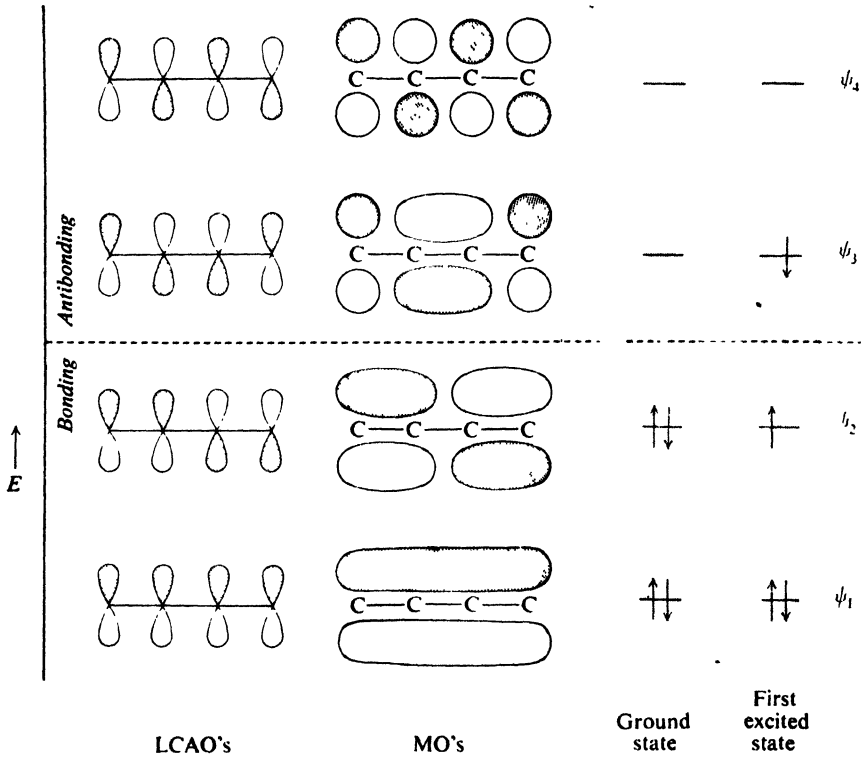


Figure 29.6. 1,3-Butadiene. Configuration of π electrons in ground state and first excited state.

energy. Orbital ψ_1 encompasses all four carbons; this delocalization provides the net stabilization of the conjugated system. Absorption of light of the right frequency raises one electron to ψ_3.

$$\underset{\text{Ground state}}{\psi_1^2\psi_2^2} \xrightarrow{h\nu} \underset{\text{Lowest excited state}}{\psi_1^2\psi_2\psi_3}$$

Next, let us look at the allyl system: cation, free radical, and anion. Regardless

$$\underbrace{CH_2{=}CH{=}CH_2}_{\oplus} \qquad \underbrace{CH_2{=}CH{=}CH_2}_{\cdot} \qquad \underbrace{CH_2{=}CH{=}CH_2}_{\ominus}$$

Allyl cation Allyl free radical Allyl anion

of the number of π electrons, there are three component p orbitals, one on each carbon, and they give rise to three molecular orbitals, ψ_1, ψ_2, and ψ_3. As shown in Fig 29.7, ψ_1 is bonding and ψ_3 is antibonding. Orbital ψ_2 encompasses only

the end carbons (there is a node at the middle carbon) and is of the same energy as an isolated p orbital; it is therefore non-bonding.

The allyl cation has π electrons only in the bonding orbital. The free radical has one electron in the non-bonding orbital as well, and the anion has two in the non-bonding orbital. The bonding orbital ψ_1 encompasses all three carbons, and

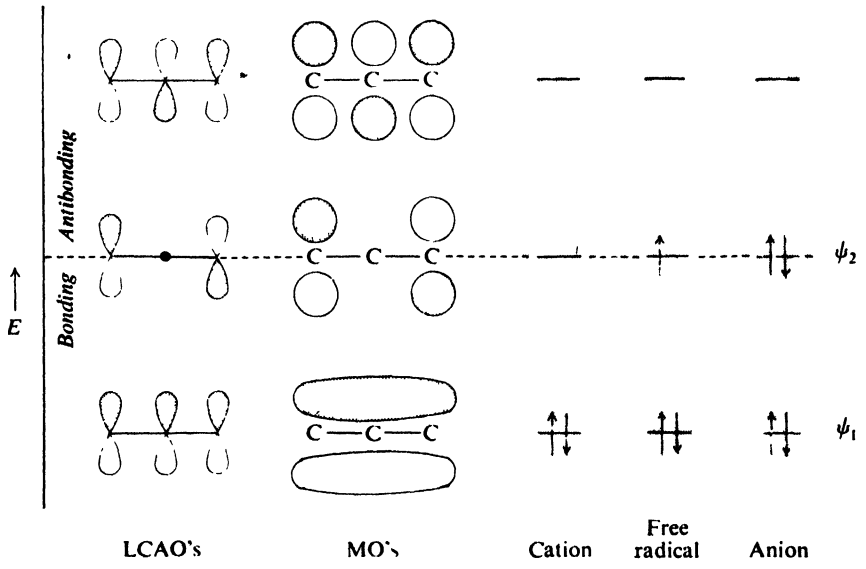
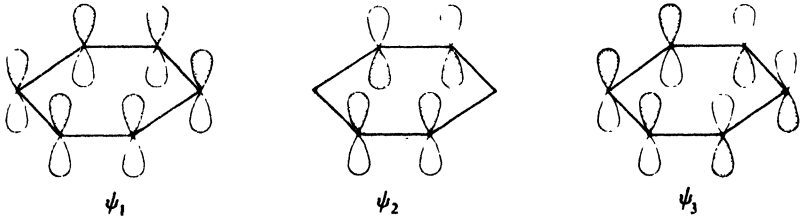


Figure 29.7. Allyl system. Configuration of π electrons in cation, free radical, and anion.

is more stable than a localized π orbital involving only two carbons; it is this delocalization that gives allylic particles their special stability. We see the symmetry we have attributed to allylic particles on the basis of the resonance theory; the two ends of each of these molecules are equivalent.

Finally, let us look at benzene. There are six combinations of the six component p orbitals, and hence six molecular orbitals. Of these, we shall consider only these combinations, which correspond to the three most stable molecular



Benzene: first three LCAO's

orbitals, all bonding orbitals (Fig. 29.8). Each contains a pair of electrons. The lowest orbital, ψ_1, encompasses all six carbons. Orbitals ψ_2 and ψ_3 are of different shape, but equal energy; together they provide—as does ψ_1—equal electron density

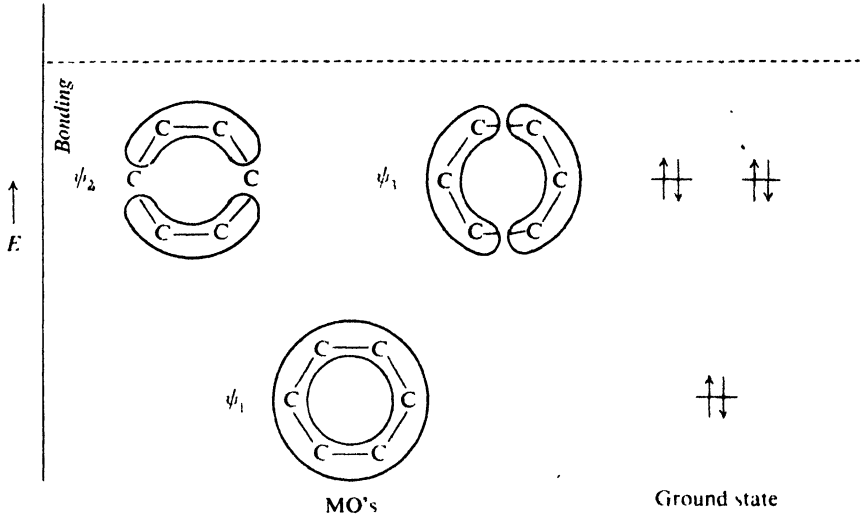


Figure 29.8. Benzene. Configuration of π electrons in ground state.

at all six carbons. The net result, then, is a highly symmetrical molecule with considerable delocalization of π electrons. But this is only part of the story; in the next section we shall look more closely at just what makes benzene such a special kind of molecule.

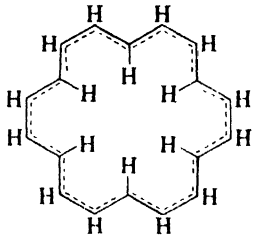
29.6 Aromatic character. The Hückel $4n + 2$ rule

In Chap. 10 we discussed the structure of aromatic compounds. An aromatic molecule is flat, with cyclic clouds of delocalized π electrons above and below the plane of the molecule. We have just seen, for benzene, the molecular orbitals that permit this delocalization. But delocalization alone is not enough. For that special degree of stability we call *aromaticity*, the number of π electrons must conform to **Hückel's rule**: *there must be a total of* **$(4n + 2)$ π electrons.**

Cyclopropenyl cation	Benzene	Cyclopentadienyl anion	Cycloheptatrienyl cation	Cyclooctatetraenyl dianion
Two π electrons	*Six π electrons*	*Six π electrons*	*Six π electrons*	*Ten π electrons*

All aromatic

In Sec. 10.10, we saw evidence of special stability associated with the "magic" numbers of 2, 6, and 10 π electrons, that is, with systems where n is 0, 1, and 2 respectively. Problem 5 (p. 447) described the nmr spectrum of cyclooctadecanonaene, which contains 18 π electrons (n is 4). Twelve protons lie outside the ring,



Cyclooctadecanonaene
Eighteen π electrons
Aromatic

are deshielded, and absorb downfield; but, because of the particular geometry of the large flat molecule, six protons lie *inside* the ring, are shielded (see Fig. 13.4, p. 419), and absorb upfield. The spectrum is unusual, but exactly what we would expect if this molecule were aromatic.

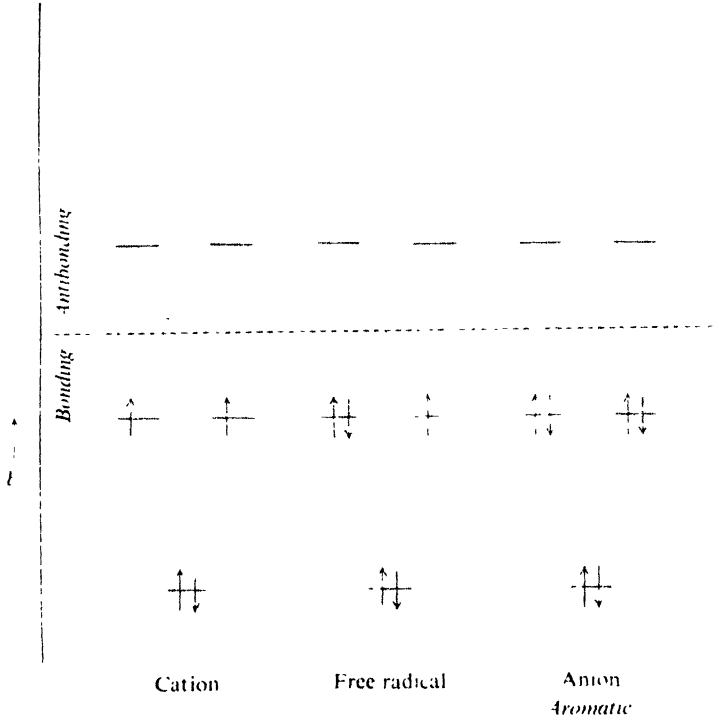


Figure 29.9. Cyclopentadienyl system. Configuration of π electrons in cation, free radical, and anion.

Hückel (p. 328) was a pioneer in the field of molecular orbital theory. He developed the LCAO method in its simplest form, yet "Hückel molecular orbitals" have proved enormously successful in dealing with organic molecules. Hückel proposed the $4n + 2$ rule in 1931. It has been tested in many ways since then, and it *works*. Now, what is the theoretical basis for this rule?

Let us begin with the cyclopentadienyl system. Five sp^2-hybridized carbons have five component p orbitals, which give rise to five molecular orbitals (Fig. 29.9, p. 935). At the lowest energy level there is a single molecular orbital. Above this, the orbitals appear as *degenerate* pairs, that is, pairs of orbitals of equal energy. The lowest degenerate pair are bonding, the higher ones are antibonding.

The cyclopentadienyl cation has four electrons. Two of these go into the lower orbital. Of the other two electrons, one goes into each orbital of the lower degenerate pair. The cyclopentadienyl free radical has one more electron, which fills one orbital of the pair. The anion has still another electron, and with this we fill the remaining orbital of the pair. The six π electrons of the cyclopentadienyl anion are *just enough to fill all the bonding orbitals*. Fewer than six leaves bonding orbitals unfilled; more than six, and electrons would have to go into antibonding orbitals. Six π electrons gives maximum bonding and hence maximum stability.

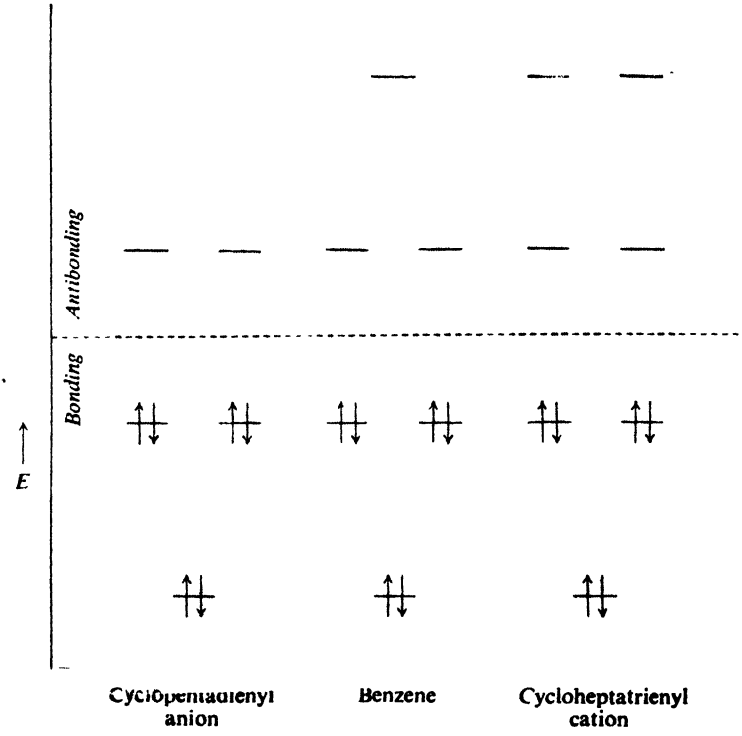


Figure 29.10. Aromatic compounds with 6 π electrons. Configuration of π electrons in cyclopentadienyl anion, benzene, and cycloheptatrienyl cation.

Figure 29.10 shows the molecular orbitals for rings containing five, six, and seven sp^2-hybridized carbons. We see the same pattern for all of them: a single orbital at the lowest level, and above it a series of degenerate pairs. It takes $(4n + 2)$ π electrons to *fill* a set of these bonding orbitals: 2 electrons for the lowest orbital, and 4 for each of n degenerate pairs. Such an electron configuration has been likened to the rare gas configuration of an atom, with its closed shell. It is the filling of these molecular orbital shells that makes these molecules aromatic.

In Problem 10.6 (p. 330) we saw that the cyclopropenyl cation is unusually stable: 20 kcal/mole more stable even than the allyl cation. In contrast, the cyclo-

propenyl free radical and anion are *not* unusually stable; indeed, the anion seems to be particularly *unstable*. The cation has the Hückel number of two π electrons (n is zero) and is aromatic. Here, too, aromaticity results from the filling up of a molecular orbital shell (Fig. 29.11).

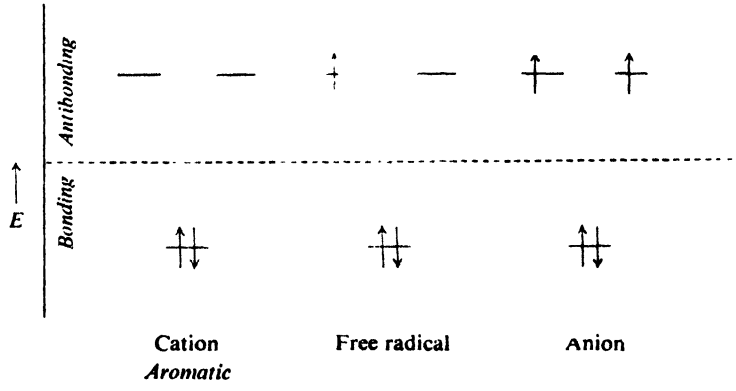
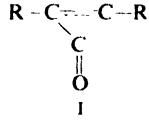


Figure 29.11. Cyclopropenyl system. Configuration of π electrons in cation, free radical, and anion.

In the allyl system (Fig. 29.7) the third and fourth electrons go into a non-bonding orbital, whereas here they go into antibonding orbitals. As a result, the cyclopropenyl free radical and anion are less stable than their open-chain counterparts. For the cyclopropenyl anion in particular, with two electrons in antibonding orbitals, simple calculations indicate no net stabilization due to delocalization, that is, zero resonance energy. Some calculations indicate that the molecule is actually less stable than if there were no conjugation at all. Such cyclic molecules, in which delocalization actually leads to *de*stabilization, are not just non-aromatic; they are *anti*aromatic.

Problem 29.1 When 3,4-dichloro-1,2,3,4-tetramethylcyclobutene was dissolved at -78 in SbF_5–SO_2, the solution obtained gave three nmr peaks, at δ 2.07, δ 2.20, and δ 2.68, in the ratio 1:1:2. As the solution stood, these peaks slowly disappeared and were replaced by a single peak at δ 3.68. What compound is each spectrum probably due to? Of what theoretical significance are these findings?

Problem 29.2 (a) Cyclopropenones (I) have been made, and found to have rather unusual properties.



R = phenyl or *n*-propyl

I

They have very high dipole moments: about 5 D, compared with about 3 D for benzophenone or acetone. They are highly basic for ketones, reacting with perchloric acid to yield salts of formula $(R_2C_3OH)^+ClO_4^-$. What factor may be responsible for these unusual properties?

(b) Diphenylcyclopropenone was allowed to react with phenylmagnesium bromide, and the reaction mixture was hydrolyzed with perchloric acid. There was obtained, not a tertiary alcohol, but a salt of formula $[(C_6H_5)_3C_3]^+ClO_4^-$. Account for the formation of this salt.

(c) The synthesis of the cyclopropenones involved the addition to alkynes of CCl_2, which was generated from $Cl_3CCOONa$. Show all steps in the most likely mechanism for the formation of CCl_2. (*Hint* See Sec. 9.16.)

29.7 Orbital symmetry and the chemical reaction

A chemical reaction involves the crossing of an energy barrier. In crossing this barrier, the reacting molecules seek the easiest path: a low path, to avoid climbing any higher than is necessary; and a broad path, to avoid undue restrictions on the arrangement of atoms. As reaction proceeds, there is a change in bonding among the atoms, from the bonding in the reactants to the bonding in the products. Bonding is a stabilizing factor; the stronger the bonding, the more stable the system. If a reaction is to follow the easiest path, it must take place in the way that *maintains maximum bonding during the reaction process*. Now, bonding, as we visualize it, results from overlap of orbitals. Overlap requires that portions of different orbitals occupy the same space, and that they be *of the same phase*.

This line of reasoning seems perfectly straightforward. Yet the central idea, that the course of reaction can be controlled by orbital symmetry, was a revolutionary one, and represents one of the really giant steps forward in chemical theory. A number of people took part in the development of this concept: K. Fukui in Japan, H. C. Longuet-Higgins in England. But organic chemists became aware of the power of this approach chiefly through a series of papers published in 1965 by R. B. Woodward and Roald Hoffmann working at Harvard University.

Very often in organic chemistry, theory lags behind experiment; many facts are accumulated, and a theory is proposed to account for them. This is a perfectly respectable process, and extremely valuable. But with orbital symmetry, just the reverse has been true. The theory lay in the mathematics, and what was needed was the spark of genius to see the applicability to chemical reactions. Facts were

sparse, and Woodward and Hoffmann made *predictions*, which have since been borne out by experiment. All this is the more convincing because these predictions were of the kind called "risky": that is, the events predicted seemed unlikely on any grounds other than the theory being tested.

Orbital symmetry effects are observed in *concerted* reactions, that is, in reactions where several bonds are being made or broken simultaneously. Woodward and Hoffmann formulated "rules," and described certain reaction paths as *symmetry-allowed* and others as *symmetry-forbidden. All of this applies only to concerted reactions*, and refers to the relative ease with which they take place. A "symmetry-forbidden" reaction is simply one for which the concerted mechanism is very difficult, so difficult that, if reaction is to occur at all, it will probably do so in a different way: by a different concerted path that is symmetry-allowed; or, if there is none, by a stepwise, non-concerted mechanism. In the following brief discussion, and in the problems based on it, we have not the space to give the evidence indicating that each reaction is indeed concerted; but there must *be* such evidence, and gathering it is often the hardest job the investigator has to do.

Nor have we space here for a full, rigorous treatment of concerted reactions, which considers the correlation of symmetry between all the molecular orbitals of the products. We shall focus our attention on certain key orbitals, which contain the "valence" electrons of the molecules. Even this simplified approach, we shall find, is tremendously powerful; it is highly graphic, and in some cases gives information that the more detailed treatment does not.

29.8 Electrocyclic reactions

Under the influence of heat or light, a conjugated polyene can undergo isomerization to form a cyclic compound with a single bond between the terminal carbons of the original conjugated system; one double bond disappears, and the remaining double bonds shift their positions. For example, 1,3,5-hexatrienes yield 1,3-cyclohexadienes:

A 1,3,5-hexatriene A 1,3-cyclohexadiene

The reverse process can also take place: a single bond is broken and a cyclic compound yields an open-chain polyene. Cyclobutenes, for example, are converted into butadienes:

A cyclobutene A 1,3-butadiene

Such interconversions are called **electrocyclic reactions.**

It is the stereochemistry of electrocyclic reactions that is of chief interest to us. To observe this, we must have suitably substituted molecules. Let us consider first the interconversion of 3,4-dimethylcyclobutene and 2,4-hexadiene (Fig. 29.12). The cyclobutene exists as *cis* and *trans* isomers. The hexadiene exists in three forms: *cis,cis*; *cis,trans*; and *trans,trans*. As we can see, the *cis* cyclobutene yields only

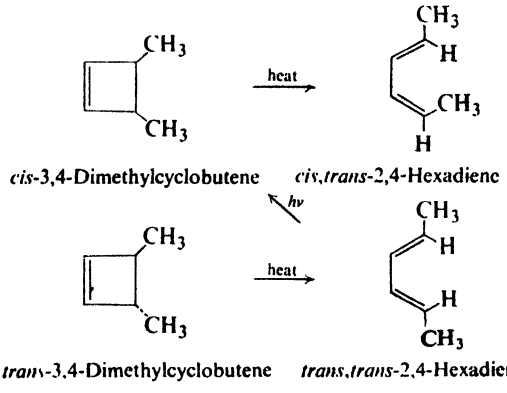


Figure 29.12. Interconversions of 3,4-dimethylcyclobutenes and 2,4-hexadienes.

one of the three isomeric dienes; the *trans* cyclobutene yields a different isomer. Reaction is thus *completely stereospecific*. Furthermore, photochemical cyclization of the *cis,trans* diene gives a different cyclobutene than the one from which the diene is formed by the thermal (heat-promoted) ring-opening.

The interconversions of the corresponding dimethylcyclohexadienes and the 2,4,6-octatrienes are also stereospecific (Fig. 29.13). Here, too, thermal and photochemical reactions differ in stereochemistry. If we examine the structures closely, we see something else: the stereochemistry of the triene-cyclohexadiene interconversions is *opposite to* that of the diene-cyclobutene interconversions. For the thermal reactions, for example, *cis* methyl groups in the cyclobutene become *cis* and *trans* in the diene; *cis* methyl groups in the cyclohexadiene are *trans* and *trans* in the related triene.

Electrocyclic reactions, then, are completely stereospecific. The exact stereochemistry depends upon two things: (a) the number of double bonds in the polyene, and (b) whether reaction is thermal or photochemical. It is one of the triumphs of the orbital symmetry approach that it can account for all these facts; indeed, most of the examples known today were *predicted* by Woodward and Hoffmann before the facts were known.

It is easier to examine these interconversions from the standpoint of cyclization; according to the principle of microscopic reversibility, whatever applies to this reaction applies equally well to the reverse process, ring-opening. In cyclization, two π electrons of the polyene form the new σ bond of the cycloalkene. But which two electrons? We focus our attention on the *highest occupied molecular orbital (HOMO) of the polyene*. Electrons in this orbital are the "valence" elec-

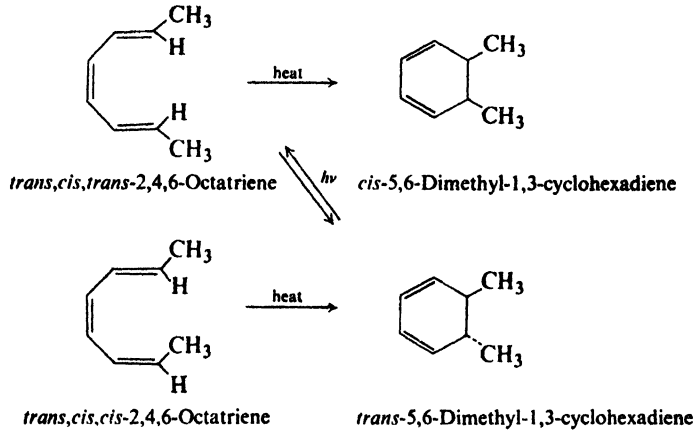
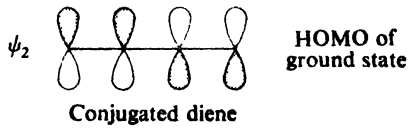


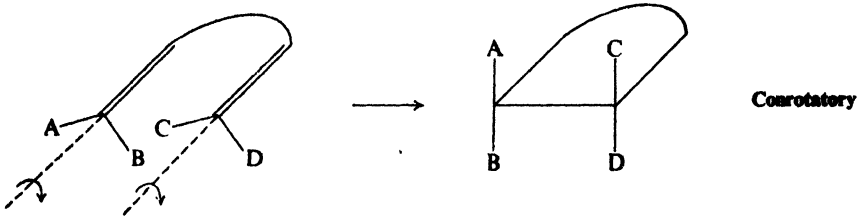
Figure 29.13. Interconversions of 2,4,6-octatrienes and 5,6-dimethyl-1,3-cyclohexadienes.

trons of the molecule; they are the least tightly held, and the most easily pushed about during reaction.

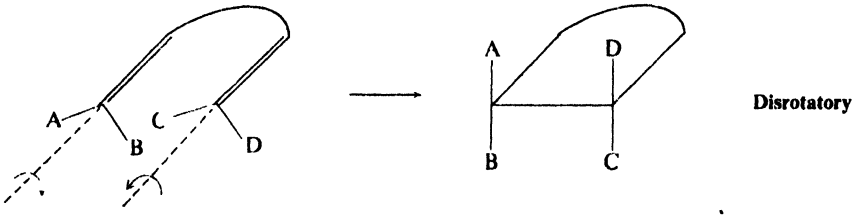
Let us begin with the thermal cyclization of a disubstituted butadiene, RCH=CH—CH=CHR. As we have already seen (Fig. 29.6, p. 932), the highest occupied molecular orbital of a conjugated diene is ψ_2. It is the electrons in this



orbital that will form the bond that closes the ring. Bond formation requires overlap, in this case overlap of lobes on C–1 and C–4 of the diene: the front carbons in Fig. 29.14. We see that to bring these lobes into position for overlap, there must be rotation about two bonds, C_1—C_2 and C_3—C_4. This rotation can take place in two different ways: there can be **conrotatory** motion, in which the bonds rotate in the same direction,



or there can be **disrotatory** motion, in which the bonds rotate in opposite directions.



Now, in this case, as we see in Fig. 29.14, conrotatory motion brings together lobes of the *same phase*; overlap occurs and a bond forms. Disrotatory motion, on

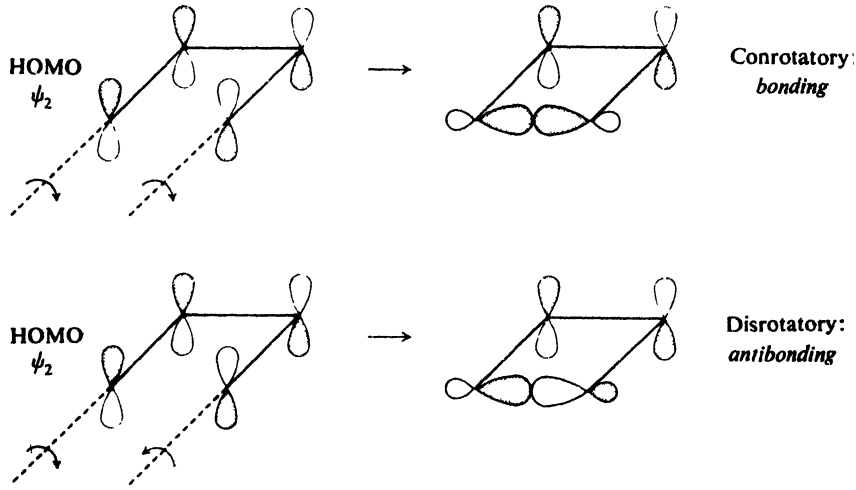


Figure 29.14. Thermal cyclization of a 1,3-butadiene to a cyclobutene. Conrotatory motion leads to bonding. Disrotatory motion leads to antibonding.

the other hand, brings together lobes of *opposite phase*; here interaction is antibonding, and repulsive. As Fig. 29.15 on opposite page shows, it is conrotatory motion that produces the stereochemistry actually observed.

How are we to account for the opposite stereochemistry in the photochemical reaction? On absorption of light, butadiene is converted into the excited state shown in Fig. 29.6, in which one electron from ψ_2 has been raised to ψ_3. Now the highest occupied orbital is ψ_3, and it is the electron here that we are concerned

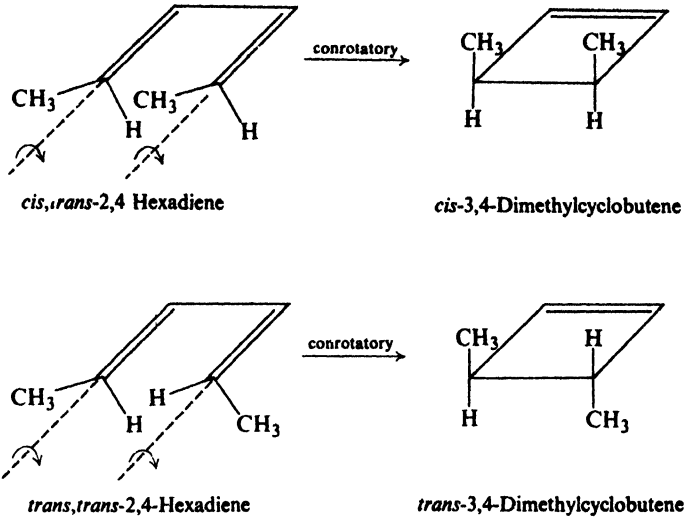


Figure 29.15. Thermal cyclization of substituted butadienes. Observed stereochemistry indicates conrotatory motion.

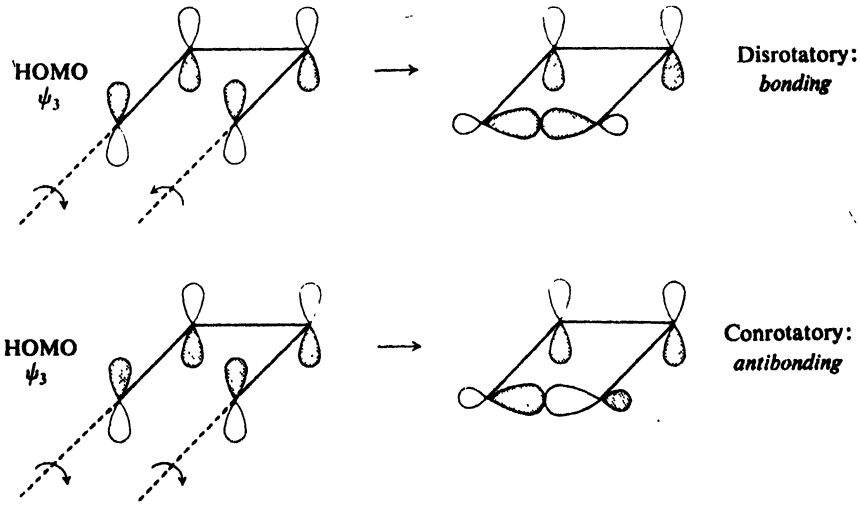


Figure 29.16. Photochemical cyclization of a 1,3-butadiene to a cyclobutene. Disrotatory motion leads to bonding. Conrotatory motion leads to antibonding.

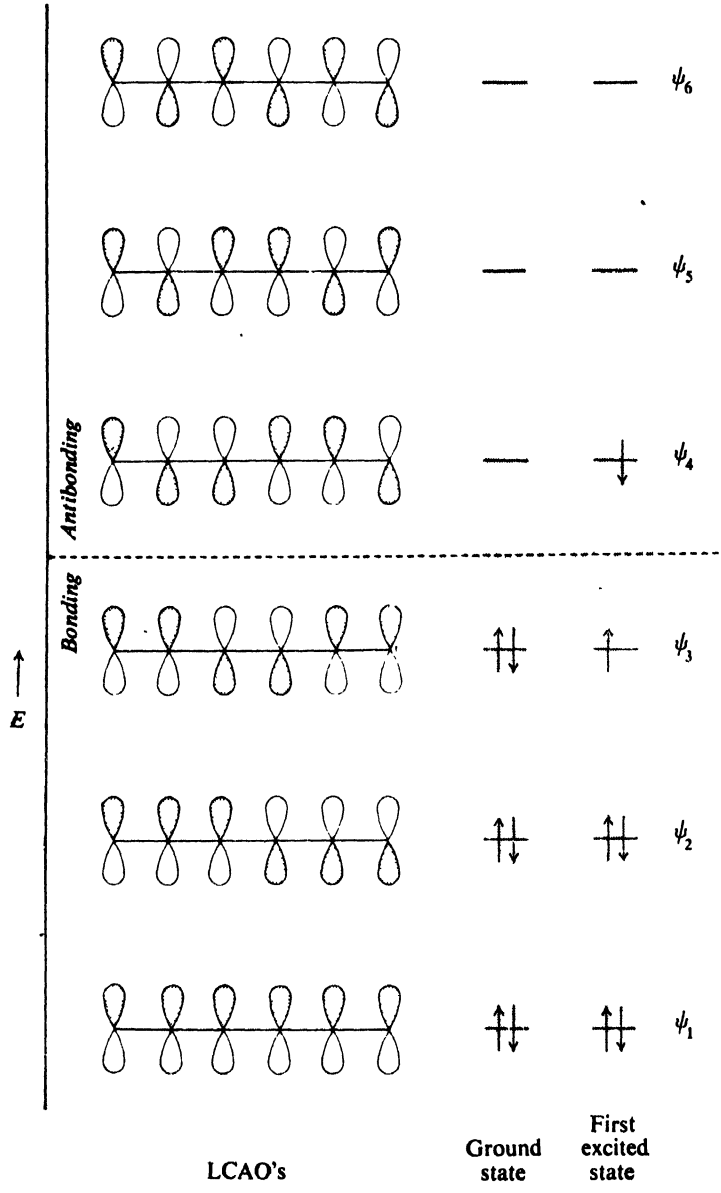
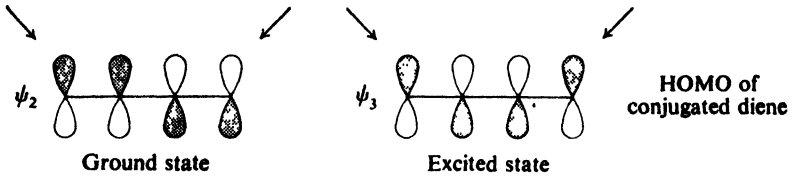
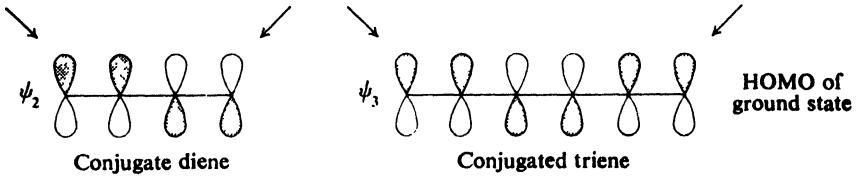


Figure 29.17. A 1,3,5-hexatriene. Configuration of π electrons in ground state and first excited state.



with. But in ψ_3 the relative symmetry of the terminal carbons is opposite to that in ψ_2. Now it is the *disrotatory* motion that brings together lobes of the same phase, and the stereochemistry is reversed (Fig. 29.16).

Next, let us look at the thermal cyclization of a disubstituted hexatriene, RCH=CH—CH=CH—CH=CHR, whose electronic configuration is shown in Fig. 29.17. The HOMO for the ground state of the hexatriene is ψ_3. If we compare this with the HOMO for the ground state of butadiene (ψ_2 in Fig. 29.6), we see that the relative symmetry about the terminal carbons is opposite in the two cases.



For ground state hexatriene it is disrotatory motion that leads to bonding and, as shown in Fig. 29.18, gives rise to the observed stereochemistry.

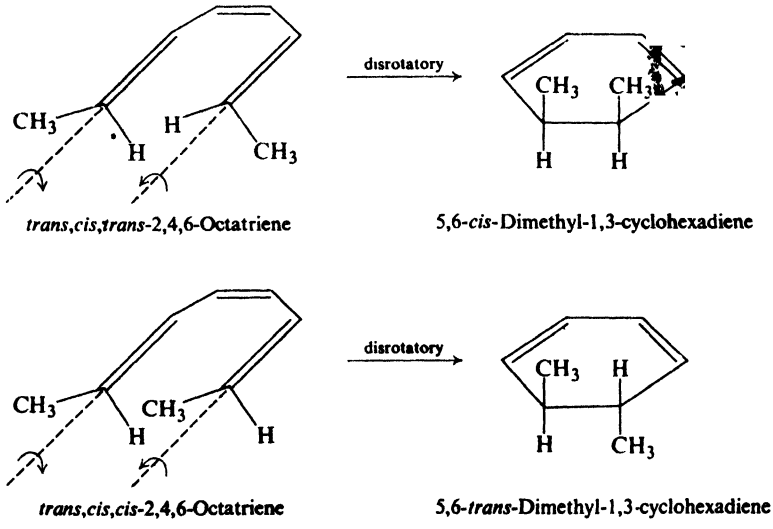


Figure 29.18. Thermal cyclization of substituted hexatrienes. Observed stereochemistry indicates disrotatory motion.

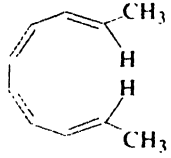
In the excited state of hexatriene, ψ_2 is the HOMO, and once again we see a reversal of symmetry: here, conrotatory motion is the favored process.

What we see here is part of a regular pattern (Table 29.1) that emerges from the quantum mechanics. As the number of pairs of π electrons in the polyene increases, the relative symmetry about the terminal carbons in the HOMO alternates regularly. Furthermore, symmetry in the HOMO of the first excited state is always opposite to that in the ground state.

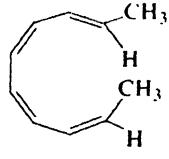
Table 29.1 WOODWARD-HOFFMANN RULES FOR ELECTROCYCLIC REACTIONS

Number of π electrons	Reaction	Motion
$4n$	thermal	conrotatory
$4n$	photochemical	disrotatory
$4n + 2$	thermal	disrotatory
$4n + 2$	photochemical	conrotatory

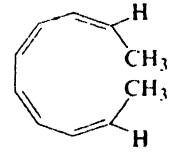
Problem 29.3 Thermal ring closure of three stereoisomeric 2,4,6,8-decatetraenes (I, II, and III) has been found to be in agreement with the Woodward-Hoffmann rules.



I



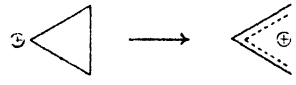
II



III

Two of these stereoisomers give one dimethylcyclooctatriene, and the third stereoisomer gives a different dimethylcyclooctatriene. (a) Which decatetraenes give which cyclooctatrienes? (b) Predict the product of photochemical ring closure of each.

Problem 29.4 The commonly observed conversion of cyclopropyl cations into allyl cations is considered to be an example of an electrocyclic reaction. (a) What is



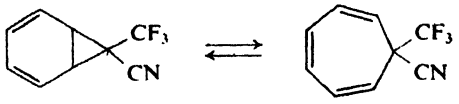
Cyclopropyl cation Allyl cation

the HOMO of the allyl cation? How many electrons are in it? (b) Where does this reaction fit in Table 29.1? Would you expect conrotatory or disrotatory motion? (c) What prediction would you make about interconversion of allyl and cyclopropyl *anions*? (d) About the interconversion of pentadienyl cations and cyclopentenyl cations?

Pentadienyl cation Cyclopentenyl cation

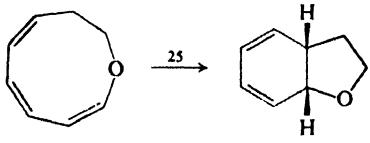
Problem 29.5 Each of the following reactions involves one or more concerted steps that take place in accordance with the Woodward-Hoffmann rules. In each case, show exactly what is happening.

(a)

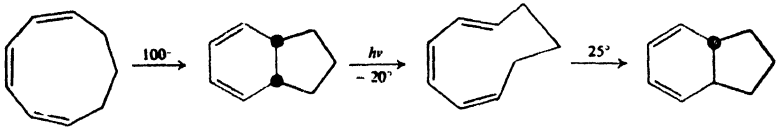


7-Cyano-7-trifluoromethyl-norcaradiene — 7-Cyano-7-trifluoromethyl-tropylidene

(b)

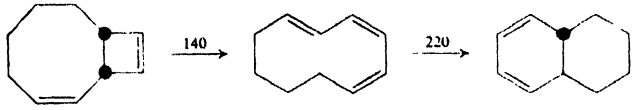


(c)



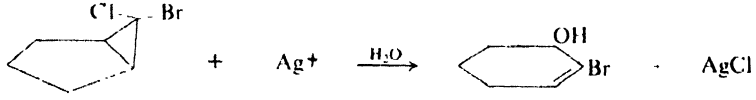
cis,cis,trans-Cyclonona-1,3,5-triene — *cis*-Bicyclo[4.3.0]-nona-2,4-diene — *cis,cis,trans*-Cyclonona-1,3,5-triene — *trans*-Bicyclo[4.3.0]-nona-2,4-diene

(d)



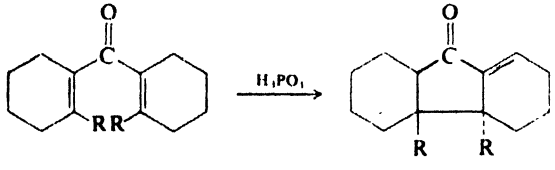
cis-Bicyclo[6.2.0]-deca-2,9-diene — *cis,cis,cis*-Cyclodeca-1,3,5-triene — *trans*-Bicyclo[4.4.0]-deca-2,4-diene

(e)

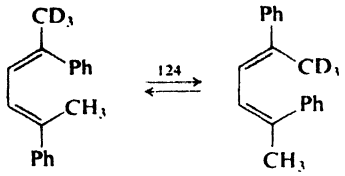


endo-2-Chloro-*exo*-2-bromobicyclo[3.1.0]hexane — 2-Bromo-2-cyclohexenol

(f)

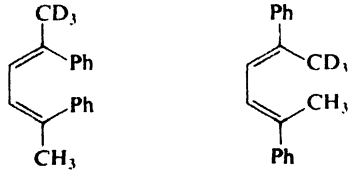


Problem 29.6 Stereoisomers IV and V are easily interconverted by heating. After 51 days at 124°—during which time, it was calculated, 2.6×10^6 interconversions took



IV V

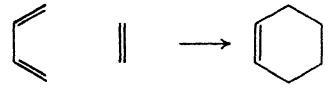
place—*only* IV and V were found to be present; there was *none* of their stereoisomers VI and VII. Propose a mechanism for the interconversion that would account for this remarkable stereospecificity.



VI VII

29.9 Cycloaddition reactions

In Sec. 27.8, we encountered the Diels-Alder reaction, in which a conjugated diene and a substituted alkene—the dienophile—react to form a cyclohexene.



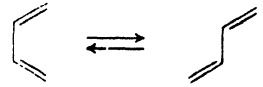
Diene Dienophile Adduct

Diels-Alder reaction:
a [4 + 2] cycloaddition

This is an example of **cycloaddition**, a reaction in which two unsaturated molecules combine to form a cyclic compound, with π electrons being used to form two new σ bonds. The Diels-Alder reaction is a [4 + 2] cycloaddition, since it involves a system of 4 π electrons and a system of 2 π electrons.

Reaction takes place very easily, often spontaneously, and at most requires moderate application of heat.

There are several aspects to the stereochemistry of the Diels-Alder reaction. (a) First, we have taken for granted—correctly—that the diene must be in the

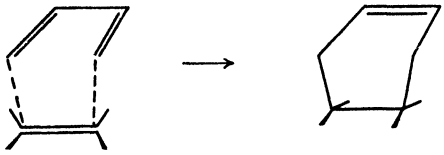


s-cis *s-trans*

Required for Diels-Alder reaction

conformation (*s-cis*) that permits the ends of the conjugated system to *reach* the doubly-bonded carbons of the dienophile.

(b) Next, with respect to the alkene (dienophile) addition is clear-cut *syn* (Problem 8, p. 880); this stereospecificity is part of the evidence that the Diels-Alder



reaction is, indeed, a concerted one, that is, that both new bonds are formed in the same transition state.

(c) Finally, the Diels-Alder reaction takes place in the *endo*, rather than *exo*, sense. That is to say, any other unsaturated groups in the dienophile (for example, —CO—O—CO— in maleic anhydride) tend to lie *near* the developing double bond in the diene moiety (Fig. 29.19). For the *endo* preference to be *seen*, of course, the diene must be suitably substituted.

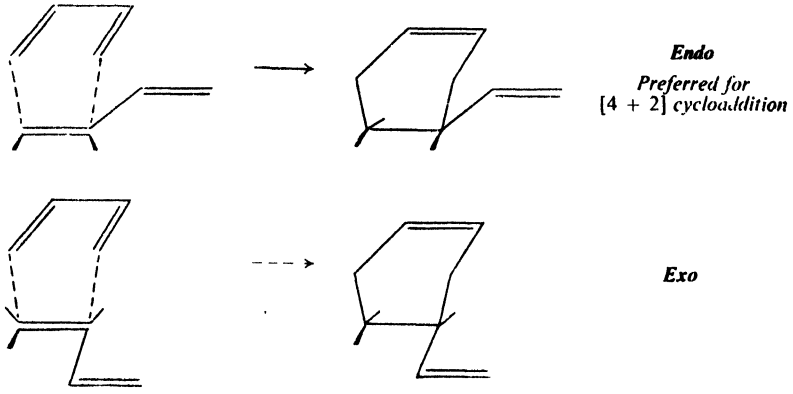
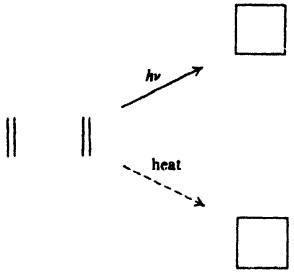


Figure 29.19. Stereochemistry of the Diels-Alder reaction, illustrated for the reaction between two moles of 1,3-butadiene.

Now are there such reactions as [2 + 2] cycloadditions? Can, say, two molecules of ethylene combine to form cyclobutane? The answer is: yes, but not easily under thermal conditions. Under vigorous conditions cycloaddition may occur, but step-wise—via diradicals—and not in a concerted fashion. Photochemical [2 + 2] cycloadditions, on the other hand, are very common. (Although some of these, too, may be stepwise reactions, many are clearly concerted.)

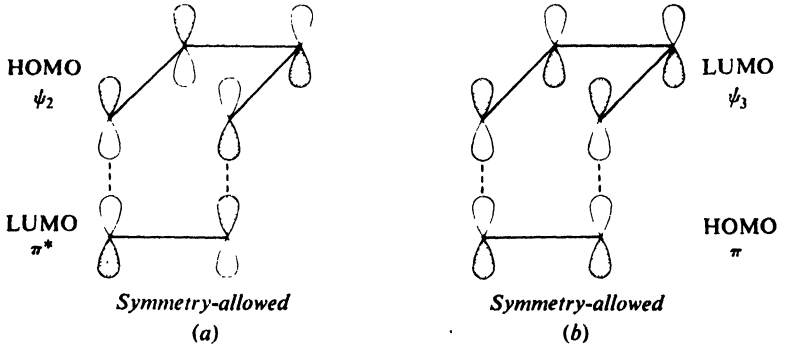
Of thermal cycloadditions, then, [4 + 2] is easy and [2 + 2] is difficult. Of [2 + 2] cycloadditions, the thermal reaction is difficult and the photochemical reaction is easy. How are we to account for these contrasts?



Difficult:
not a concerted reaction

In cycloaddition, two new σ bonds are formed by use of π electrons of the reactants. The concerted reaction results from overlap of orbitals of one molecule with orbitals of the other. As before, it is on electrons in the HOMO that we focus attention. But which orbital does the HOMO overlap? Each new orbital in the product can contain only two electrons. The HOMO of each reactant already contains two electrons, so it must overlap an *empty* orbital of the other reactant; it picks the most stable of these, the lowest unoccupied molecular orbital (LUMO). In the transition state of cycloaddition, then, *stabilization comes chiefly from overlap between the HOMO of one reactant and the LUMO of the other.*

On this basis, let us examine the [4 + 2] cycloaddition of 1,3-butadiene and ethylene, the simplest example of the Diels-Alder reaction. The electronic configurations of these compounds—and of dienes and alkenes in general—have been given in Fig. 29.5 (p. 931) and Fig. 29.6 (p. 932). There are two combinations: overlap of the HOMO of butadiene (ψ_2) with the LUMO of ethylene (π^*); and overlap of the HOMO of ethylene (π) with the LUMO of butadiene (ψ_3). In either case, as Fig. 29.20 shows, overlap brings together lobes of the same phase. There is a flow of electrons from HOMO to LUMO, and bonding occurs.



Symmetry-allowed (*a*) *Symmetry-allowed* (*b*)

Figure 29.20. Symmetry-allowed thermal [4 + 2] cycloaddition: 1,3-butadiene and ethylene. Overlap of (*a*) HOMO of 1,3-butadiene and LUMO of ethylene, and (*b*) HOMO of ethylene and LUMO of 1,3-butadiene.

Now, consider a thermal [2 + 2] cyclization, dimerization of ethylene. This would involve overlap of the HOMO, π, of one molecule with the LUMO, π^*, of the other. But π and π^* are of opposite symmetry, and, as Fig. 29.21 shows, lobes of opposite phase would approach each other. Interaction is antibonding and repulsive, and concerted reaction does not occur.

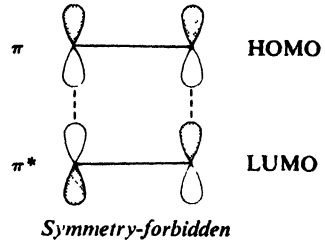


Figure 29.21. Symmetry-forbidden thermal [2 + 2] cycloaddition: two molecules of ethylene. Interaction is antibonding.

Photochemical [2 + 2] cycloadditions are symmetry-allowed. Here we have (Fig. 29.22) overlap of the HOMO (π^*) of an excited molecule with the LUMO (also π^*) of a ground-state molecule.

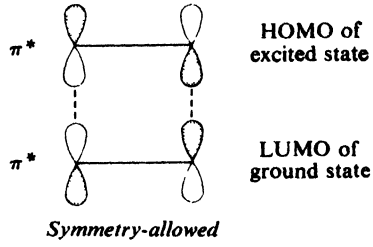
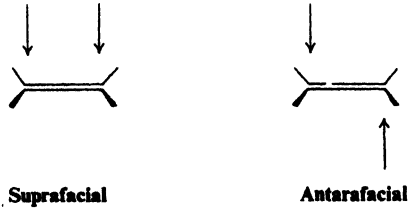


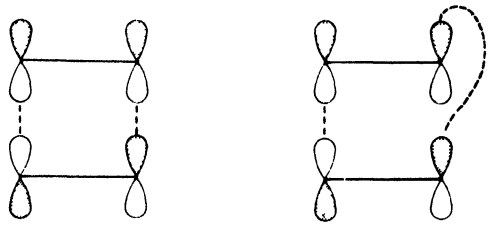
Figure 29.22. Symmetry-allowed photochemical [2 + 2] cycloaddition: two molecules of ethylene, one excited and one in ground-state. Interaction is bonding.

If, in a concerted reaction of this kind, both bonds to a component are being formed (or broken) on the same face, the process is said to be *suprafacial.* If the bonds are being formed (or broken) on opposite faces, the process is *antarafacial.*



These terms resemble the familiar ones *syn* and *anti*, but with this difference. *Syn* and *anti* describe the net stereochemistry of a reaction. We have seen *anti* addition, for example, as the overall result of a two-step mechanism. *Suprafacial* and *antarafacial*, in contrast, refer to actual processes: the simultaneous making (or breaking) of two bonds on the same face or opposite faces of a component.

So far, our discussion of cycloaddition has assumed that reaction is suprafacial with respect to both components. For [4 + 2] cycloadditions, the stereochemistry shows that this is indeed the case. Now, as far as orbital symmetry is concerned, thermal [2 + 2] cycloaddition *could* occur if it were suprafacial with respect to one component and antarafacial with respect to the other (Fig. 29.23).



supra,supra
Symmetry-forbidden

supra,antara
Symmetry-allowed

Figure 29.23. [2 + 2] Cycloaddition. *Supra,supra*: geometrically possible, but symmetry-forbidden. *Supra,antara*: symmetry-allowed, but geometrically difficult.

Almost certainly, such a *supra,antara* process is impossible here on geometric grounds. But if the ring being formed is big enough, both *supra,supra* and *supra, antara* processes are geometrically possible; in that case orbital symmetry determines, not *whether* cycloaddition occurs, but *how* it occurs (Table 29.2).

Table 29.2 WOODWARD-HOFFMANN RULES FOR [*i* + *j*] CYCLOADDITIONS

i + *j*	Thermal	Photochemical
4*n*	supra-antara antara-supra	supra-supra antara-antara
4*n* + 2	supra-supra antara-antara	supra-antara antara-supra

Cycloadditions are reversible. These *cycloreversions* (for example, the *retro*-Diels-Alder reaction) follow the same symmetry rules as cycloadditions—as they must, of course, since they occur via the same transition states.

Problem 29.7 Give structural formulas for the products expected from each of the following reactions. Tell *why* you expect the particular products.

(a) *trans,trans*-2,4-hexadiene + ethylene
(b) *trans*-4-methyl-1,3-butadiene + maleic anhydride

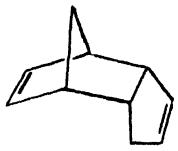
(c) *trans,trans*-1,4-diphenyl-1,3-butadiene + maleic anhydride

(d) *cis*-2-butene $\xrightarrow{h\nu}$ A + B

(e) *trans*-2-butene $\xrightarrow{h\nu}$ A + C

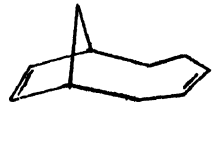
(f) *cis*-2-butene + *trans*-2-butene $\xrightarrow{h\nu}$ A + B + C + D

Problem 29.8 On standing, cyclopentadiene spontaneously forms *dicyclopentadiene* (I), from which it can be regenerated by heating under a fractionating column.



I

Dicyclopentadiene

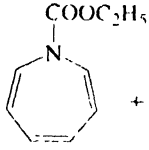


II

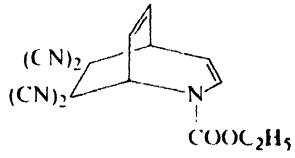
(a) What reaction has taken place in the formation of dicyclopentadiene? In the regeneration of cyclopentadiene? (b) On what basis could you have predicted that dicyclopentadiene would have the structure I rather than the structure II?

Problem 29.9 Each of the following reactions is believed to be concerted. Tell what kind of reaction is involved in each case, and what significance it bears on orbital symmetry theory.

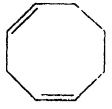
(a)



+ $(CN)_2C{=}C(CN)_2$ ⟶

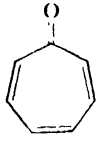


(b)



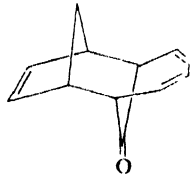
$\xrightarrow{h\nu}$

(c)

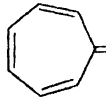


+

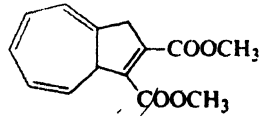
⟶

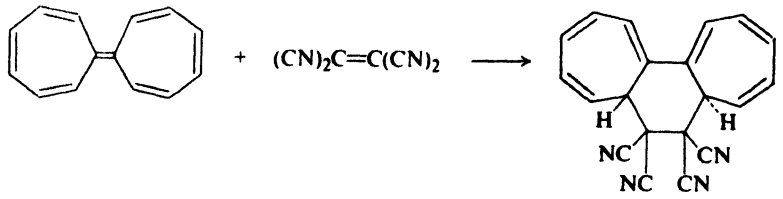


(d)



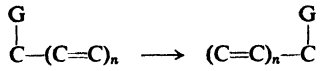
+ $CH_3OOCC{\equiv}CCOOCH_3$ ⟶



(e) 

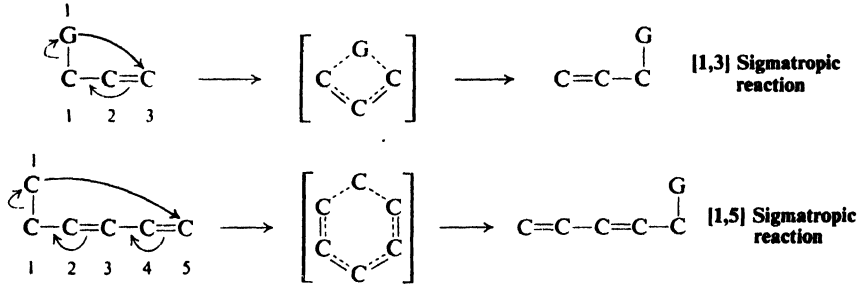
29.10 Sigmatropic reactions

A concerted reaction of the type,

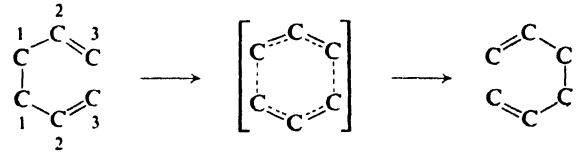


in which a group migrates with its σ bond within a π framework—an ene or a polyene—is called a **sigmatropic reaction.**

The migration is accompanied by a shift in π bonds. For example:



In the designations [1,3] and [1,5] the "3" and "5" refer to the number of the carbon to which group G is migrating (the migration terminus). The "1" does *not* refer to the migration source; instead, it specifies that in both reactant and product bonding is to the same atom (number 1) in the migrating group. The important *Cope rearrangement* of hexa-1,5-dienes, for example, is a



A 1,5-hexadiene

[3,3] sigmatropic reaction, in which there is a change in position of attachment in G as well as in the π framework—indeed, G itself is a π framework.

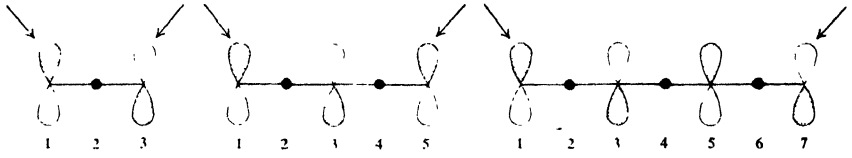
In the transition state of a sigmatropic reaction, the migrating group is bonded to both the migration source and the migration terminus; it is the nature of this transition state that we are concerned with. In Sec. 1.8, for convenience we con-

sidered bonding in the H_2 molecule to arise from overlap between orbitals on two hydrogen atoms. In the same way, and simply *for convenience*, we consider bonding in the transition state for sigmatropic reactions to arise from overlap between an orbital of an atom or free radical (G) and an orbital of an allylic free radical (the π framework).

This does *not* mean that rearrangement actually involves the separation and reattachment of a free radical. Such a stepwise reaction would not be a concerted one, and hence is not the kind of reaction we are dealing with here. Indeed, a stepwise reaction would be a (high-energy) alternative open to a system if a (concerted) sigmatropic rearrangement were symmetry-forbidden.

In the transition state, there is overlap between the HOMO of one component and the HOMO of the other. Each HOMO is singly occupied, and together they provide a pair of electrons.

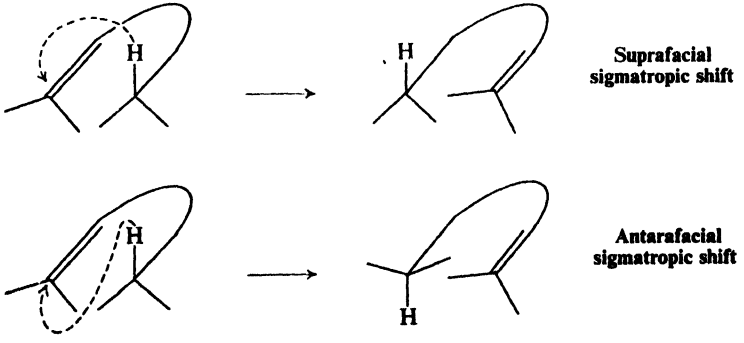
The HOMO of an allylic radical depends on the number of carbons in the π framework. The migrating group is passed from one end of the allylic radical to the other, and so it is the end carbons that we are concerned with. We see that



HOMO of allylic radicals

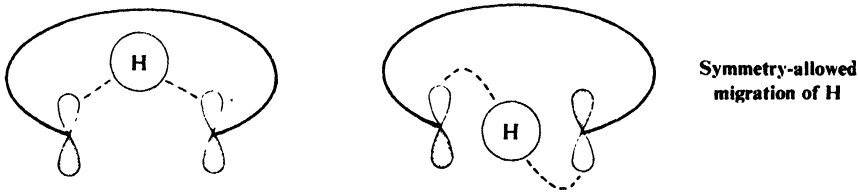
the symmetry at these end carbons alternates regularly as we pass from C–3 to C–5 to C–7, and so on. The HOMO of the migrating group depends, as we shall see, on the nature of the group.

Let us consider first the simplest case: **migration of hydrogen.** Stereochemically, this shift can be suprafacial or antarafacial:



In the transition state, a *three-center bond* is required, and this must involve overlap between the *s* orbital of the hydrogen and lobes of *p* orbitals of the two ter-

minal carbons. Whether a suprafacial or antarafacial shift is allowed depends upon the symmetry of these terminal orbitals:



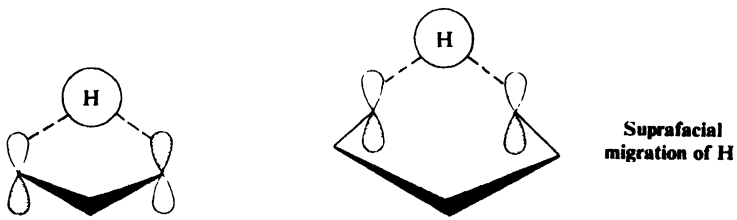
Suprafacial

Antarafacial

Difficult for [1,3] *or* [1,5] *shift*

Whether a sigmatropic rearrangement actually takes place, though, depends not only on the symmetry requirements but also on the *geometry* of the system. In particular, [1,3] and [1,5] *antara* shifts should be extremely difficult, since they would require the π framework to be twisted far from the planarity that it requires for delocalization of electrons.

Practically, then, [1,3] and [1,5] sigmatropic reactions seem to be limited to *supra* shifts. A [1,3] *supra* shift of hydrogen is symmetry-forbidden; since the *s* orbital of hydrogen would have to overlap *p* lobes of opposite phase, hydrogen cannot be bonded simultaneously to both carbons. A [1,5] *supra* shift of hydrogen, on the other hand, is symmetry-allowed.



[1,3]

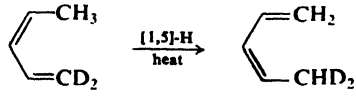
Symmetry-forbidden

[1,5]

Symmetry-allowed

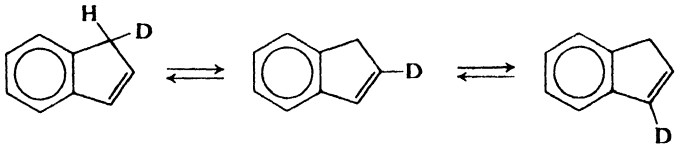
For larger π frameworks, both *supra* and *antara* shifts should be possible on geometric grounds, and here we would expect the stereochemistry to depend simply on orbital symmetry. A [1,7]-H shift, for example, should be *antara*, a [1,9]-H shift, *supra*, and so on. For photochemical reactions, as before, predictions are exactly reversed.

The facts agree with the above predictions: [1,3] sigmatropic shifts of hydrogen are not known, whereas [1,5] shifts are well known. For example:



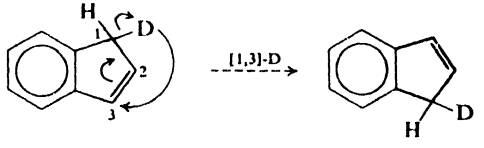
The preference for [1,5]-H shifts over [1,3]-H shifts has been demonstrated

many times. For example, the heating of 3-deuterioindene (I) causes scrambling of the label to *all three* non-aromatic positions. Let us examine this reaction.

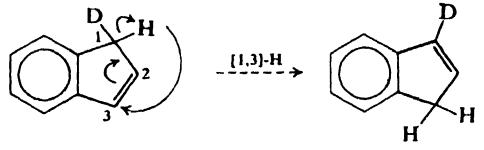


I II III

We cannot account for the formation of II on the basis of [1,3] shifts: migration of D would regenerate I; migration of H would yield only III.

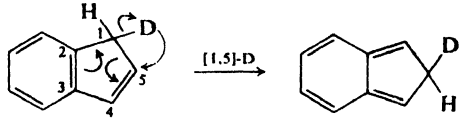


I I



I III

But if we include the *p* orbitals of the benzene ring, and count along the edge of this ring, we see that a [1,5] shift of D would yield the unstable non-aromatic



I IV*a*

intermediate IV*a*. This, in turn, can transfer H or D by [1,5] shifts to yield all the observed products (see Fig. 29.24).

So far we have discussed only migration of hydrogen, which is necessarily limited to the overlap of an *s* orbital. Now let us turn to **migration of carbon.** Here, we have two possible kinds of bonding to the migrating group. One of these is similar to what we have just described for migration of hydrogen: bonding of both ends of the π framework to the same lobe on carbon. Depending on the symmetry of the π framework, the symmetry-allowed migration may be suprafacial or antarafacial.

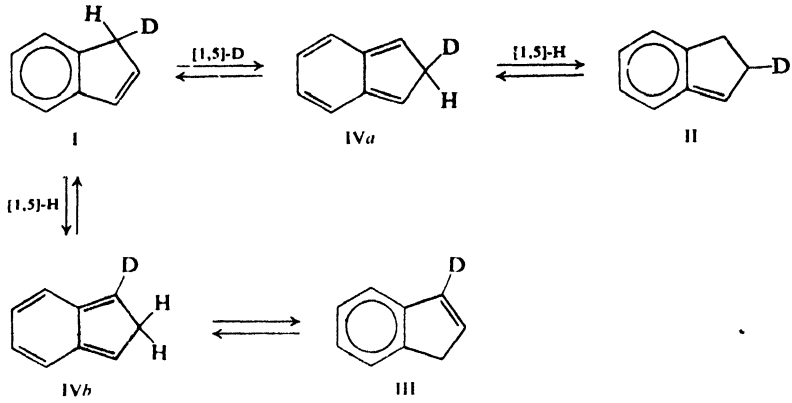
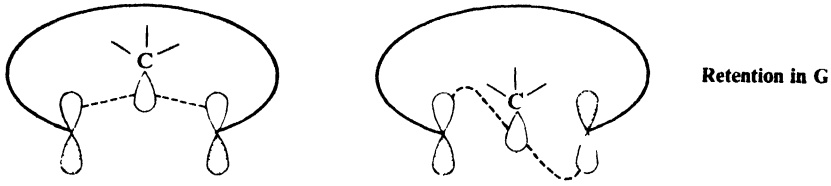
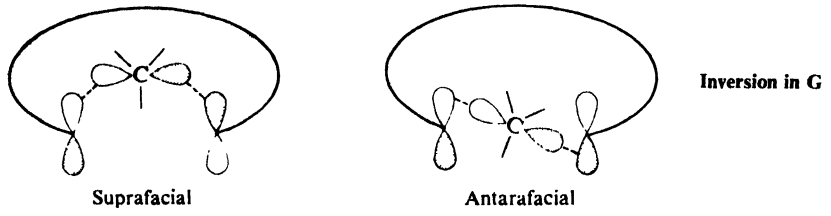


Figure 29.24. Deuterium scrambling in indene via unstable intermediates IV*a* and IV*b*: a series of [1,5] hydrogen shifts.

With carbon, a new aspect appears: the stereochemistry in the migrating group. Bonding through the same lobe on carbon means attachment to the same face of the atom, that is to say, *retention of configuration in the migrating group.*

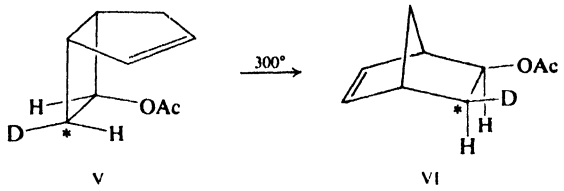


But there is a second possibility for carbon: bonding to the two ends of the π framework through different lobes of a p orbital. These lobes are on opposite faces of carbon—exactly as in an S_N2 reaction—and there is *inversion of configuration in the migrating group.*



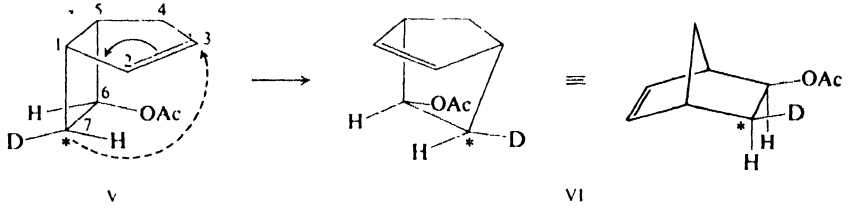
For [1,3] and [1,5] shifts, the geometry pretty effectively prevents antarafacial migration. Limiting ourselves, then, to suprafacial migrations, we make these predictions: [1,3] migration with inversion; [1,5] migration with retention. *These predictions have been borne out by experiment.*

In 1968, Jerome Berson (of the University of Wisconsin) reported that the deuterium-labeled bicyclo[3.2.0]heptene V is converted stereospecifically into the



V VI

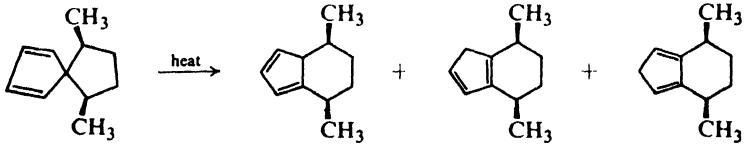
exo-norbornene VI. As Fig. 29.25 shows, this reaction proceeds by a [1,3] migration and with *complete inversion* of configuration in the migrating group.



V VI

Figure 29.25. The deuterium-labeled bicyclo[3.2.0]heptene V rearranges via a [1,3]-C shift to the norbornene VI. There is *inversion of configuration* at C–7: from R to S. (Or, using C–6 as our standard, we see that H eclipses OAc in V, and D eclipses OAc in VI.)

In 1970, H. Kloosterziel (of the University of Technology, Eindhoven, The Netherlands) reported a study of the rearrangement of the diastereomeric 6,9-dimethylspiro[4.4]nona-1,3-dienes (*cis*-VII and *trans*-VII) to the dimethylbicyclo-[4.3.0]nonadienes VIII, IX, and X. These reactions are completely stereospecific.

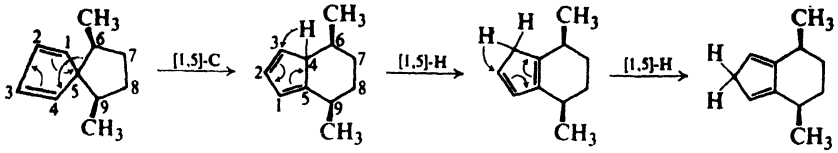


cis-VIII *cis*-VIII *cis*-IX *cis*-X

Chief product

As Fig. 29.26 shows, they proceed by [1,5] migrations and with *complete retention* of configuration in the migrating group.

To predict a different stereochemistry between [1,3] and [1,5] migrations, and in particular to predict *inversion* in the [1,3] shift—certainly not the easier path on geometric grounds—is certainly "risky". The fulfillment of such predictions demonstrates both the validity and the power of the underlying theory.

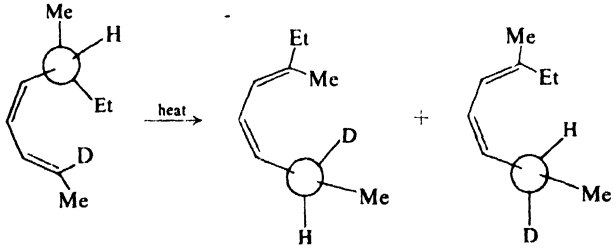


cis-VII *cis*-VIII *cis*-IX *cis*-X

Figure 29.26. Rearrangement of *cis*-6,9-dimethylspiro[4.4]nona-1,3-diene. Migration of C–6 from C–5 to C–4 is a [1,5]-C shift. (We count 5, 1, 2, 3, 4.) Configuration at C–6 is *retained*, as shown by its relationship to configuration at C–9. Successive [1,5]-H shifts then yield the other products.

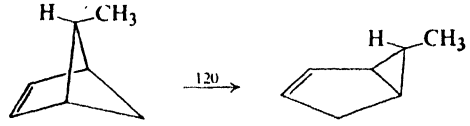
Problem 29.10 In each of the following, the high stereospecificity or regiospecificity provides confirmation of predictions based on orbital symmetry. Show how this is so. (*Use models.*)

(a)



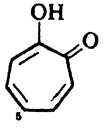
(b) When 1,3,5-cyclooctatriene labeled with deuterium at the 7 and 8 positions was heated, it gave products labeled only at the 3, 4, 7, and 8 positions.

(c)



PROBLEMS

1. Tropolone (I, $C_7H_7O_2$) has a flat molecule with all carbon–carbon bonds of the



Tropolone

I

same length (1.40 A). The measured heat of combustion is 20 kcal lower than that calculated by the method of Problem 10.2 (p. 323). Its dipole moment is 3.71 D; that of 5-bromotropolone is 2.07 D.

Tropolone undergoes the Reimer-Tiemann reaction, couples with diazonium ions, and is nitrated by dilute nitric acid. It gives a green color with ferric chloride, and does not react with 2,4-dinitrophenylhydrazine. Tropolone is both acidic ($K_a = 10^{-7}$) and weakly basic, forming a hydrochloride in ether.

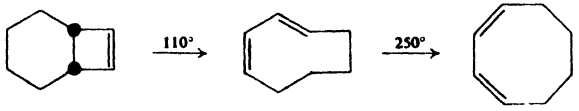
(a) What class of compounds does tropolone resemble? Is it adequately represented by formula I? (b) Using both valence-bond and orbital structures, account for the properties of tropolone.

(c) In what direction is the dipole moment of tropolone? Is this consistent with the structure you have proposed?

(d) The infrared spectrum of tropolone shows a broad band at about 3150 cm^{-1} that changes only slightly upon dilution. What does this tell you about the structure of tropolone?

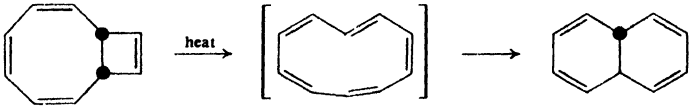
2. Each transformation shown below is believed to involve a concerted reaction. In each case show just what is happening.

(a)



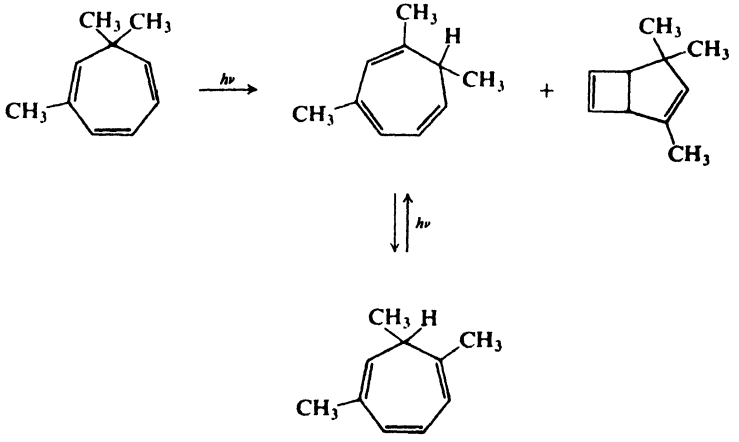
cis-Bicyclo[4.2.0]-octa-7-ene | *cis,trans*-Cyclo-octa-1,3-diene | *cis,cis*-Cyclo-octa-1,3-diene

(b)

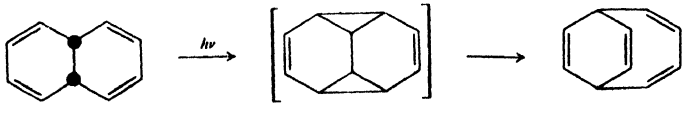


cis-Bicyclo[6.2.0]-deca-2,4,6,9-tetraene | *cis,cis,cis,cis,trans*-Deca-1,3,5,7,9-pentaene | *cis*-9,10-Dihydronaphthalene

(c)

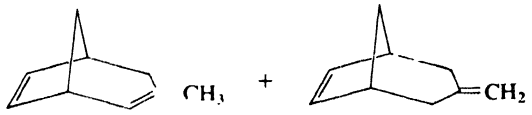


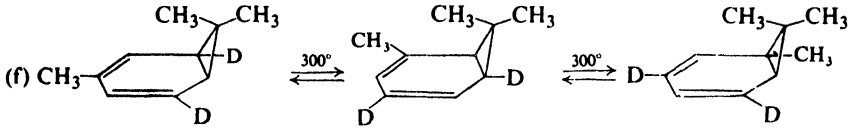
(d)



cis-9,10-Dihydronaphthalene

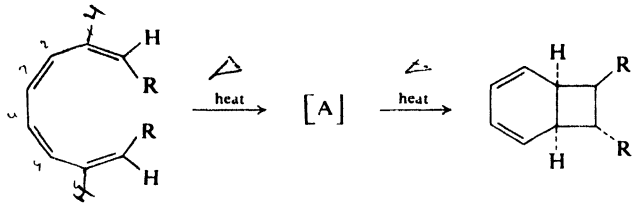
(e)  + $CH_2{=}C(CH_3)CH_2I$ + $AgOOCCCl_3$ ⟶



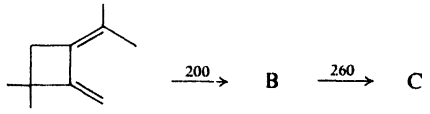
(f) 

3. Each of the following transformations is believed to proceed by the indicated sequence of concerted reactions. Show just what each step involves, and give structures of compounds A–J.

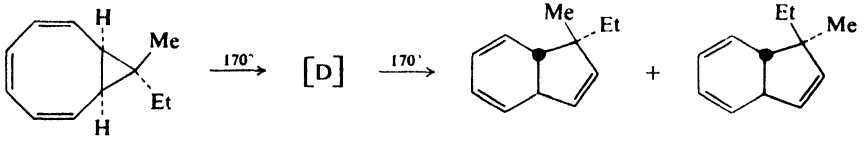
(a) Electrocyclic closure; electrocyclic closure.



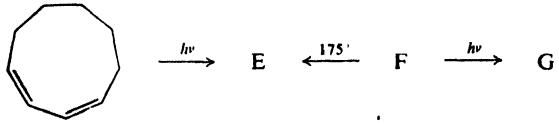
(b) [1,5]-H shift; electrocyclic opening.



(c) Electrocyclic opening; electrocyclic closure. Final products are not interconvertible at 170°; be sure you account for *both* of them.

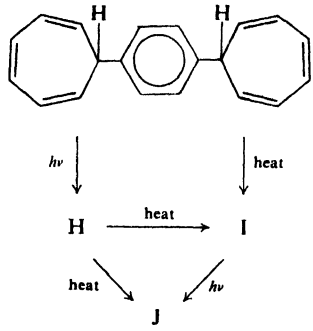


(d) Three electrocyclic closures.

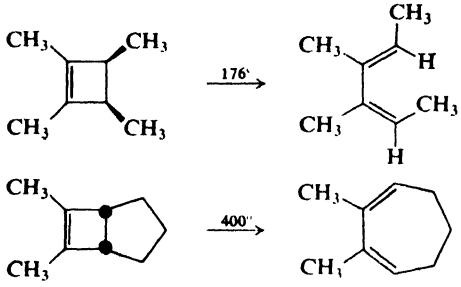


cis,cis-Cyclonona-1,3-diene

(e) A series of *supra* H shifts.



4. Account for the difference in conditions required to bring about the following transformations:



5. Give stereochemical structures of K and L, and tell exactly what process is taking place in each reaction.

cis,cis,cis-Cycloocta-1,3,5-triene $\xrightarrow{80\text{–}100°}$ K (C_8H_{10})

K + $CH_3OOCC{\equiv}CCOOCH_3$ $\longrightarrow$ L ($C_{14}H_{16}O_4$)

L $\xrightarrow{\text{heat}}$ cyclobutene + dimethyl phthalate

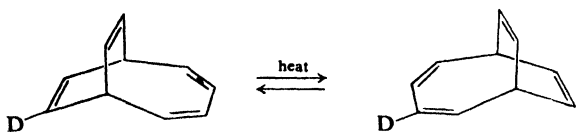
6. (a) The familiar rearrangement of a carbonium ion by a 1,2-alkyl shift is, as we have described it (Sec. 5.22), a concerted reaction. Its ease certainly suggests that it is symmetry-allowed. Discuss the reaction from the standpoint of orbital symmetry. What stereochemistry would you predict in the migrating group?

(b) There is evidence that concerted 1,4-alkyl shifts of the kind

can occur. What stereochemistry would you predict in the migrating group?

7. Discuss the direct, concerted, non-catalytic addition of H_2 to an alkene from the standpoint of orbital symmetry.

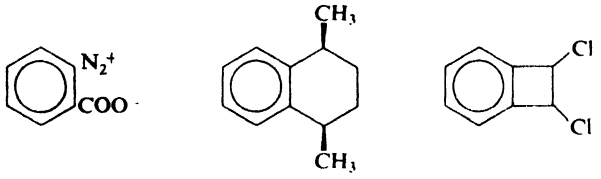
8. The deuterium scrambling between II and III has been accounted for on the basis of intramolecular Diels-Alder and *retro*-Diels-Alder reactions. Show how this might occur. (*Hint:* Look for an intermediate that is symmetrical except for the presence of deuterium.)



II III

9. Suggest an explanation for each of the following facts.

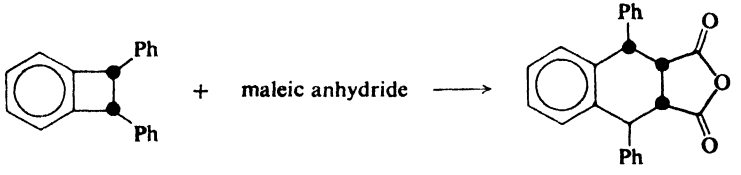
(a) When the diazonium salt IV is treated with *trans,trans*-2,4-hexadiene, N_2 and CO_2 are evolved, and there is obtained stereochemically pure V. (*Hint:* See Problem 18, p. 844.)

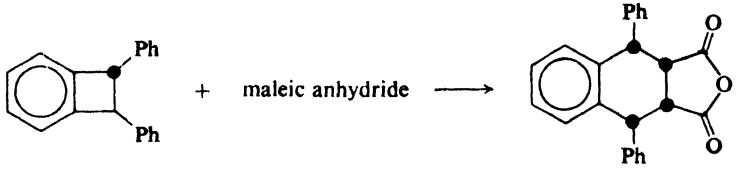


IV *cis*-V VI

(b) In contrast, decomposition of IV in *either cis-* or *trans*-1,2-dichloroethene yields a mixture of *cis-* and *trans*-VI.

10. For each of the following reactions suggest an intermediate that would account for the formation of the product. *Show exact stereochemistry.* (For a hint, see Fig. 29.24, p. 958.)

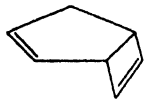




11. (a) The diastereomeric 6,9-dimethylspiro[4.4]nona-1,3-dienes (p. 959) were synthesized by reaction of cyclopentadiene with diastereomeric 2,5-dibromohexanes in the presence of sodium amide. Which 2,5-dibromohexane would you expect to yield each spirane?

(b) The stereochemistry of the spiranes obtained was shown by comparison of their nmr spectra, specifically, of the peaks due to the olefinic hydrogens. Explain.

12. (a) Berson synthesized the stereospecifically labeled compound V (p. 959) by the following sequence. Give structures for compounds M–R.



+ B_2D_6, then H_2O_2 ⟶ M + N (both C_7H_9DO)

M + N $\xrightarrow{\text{oxidation}}$ O + P (both C_7H_7DO), *separated*

O + $LiAl(OBu\text{-}t)_3H$, then $(CH_3CO)_2O$ ⟶ Q + R (both $C_8H_{11}O_2$), *separated*

Q is compound V on p. 959.

(b) Berson's study of the rearrangement of V to VI (p. 959) was complicated by the tendency of VI, once formed, to decompose into cyclopentadiene and vinyl acetate. What kind of reaction is this decomposition?

13. (a) Woodward and Hoffmann have suggested that the *endo* preference in Diels-Alder reactions is a "secondary" effect of orbital symmetry, and there is experimental evidence to support this suggestion. Using the dimerization of butadiene (Fig. 29.19, p. 949) as example, show how these secondary effects could arise. (*Hint:* Draw the orbitals involved and examine the structures closely.)

(b) In contrast, [6 + 4] cycloaddition was predicted to take place in the *exo* sense. This has been confirmed by experiment. Using the reaction of *cis*-1,3,5-hexatriene with 1,3-butadiene as example, show how this prediction could have been made.

14. (a) The sex attractant of the male boll weevil has been synthesized by the following sequence. Give stereochemical structures for compounds S–Y.

ethylene + 3-methyl-2-cyclohexenone $\xrightarrow{h\nu}$ S ($C_9H_{14}O$)

S $\xrightarrow{\text{bromination}}$ T ($C_9H_{13}OBr$)

T + CO_3^{--} ⟶ U ($C_9H_{12}O$)

U + CH_3Li ⟶ V ($C_{10}H_{16}O$), *a single stereoisomer* (*Hint:* Examine structure of U.)

V + IO_4^-/OsO_4 ⟶ W ($C_9H_{14}O_3$), *a carboxylic acid*

W + excess $Ph_3P{=}CH_2$ ⟶ X ($C_{10}H_{16}O_2$) $\xrightarrow{NaAl(OR)_2H_2}$ Y ($C_{10}H_{18}O$), *the sex attractant*

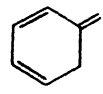
(b) The stereochemistry of the sex attractant was confirmed by the following reaction. Give a stereochemical formula for Z, and show how this confirms the stereochemistry.

Y + $Hg(OAc)_2$, then $NaBH_4$ ⟶ Z ($C_{10}H_{18}O$)

15. (a) Although "Dewar benzene," VII, is less stable by 60 kcal than its isomer benzene, its conversion into benzene is surprisingly slow, with an E_{act} of about 37 kcal. It has a half-life at room temperature of two days; at 90° complete conversion into benzene takes one-half hour.

The high E_{act} for conversion of VII into benzene is attributed to the fact that the reaction is symmetry-forbidden. Explain.

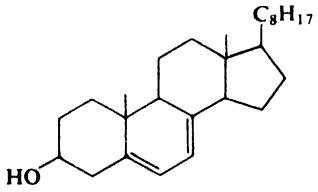
VII



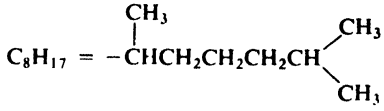
VIII

(b) In Problem 18, p. 883, we outlined the synthesis of VIII. Although much less stable than its aromatic isomer toluene, this compound is surprisingly long-lived. Here, too, the conversion is considered to be symmetry-forbidden. Explain.

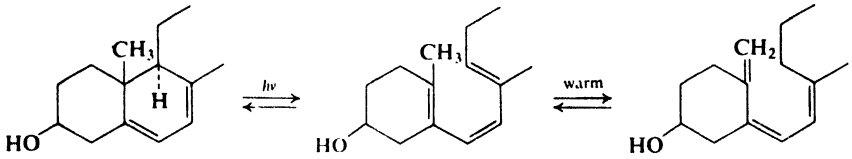
16. (a) In the skin of animals exposed to sunlight, 7-dehydrocholesterol is converted



7-Dehydrocholesterol



into the hormone *cholecalciferol*, the so-called "vitamin" D_3 that plays a vital role in the development of bones. In the laboratory, the following sequence was observed:



7-Dehydrocholesterol Pre-cholecalciferol Cholecalciferol

What processes are actually taking place in these two reactions? Show details.

(b) An exactly analogous reaction sequence is used to convert the plant steroid ergosterol (p. 515) into *ergocalciferol*, the "vitamin" D_2 that is added to milk:

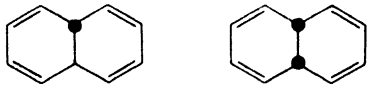
$$\text{ergosterol} \xrightarrow{hv} \text{pre-ergocalciferol} \xrightarrow{\text{warm}} \text{ergocalciferol}$$

What is the structure of pre-ergocalciferol? Of ergocalciferol?

(c) On heating at 190°, pre-ergocalciferol is converted into IX and X, stereoisomers of ergosterol. What reaction is taking place, and what are the structures of IX and X?

(d) Still another stereoisomer of ergosterol, XI, can be converted by ultraviolet light into pre-ergocalciferol. What must XI be?

17. On photolysis at room temperature, *trans*-XII was converted into *cis*-XII. When *trans*-XII was photolyzed at $-190°$, however, no *cis*-XII could be detected in the



trans-XII *cis*-XII

reaction mixture. When *trans*-XII was photolyzed at $-190°$, allowed to warm to room temperature, and then cooled again to $-190°$, *cis*-XII was obtained. If, instead, the low-temperature photolysis mixture was reduced at $-190°$, cyclodecane was formed; reduction of the room-temperature photolysis mixture gave only a trace of cyclodecane.

On the basis of these and other facts, E. E. van Tamelen (of Stanford University) proposed a two-step mechanism, consistent with orbital symmetry theory, for the conversion of *trans*-XII into *cis*-XII.

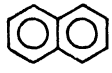
(a) Suggest a mechanism for the transformation. Show how it accounts for the facts.

(b) The intermediate proposed by van Tamelen—never isolated and never before identified—is of considerable theoretical interest. Why? What conclusion do you draw about this compound from the facts?

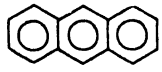
Chapter 30 Polynuclear Aromatic Compounds

30.1 Fused-ring aromatic compounds

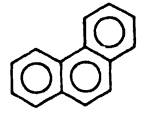
Two aromatic rings that share a pair of carbon atoms are said to be *fused.* In this chapter we shall study the chemistry of the simplest and most important of the fused-ring hydrocarbons, **naphthalene**, $C_{10}H_8$, and look briefly at two others of formula $C_{14}H_{10}$, **anthracene** and **phenanthrene.**



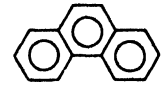
Naphthalene



Anthracene



or



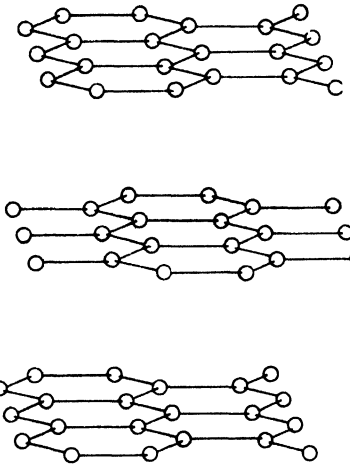
Phenanthrene

Table 30.1 POLYNUCLEAR AROMATIC COMPOUNDS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Naphthalene	80	218	1-Naphthalenesulfonic acid	90	
1,4-Dihydronaphthalene	25	212	2-Naphthalenesulfonic acid	91	
Tetralin	− 30	208	1-Naphthol	96	280
cis-Decalin	− 43	194	2-Naphthol	122	286
trans-Decalin	− 31	185	1,4-Naphthoquinone	125	
1-Methylnaphthalene	− 22	241	Anthracene	217	354
2-Methylnaphthalene	38	240	9,10-Anthraquinone	286	380
1-Bromonaphthalene	6	281	Phenanthrene	101	340
2-Bromonaphthalene	59	281	9,10-Phenanthrenequinone	207	
1-Chloronaphthalene		263	Chrysene	255	
2-Chloronaphthalene	46	265	Pyrene	150	
1-Nitronaphthalene	62	304	1,2-Benzanthracene	160	
2-Nitronaphthalene	79		1,2,5,6-Dibenzanthracene	262	
1-Naphthylamine	50	301	Methylcholanthrene	180	
2-Naphthylamine	113	294			

All three of these hydrocarbons are obtained from coal tar, naphthalene being the most abundant (5%) of all constituents of coal tar.

If diamond (p. 285) is the ultimate polycyclic aliphatic system, then the other allotropic form of elemental carbon, *graphite*, might be considered the ultimate in fused-ring aromatic systems. X-ray analysis shows that the carbon atoms are arranged in layers. Each layer is a continuous network of planar, hexagonal rings; the carbon atoms within a

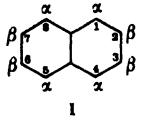


layer are held together by strong, covalent bonds 1.42 A long (only slightly longer than those in benzene, 1.39 A). The different layers, 3.4 A apart, are held to each other by comparatively weak forces. The lubricating properties of graphite (its "greasy" feel) may be due to slipping of layers (with adsorbed gas molecules between) over one another.

NAPHTHALENE

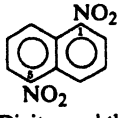
30.2 Nomenclature of naphthalene derivatives

Positions in the naphthalene ring system are designated as in I. Two isomeric

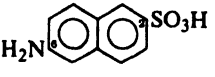


I

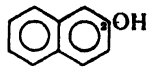
monosubstituted naphthalenes are differentiated by the prefixes 1- and 2-, or α- and β-. The arrangement of groups in more highly substituted naphthalenes is indicated by numbers. For example:



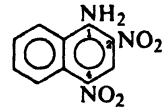
1,5-Dinitronaphthalene



6-Amino-2-naphthalenesulfonic acid



2-Naphthol
β-Naphthol



2,4-Dinitro-1-naphthylamine

Problem 30.1 How many different mononitronaphthalenes are possible? Dinitronaphthalenes? Nitronaphthylamines?

30.3 Structure of naphthalene

Naphthalene is classified as aromatic because its properties resemble those of benzene (see Sec. 10.10). Its molecular formula, $C_{10}H_8$, might lead one to expect a high degree of unsaturation; yet naphthalene is resistant (although less so than benzene) to the addition reactions characteristic of unsaturated compounds. Instead, the typical reactions of naphthalene are electrophilic substitution reactions, in which hydrogen is displaced as hydrogen ion and the naphthalene ring system is preserved. Like benzene, naphthalene is unusually stable: its heat of combustion is 61 kcal lower than that calculated on the assumption that it is aliphatic (see Problem 10.2, p. 323).

From the experimental standpoint, then, naphthalene is classified as aromatic on the basis of its properties. From a theoretical standpoint, naphthalene has the structure required of an aromatic compound: it contains flat six-membered rings, and consideration of atomic orbitals shows that the structure can provide π clouds containing six electrons—the *aromatic sextet* (Fig. 30.1). Ten carbons lie at the

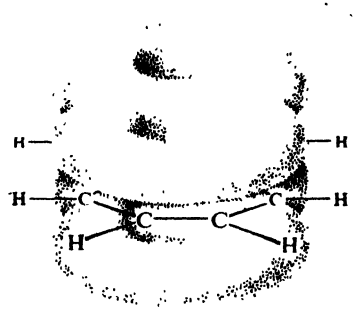
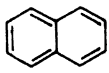
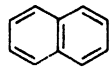


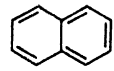
Figure 30.1. Naphthalene molecule. π clouds above and below plane of rings.

corners of two fused hexagons. Each carbon is attached to three other atoms by σ bonds; since these σ bonds result from the overlap of trigonal sp^2 orbitals, all carbon and hydrogen atoms lie in a single plane. Above and below this plane there is a cloud of π electrons formed by the overlap of p orbitals and shaped like a figure 8. We can consider this cloud as two partially overlapping sextets that have a pair of π electrons in common.

In terms of valence bonds, naphthalene is considered to be a resonance hybrid of the three structures I, II, and III. Its resonance energy, as shown by the heat of combustion, is 61 kcal/mole.

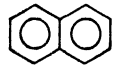

I


II


III

X-ray analysis shows that, in contrast to benzene, all carbon–carbon bonds in naphthalene are not the same; in particular, the C_1—C_2 bond is considerably shorter (1.365 A) than the C_2—C_3 bond (1.404 A). Examination of structures I, II, and III shows us that this difference in bond lengths is to be expected. The C_1—C_2 bond is double in two structures and single in only one; the C_2—C_3 bond is single in two structures and double in only one. We would therefore expect the C_1—C_2 bond to have more double-bond character than single, and the C_2–C_3 bond to have more single-bond character than double.

For convenience, we shall represent naphthalene as the single structure IV,


IV

in which the circles stand for partially overlapping aromatic sextets.

Although representation IV suggests a greater symmetry for naphthalene than exists, it has the advantage of emphasizing the aromatic nature of the system.

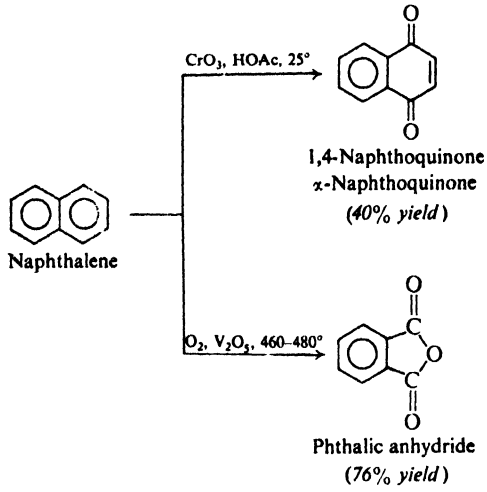
30.4 Reactions of naphthalene

Like benzene, naphthalene typically undergoes electrophilic substitution; this is one of the properties that entitle it to the designation of "aromatic." An electrophilic reagent finds the π cloud a source of available electrons, and attaches itself to the ring to form an intermediate carbonium ion; to restore the stable aromatic system, the carbonium ion then gives up a proton.

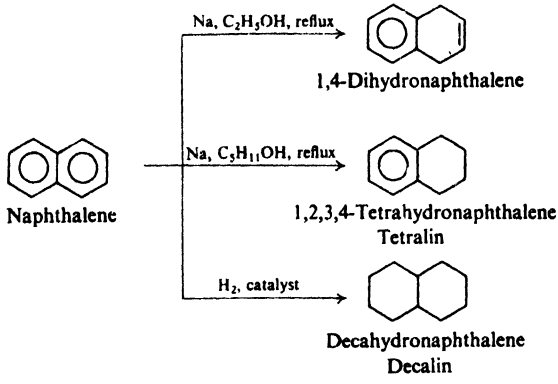
Naphthalene undergoes oxidation or reduction more readily than benzene, but only to the stage where a substituted benzene is formed; further oxidation or reduction requires more vigorous conditions. Naphthalene is stabilized by resonance to the extent of 61 kcal/mole; benzene is stabilized to the extent of 36 kcal/mole. When the aromatic character of one ring of naphthalene is destroyed, only 25 kcal of resonance energy is sacrificed; in the next stage, 36 kcal has to be sacrificed.

REACTIONS OF NAPHTHALENE

1. **Oxidation.** Discussed in Sec. 30.5.

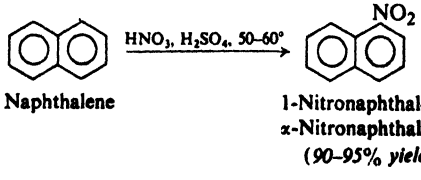


2. **Reduction.** Discussed in Sec. 30.6.

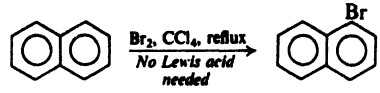


3. **Electrophilic substitution.** Discussed in Secs. 30.8–30.13.

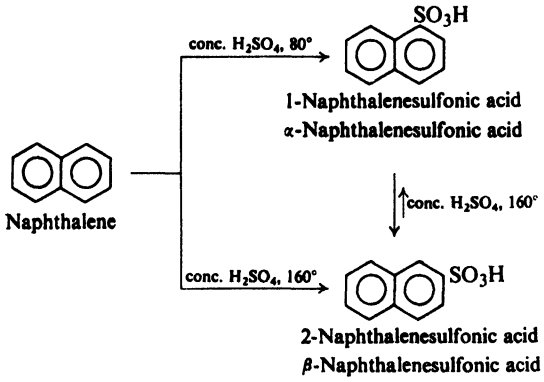
(a) **Nitration.** Discussed in Sec. 30.8.



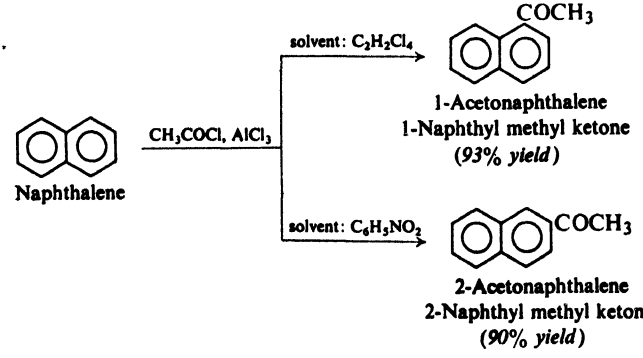
(b) Halogenation. Discussed in Sec. 30.8.



(c) Sulfonation. Discussed in Sec. 30.11.



(d) Friedel-Crafts acylation. Discussed in Sec. 30.10.

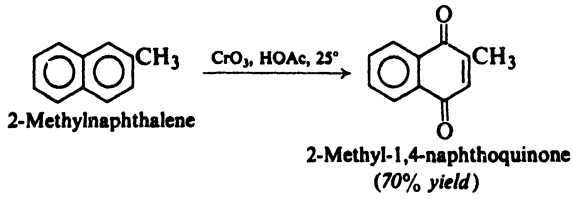


30.5 Oxidation of naphthalene

Oxidation of naphthalene by oxygen in the presence of vanadium pentoxide destroys one ring and yields phthalic anhydride. Because of the availability of naphthalene from coal tar, and the large demand for phthalic anhydride (for example, see Secs. 30.18 and 32.7), this is an important industrial process.

Oxidation of certain naphthalene derivatives destroys the aromatic character

of one ring in a somewhat different way, and yields diketo compounds known as *quinones* (Sec. 27.9). For example:



2-Methylnaphthalene

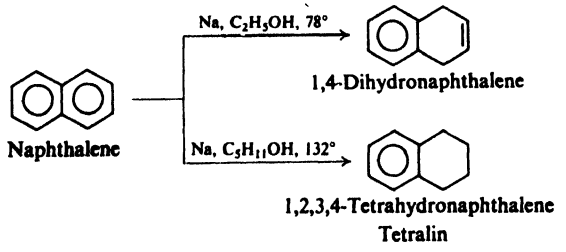
2-Methyl-1,4-naphthoquinone
(*70% yield*)

Because of this tendency to form quinones, it is not always feasible to prepare naphthalenecarboxylic acids as we do benzoic acids, by oxidation of methyl side chains.

Problem 30.2 Show how 1- and 2-naphthalenecarboxylic acids (α- and β-*naphthoic acids*) can be obtained from naphthalene by way of the corresponding acetonaphthalenes.

30.6 Reduction of naphthalene

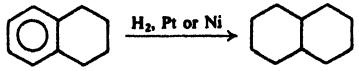
In contrast to benzene, naphthalene can be reduced by chemical reducing agents. It is converted by sodium and ethanol into 1,4-dihydronaphthalene, and by sodium and isopentyl alcohol into 1,2,3,4-tetrahydronaphthalene (*tetralin*). The temperature at which each of these sodium reductions is carried out is the boiling point of the alcohol used; at the higher temperature permitted by isopentyl alcohol (b.p. 132°), reduction proceeds further than with the lower boiling ethyl alcohol (b.p. 78°).



1,4-Dihydronaphthalene

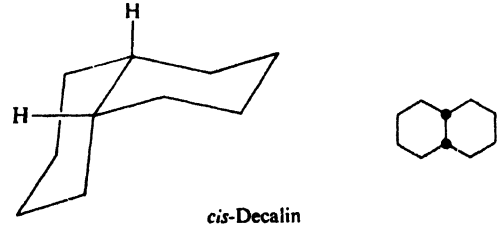
1,2,3,4-Tetrahydronaphthalene
Tetralin

The tetrahydronaphthalene is simply a dialkyl derivative of benzene. As with other benzene derivatives, the aromatic ring that remains is reduced only by vigorous catalytic hydrogenation.

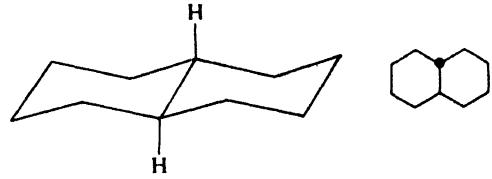


Tetralin Decalin

Problem 30.3 *Decalin* exists in two stereoisomeric forms, *cis*-decalin (b.p. 194°) and *trans*-decalin (b.p. 185°).



cis-Decalin



trans-Decalin

(a) Build models of these compounds and see that they differ from one another. Locate in the models the pair of hydrogen atoms, attached to the fused carbons, that are *cis* or *trans* to each other.

(b) In *trans*-decalin is one ring attached to the other by two equatorial bonds, by two axial bonds, or by one axial bond and one equatorial bond? In *cis*-decalin? Remembering (Sec. 9.12) that an equatorial position gives more room than an axial position for a bulky group, predict which should be the more stable isomer, *cis*- or *trans*-decalin.

(c) Account for the following facts: rapid hydrogenation of tetralin over a platinum black catalyst at low temperatures yields *cis*-decalin, while slow hydrogenation of tetralin over nickel at high temperatures yields *trans*-decalin. Compare this with 1,2- and 1,4-addition to conjugated dienes (Sec. 8.22), Friedel-Crafts alkylation of toluene (Sec. 12.11), sulfonation of phenol (Problem 24.13, p. 803), and sulfonation of naphthalene (Sec. 30.11).

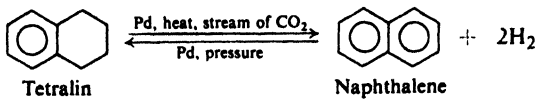
30.7 Dehydrogenation of hydroaromatic compounds. Aromatization

Compounds like 1,4-dihydronaphthalene, tetralin, and decalin, which contain the carbon skeleton of an aromatic system but too many hydrogen atoms for aromaticity, are called *hydroaromatic compounds*. They are sometimes prepared, as we have seen, by partial or complete hydrogenation of an aromatic system.

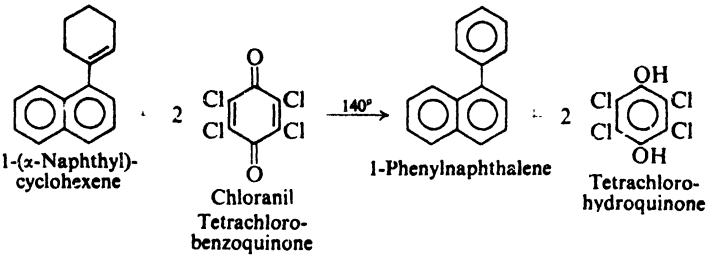
More commonly, however, the process is reversed, and hydroaromatic compounds are converted into aromatic compounds. Such a process is called **aromatization.**

One of the best methods of aromatization is **catalytic dehydrogenation,** accomplished by heating the hydroaromatic compound with a catalyst like platinum, palladium, or nickel. We recognize these as the catalysts used for hydrogenation; since they lower the energy barrier between hydrogenated and dehydrogenated compounds, they speed up reaction in *both* directions (see Sec. 6.3). The position of the equilibrium is determined by other factors: hydrogenation is

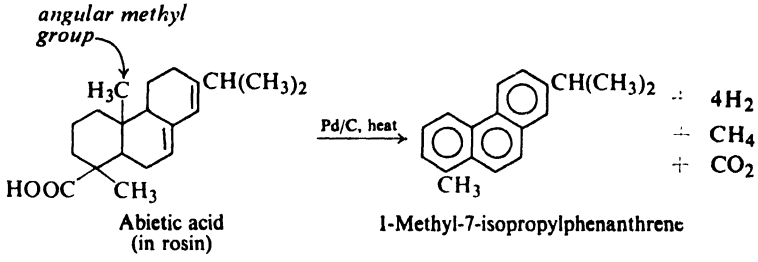
favored by an excess of hydrogen under pressure; dehydrogenation is favored by sweeping away the hydrogen in a stream of inert gas. For example:



In an elegant modification of dehydrogenation, hydrogen is *transferred* from the hydroaromatic compound to a compound that readily accepts hydrogen. For example:



The tendency to form the stable aromatic system is so strong that, when necessary, groups can be eliminated: for example, a methyl group located at the point of fusion between two rings, a so-called *angular methyl group* (Sec. 15.16).

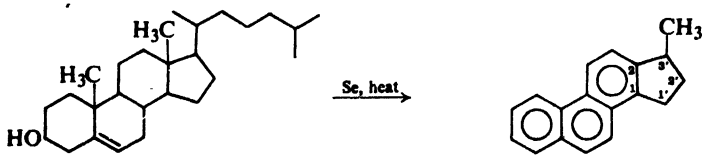


Aromatization has also been accomplished by heating hydroaromatic compounds with selenium, sulfur, or organic disulfides, RSSR. Here hydrogen is eliminated as H_2Se, H_2S, or RSH.

Problem 30.4 In a convenient laboratory preparation of dry hydrogen bromide, Br_2 is dripped into boiling tetralin; the vapors react to form naphthalene and four moles of hydrogen bromide Account, step by step, for the formation of these products. What familiar reactions are involved in this aromatization?

Aromatization is important in both *synthesis* and *analysis*. Many polynuclear aromatic compounds are made from open-chain compounds by ring closure; the last step in such a synthesis is aromatization (see, for example, Secs. 30.14, 30.19, and 31.13). Many naturally occurring substances are hydroaromatic;

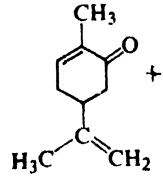
conversion into identifiable aromatic compounds gives important information about their structures. For example:



Cholesterol: a steroid
Occurs in all animal tissues

3'-Methyl-1,2-cyclopentenophenanthrene
(Diels' hydrocarbon)

Problem 30.5 *Cadinene*, $C_{15}H_{24}$, is found in oil of cubebs. Dehydrogenation with sulfur converts cadinene into *cadalene*, $C_{15}H_{18}$, which can be synthesized from *carvone* by the following sequence:



Carvone

$$+ \ BrCH_2COOC_2H_5 \ + \ Zn \longrightarrow A \ (C_{14}H_{22}O_3)$$

$$A + \text{acid} \xrightarrow{\text{heat}} [B] \xrightarrow{\text{isomerization}} C \ (C_{12}H_{16}O_2), \textit{ a benzene derivative}$$

$$C + C_2H_5OH + H_2SO_4 \longrightarrow D \ (C_{14}H_{20}O_2)$$

$$D + \text{Na} + \text{alcohol} \longrightarrow E \ (C_{12}H_{18}O) \xrightarrow{HBr} F \ (C_{12}H_{17}Br)$$

$$F + CH_3C(COOC_2H_5)_2^-Na^+ \longrightarrow G \ (C_{20}H_{30}O_4)$$

$$G + H_2SO_4 \xrightarrow{\text{heat}} H \ (C_{15}H_{22}O_2) \xrightarrow{SOCl_2} I \ (C_{15}H_{21}OCl)$$

$$I + AlCl_3 \longrightarrow J \ (C_{15}H_{20}O) \xrightarrow{H_2, Ni} K \ (C_{15}H_{22}O)$$

$$K + \text{sulfur} \xrightarrow{\text{strong heating}} \text{cadalene}$$

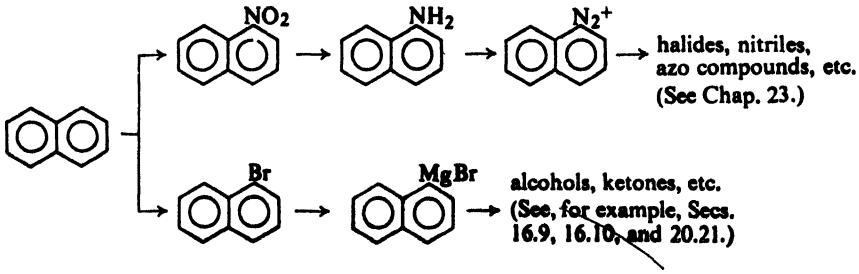
(a) What is the structure and systematic name of cadalene? (b) What is a likely carbon skeleton for cadinene?

30.8 Nitration and halogenation of naphthalene

Nitration and halogenation of naphthalene occur almost exclusively in the 1-position. Chlorination or bromination takes place so readily that a Lewis acid is not required for catalysis.

As we would expect, introduction of these groups opens the way to the preparation of a series of *alpha*-substituted naphthalenes: from 1-nitronaphthalene via the amine and diazonium salts, and from 1-bromonaphthalene via the Grignard reagent.

Synthesis of α-substituted naphthalenes



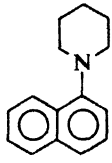
Problem 30.6 Starting with 1-nitronaphthalene, and using any inorganic or aliphatic reagents, prepare:

(a) 1-naphthylamine
(b) α-iodonaphthalene
(c) α-naphthonitrile
(d) α-naphthoic acid (1-naphthalenecarboxylic acid)
(e) α-naphthoyl chloride
(f) 1-naphthyl ethyl ketone
(g) 1-(aminomethyl)naphthalene, $C_{10}H_7CH_2NH_2$
(h) 1-(*n*-propyl)naphthalene
(i) α-naphthaldehyde
(j) (1-naphthyl)methanol
(k) 1-chloromethylnaphthalene
(l) (1-naphthyl)acetic acid
(m) N-(1-naphthyl)acetamide

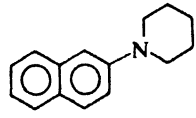
Problem 30.7 Starting with 1-bromonaphthalene, and using any inorganic or aliphatic reagents, prepare:

(a) 1-naphthylmagnesium bromide
(b) α-naphthoic acid (1-naphthalenecarboxylic acid)
(c) 2-(1-naphthyl)-2-propanol (dimethyl-1-naphthylcarbinol)
(d) 1-isopropylnaphthalene
(e) 1-naphthylcarbinol (1-$C_{10}H_7CH_2OH$)
(f) methyl-1-naphthylcarbinol (1-(1-naphthyl)ethanol)
(g) 2-(1-naphthyl)ethanol

Problem 30.8 (a) When 1-chloronaphthalene is treated with sodium amide, $Na^+NH_2^-$, in the secondary amine *piperidine* (Sec. 31.12), there is obtained not only I but also II,



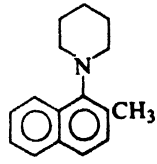
I



II

in the ratio of 1:2. Similar treatment of 1-bromo- or 1-iodonaphthalene yields the same products *and in the same* 1:2 *ratio*. Show all steps in a mechanism that accounts for these observations. Can you suggest possible factors that might tend to favor II over I?

(b) Under the conditions of part (a), 1-fluoro-2-methylnaphthalene reacts to



III

yield III. By what mechanism must this reaction proceed?

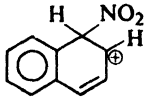
(c) Under the conditions of part (a), 1-fluoronaphthalene yields I and II, but in the ratio of 3:2. How do you account for this different ratio of products? What two factors make the fluoronaphthalene behave differently from the other halonaphthalenes?

30.9 Orientation of electrophilic substitution in naphthalene

Nitration and halogenation of naphthalene take place almost exclusively in the α-position. Is this orientation of substitution what we might have expected?

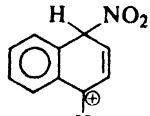
In our study of electrophilic substitution in the benzene ring (Chap. 11), we found that we could account for the observed orientation on the following basis: (a) the controlling step is the attachment of an electrophilic reagent to the aromatic ring to form an intermediate carbonium ion; and (b) this attachment takes place in such a way as to yield the most stable intermediate carbonium ion. Let us see if this approach can be applied to the nitration of naphthalene.

Attack by nitronium ion at the α-position of naphthalene yields an intermediate carbonium ion that is a hybrid of structures I and II in which the positive charge is accommodated by the ring under attack, and several structures like III in which the charge is accommodated by the other ring.



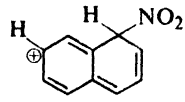
I

More stable:
aromatic sextet preserved



II

More stable:
aromatic sextet preserved

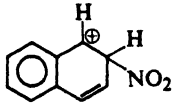


III

Less stable:
aromatic sextet disrupted

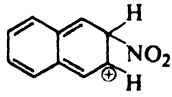
Alpha attack

Attack at the β-position yields an intermediate carbonium ion that is a hybrid of IV and V in which the positive charge is accommodated by the ring under attack, and several structures like VI in which the positive charge is accommodated by the other ring.



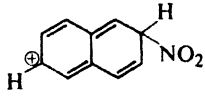
IV

More stable:
aromatic sextet preserved



V

Less stable:
aromatic sextet disrupted



VI

Less stable:
aromatic sextet disrupted

Beta attack

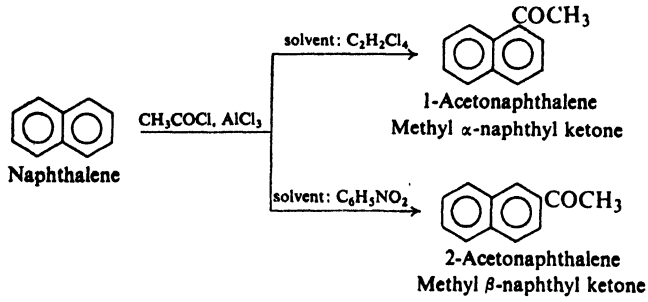
In structures I, II, and IV, the aromatic sextet is preserved in the ring that is not under attack; these structures thus retain the full resonance stabilization of one benzene ring (36 kcal/mole). In structures like III, V, and VI, on the other hand, the aromatic sextet is disrupted in both rings, with a large sacrifice of resonance stabilization. Clearly, structures like I, II, and IV are much the more stable.

But there are two of these stable contributing structures (I and II) for attack at the α-position and only one (IV) for attack at the β-position. On this basis we would expect the carbonium ion resulting from attack at the α-position (and also the transition state leading to that ion) to be much more stable than the carbonium ion (and the corresponding transition state) resulting from attack at the β-position, and that nitration would therefore occur much more rapidly at the α-position.

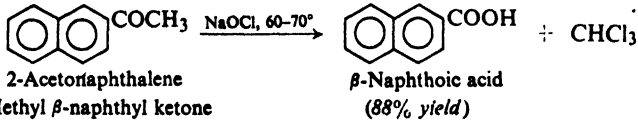
Throughout our study of polynuclear hydrocarbons, we shall find that the matter of orientation is generally understandable on the basis of this principle: of the large number of structures contributing to the intermediate carbonium ion, the important ones are those that require the smallest sacrifice of resonance stabilization. Indeed, we shall find that this principle accounts for orientation not only in electrophilic substitution but also in oxidation, reduction, and addition.

30.10 Friedel-Crafts acylation of naphthalene

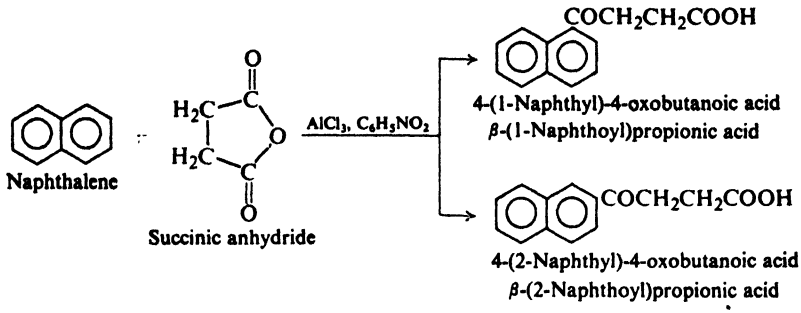
Naphthalene can be acetylated by acetyl chloride in the presence of aluminum chloride. The orientation of substitution is determined by the particular solvent used: predominantly *alpha* in carbon disulfide or solvents like tetrachloroethane, predominantly *beta* in nitrobenzene. (The effect of nitrobenzene has been attributed to its forming a complex with the acid chloride and aluminum chloride which, because of its bulkiness, attacks the roomier *beta* position.)



Thus acetylation (as well as sulfonation, Sec. 30.11) affords access to the *beta* series of naphthalene derivatives. Treatment of 2-acetonaphthalene with hypohalite, for example, provides the best route to β-naphthoic acid.



Acylation of naphthalene by succinic anhydride yields a mixture of *alpha* and *beta* products. These are separable, however, and both are of importance in the synthesis of higher ring systems (see Sec. 30.19).



Friedel-Crafts alkylation of naphthalene is of little use, probably for a combination of reasons: the high reactivity of naphthalene which causes side reactions and polyalkylations, and the availability of alkylnaphthalenes via acylation or ring closure (Sec. 30.14).

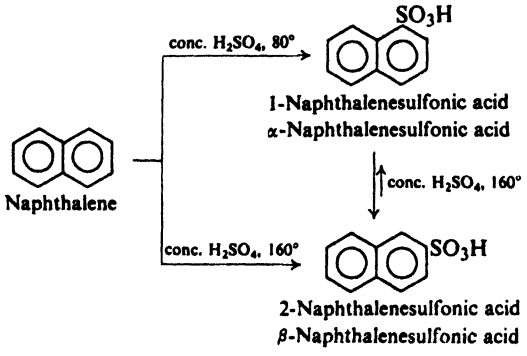
Problem 30.9 The position of the —COOH in β-naphthoic acid was shown by vigorous oxidation and identification of the product. What was this product? What product would have been obtained from α-naphthoic acid?

Problem 30.10 Outline the synthesis of the following compounds via an initial acylation:

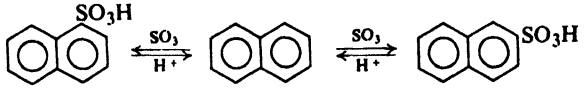
(a) 2-ethylnaphthalene
(b) methylethyl-2-naphthylcarbinol (2-(2-naphthyl)-2-butanol)
(c) 2-(*sec*-butyl)naphthalene
(d) 1-(2-naphthyl)ethanol
(e) γ-(2-naphthyl)butyric acid
(f) 4-(2-naphthyl)-1-butanol
(g) 5-(2-naphthyl)-2-methyl-2-pentanol
(h) 2-isohexylnaphthalene
(i) 1-amino-1-(2-naphthyl)ethane
(j) β-vinylnaphthalene

30.11 Sulfonation of naphthalene

Sulfonation of naphthalene at 80° yields chiefly 1-naphthalenesulfonic acid; sulfonation at 160° or higher yields chiefly 2-naphthalenesulfonic acid. When 1-naphthalenesulfonic acid is heated in sulfuric acid at 160°, it is largely converted into the 2-isomer. These facts become understandable when we recall that sulfonation is readily reversible (Sec. 11.12).



Sulfonation, like nitration and halogenation, occurs more rapidly at the α-position, since this involves the more stable intermediate carbonium ion. But, for the same reason, attack by hydrogen ion, with subsequent desulfonation, also occurs more readily at the α-position. Sulfonation at the β-position occurs more slowly but, once formed, the β-sulfonic acid tends to resist desulfonation. At low temperatures desulfonation is slow and we isolate the product that is formed faster, the *alpha* naphthalenesulfonic acid. At higher temperatures, desulfonation becomes important, equilibrium is more readily established, and we isolate the product that is more stable, the *beta* naphthalenesulfonic acid.



α-Isomer
Formed rapidly; desulfonated rapidly

β-Isomer
Formed slowly; desulfonated slowly

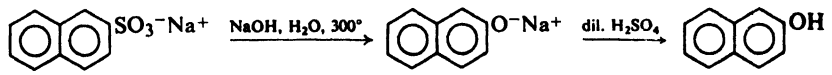
We see here a situation exactly analogous to one we have encountered several times before: in 1,2- and 1,4-addition to conjugated dienes (Sec. 8.22), in Friedel-Crafts alkylation of toluene (Sec. 12.11), and in sulfonation of phenols (Problem 24.13, p. 803). At low temperatures the controlling factor is *rate of reaction*, at high temperatures, *position of equilibrium*.

Sulfonation is of special importance in the chemistry of naphthalene because it gives access to the *beta*-substituted naphthalenes, as shown in the next section.

Problem 30.11 (a) Show all steps in the sulfonation and desulfonation of naphthalene. (b) Draw a potential energy curve for the reactions involved. (Compare your answer with Fig. 8.8, p. 272.)

30.12 Naphthols

Like the phenols we have already studied, naphthols can be prepared from the corresponding sulfonic acids by fusion with alkali. Naphthols can also be made

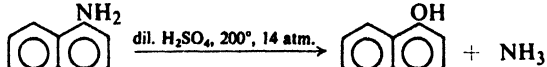


Sodium 2-naphthalenesulfonate

Sodium 2-naphthoxide

2-Naphthol β-Naphthol

from the naphthylamines by direct hydrolysis under acidic conditions. (This reaction, which does not work in the benzene series, is superior to hydrolysis of diazonium salts.)

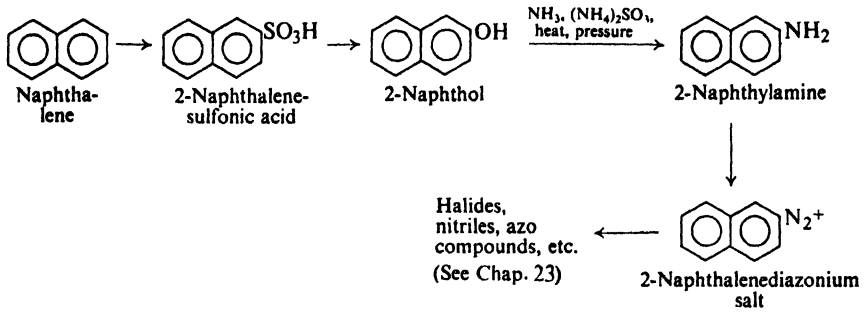


1-Naphthylamine

1-Naphthol
α-Naphthol
(95% yield)

The α-substituted naphthalenes, like substituted benzenes, are most commonly prepared by a sequence of reactions that ultimately goes back to a nitro compound (Sec. 30.8). Preparation of β-substituted naphthalenes, on the other hand, cannot start with the nitro compound, since nitration does not take place in the β-position. The route to β-naphthylamine, and through it to the versatile diazonium salts, lies through β-naphthol. β-Naphthol is made from the β-sulfonic acid; it is converted into β-naphthylamine when heated under pressure with ammonia and ammonium sulfite (the **Bucherer reaction**, not useful in the benzene series except in rare cases).

Synthesis of β-substituted naphthalenes



Naphthols undergo the usual reactions of phenols. Coupling with diazonium salts is particularly important in dye manufacture (see Sec. 23.17); the orientation of this substitution is discussed in the following section.

Problem 30.12 Starting from naphthalene, and using any readily available reagents, prepare the following compounds:

(a) 2-bromonaphthalene
(b) 2-fluoronaphthalene
(c) β-naphthonitrile
(d) β-naphthoic acid
(e) β-naphthaldehyde
(f) 3-(2-naphthyl)propenoic acid

Problem 30.13 Diazonium salts can be converted into nitro compounds by treatment with sodium nitrite, usually in the presence of a catalyst. Suggest a method for preparing 2-nitronaphthalene.

30.13 Orientation of electrophilic substitution in naphthalene derivatives

We have seen that naphthalene undergoes nitration and halogenation chiefly at the α-position, and sulfonation and Friedel-Crafts acylation at either the α- or β-position, depending upon conditions. Now, to what position will a *second* substituent attach itself, and how is the orientation influenced by the group already present?

Orientation of substitution in the naphthalene series is more complicated than in the benzene series. An entering group may attach itself either to the ring that already carries the first substituent, or to the other ring; there are seven different

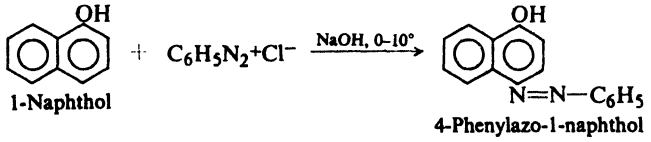
positions open to attack, in contrast to only three positions in a monosubstituted benzene.

The major products of further substitution in a monosubstituted naphthalene can usually be predicted by the following rules. As we shall see, these rules are reasonable ones in light of structural theory and our understanding of electrophilic aromatic substitution.

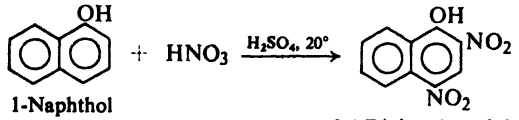
(a) An activating group (electron-releasing group) tends to direct further substitution into the same ring. An activating group in position 1 directs further substitution to position 4 (and, to a lesser extent, to position 2). An activating group in position 2 directs further substitution to position 1.

(b) A deactivating group (electron-withdrawing group) tends to direct further substitution into the other ring: at an α-position in nitration or halogenation, or at an α- or β-position (depending upon temperature) in sulfonation.

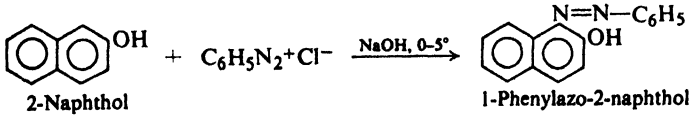
For example:



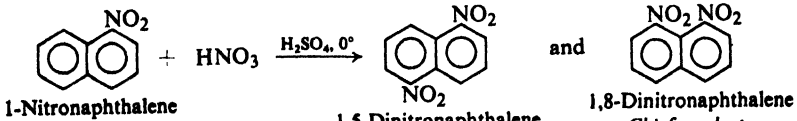
1-Naphthol 4-Phenylazo-1-naphthol



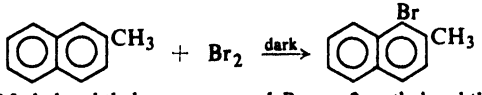
1-Naphthol 2,4-Dinitro-1-naphthol



2-Naphthol 1-Phenylazo-2-naphthol



1-Nitronaphthalene 1,5-Dinitronaphthalene and 1,8-Dinitronaphthalene *Chief product*



2-Methylnaphthalene 1-Bromo-2-methylnaphthalene

These rules do not always hold in sulfonation, because the reaction is reversible and at high temperatures tends to take place at a β-position. However, the observed products can usually be accounted for if this feature of sulfonation is kept in mind.

Problem 30.14 Predict the orientation in each of the following reactions, giving structural formulas and names for the predicted products:

(a) 1-methylnaphthalene + Br_2
(b) 1-methylnaphthalene + HNO_3 + H_2SO_4
(c) 1-methylnaphthalene + CH_3COCl + $AlCl_3$
(d) the same as (a), (b), and (c) for 2-methylnaphthalene
(e) 2-nitronaphthalene + Br_2
(f) 2-methoxynaphthalene + Br_2

Problem 30.15 How do you account for the following observed orientations?

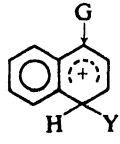
(a) 2-methoxynaphthalene + CH_3COCl + $AlCl_3$ + CS_2 $\longrightarrow$ 1-aceto compound
(b) 2-methoxynaphthalene + CH_3COCl + $AlCl_3$ + $C_6H_5NO_2$ $\longrightarrow$ 6-aceto compound
(c) 2-methylnaphthalene + H_2SO_4 above 100° $\longrightarrow$ 6-sulfonic acid
(d) 2,6-dimethylnaphthalene + H_2SO_4 at 40° $\longrightarrow$ 8-sulfonic acid
(e) 2,6-dimethylnaphthalene + H_2SO_4 + 140° $\longrightarrow$ 3-sulfonic acid
(f) 2-naphthalenesulfonic acid + HNO_3 + H_2SO_4 $\longrightarrow$ 5-nitro and 8-nitro compounds

Problem 30.16 Give the steps for the synthesis of each of the following from naphthalene and any needed reagents:

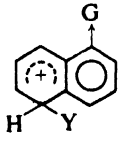
(a) 4-nitro-1-naphthylamine
(b) 1,4-dinitronaphthalene
(*Hint:* See Problem 30.13, p. 982.)
(c) 2,4-dinitro-1-naphthylamine
(d) 1,3-dinitronaphthalene
(e) 1,2-dinitronaphthalene
(f) 4-amino-1-naphthalenesulfonic acid (*naphthionic acid*)
(g) 8-amino-1-naphthalenesulfonic acid
(h) 5-amino-2-naphthalenesulfonic acid
(i) 8-amino-2-naphthalenesulfonic acid

We have seen (Sec. 30.9) that orientation in naphthalene can be accounted for on the same basis as orientation in substituted benzenes: formation of the more stable intermediate carbonium ion. In judging the relative stabilities of these naphthalene carbonium ions, we have considered that those in which an aromatic sextet is preserved are by far the more stable and hence the more important. Let us see if we can account for orientation in substituted naphthalenes in the same way.

The structures preserving an aromatic sextet are those in which the positive charge is carried by the ring under attack; it is in this ring, therefore, that the charge chiefly develops. Consequently, attack occurs most readily on whichever ring can best accommodate the positive charge: the ring that carries an electron-releasing (activating) group or the ring that does *not* carry an electron-withdrawing (deactivating) group. (We have arrived at the quite reasonable conclusion that a substituent exerts its greatest effect—activating or deactivating—on the ring to which it is attached.)

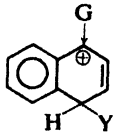


G is electron-releasing: activating, attack in same ring

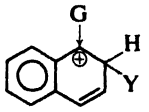


G is electron-withdrawing: deactivating, attack in other ring

An electron-releasing group located at position 1 can best help accommodate the positive charge if attack occurs at position 4 (or position 2), through the contribution of structures like I and II.



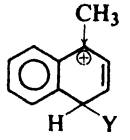
I

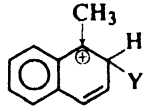


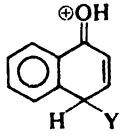
II

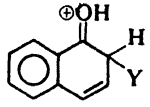
G is electron-releasing: when on position 1, it directs attack to positions 4 or 2

This is true whether the group releases electrons by an inductive effect or by a resonance effect. For example:

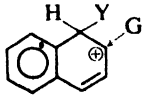






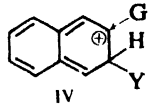


An electron-releasing group located at position 2 could help accommodate the positive charge if attack occurred at position 1 (through structures like III), or if attack occurred at position 3 (through structures like IV).



III

More stable: aromatic sextet preserved



IV

Less stable: aromatic sextet disrupted

G is electron-releasing: when on position 2, it directs attack to position 1

However, we can see that only the structures like III preserve an aromatic sextet; these are much more stable than the structures like IV, and are the important ones. It is not surprising, therefore, that substitution occurs almost entirely at position 1.

30.14 Synthesis of naphthalene derivatives by ring closure. The Haworth synthesis

Derivatives of benzene, we have seen, are almost always prepared from a compound that already contains the benzene ring: benzene itself or some simple

substituted benzene. One seldom generates the benzene ring in the course of a synthesis.

While compounds containing other aromatic ring systems, too, are often prepared from the parent hydrocarbon, there are important exceptions: syntheses in which the ring system, or part of it, is actually generated. Such syntheses usually involve two stages: **ring closure** (or **cyclization**) and **aromatization**.

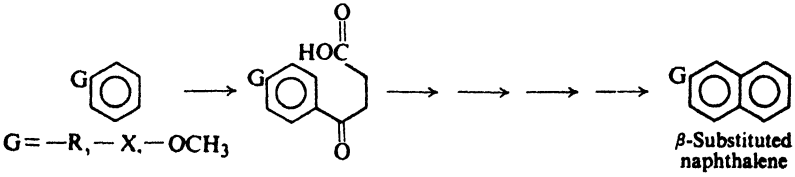
As an example, let us look at just one method used to make certain naphthalene derivatives: the **Haworth synthesis** (developed by R. D. Haworth at the University of Durham, England). Figure 30.2 (p. 987) shows the basic scheme, which would yield naphthalene itself (not, of course, actually prepared in this way).

All the steps are familiar ones. The reaction in which the second ring is formed is simply Friedel-Crafts acylation that happens to involve two parts of the same molecule. Like many methods of ring closure, this one does not involve a new reaction, but merely an adaptation of an old one.

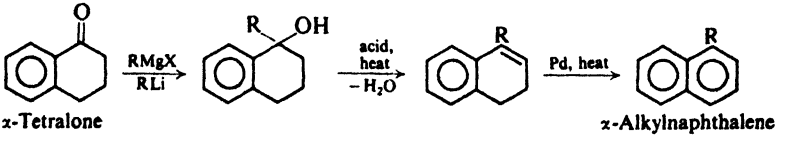
Problem 30.17 Why is ring closure possible after the first Clemmensen reduction but not before?

To obtain substituted naphthalenes, the basic scheme can be modified in any or all of the following ways:

(a) A substituted benzene can be used in place of benzene and a β-substituted naphthalene obtained. Toluene or anisole or bromobenzene, for example, undergoes the initial Friedel-Crafts reaction chiefly at the *para* position; when the ring is closed, the substituent originally on the benzene ring must occupy a β-position in naphthalene.



(b) The intermediate cyclic ketone (an α-tetralone) can be treated with a Grignard reagent, and an alkyl (or aryl) group introduced into an α-position.



(c) The original keto acid (in the form of its ester) can be treated with a Grignard reagent, and an alkyl (or aryl) group introduced into an α-position.

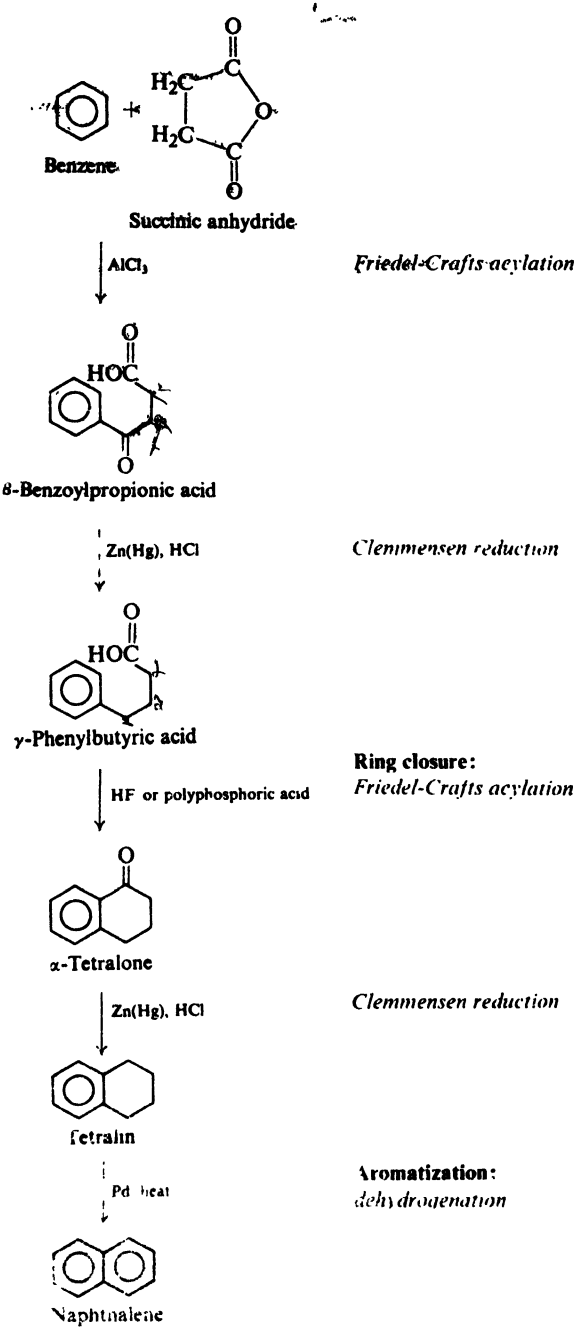
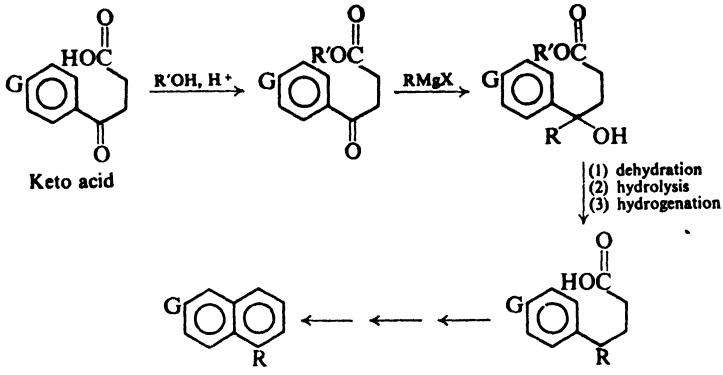


Figure 30.2. Haworth synthesis of naphthalene derivatives.

The success of this reaction depends upon the fact that a ketone reacts much faster than an ester with a Grignard reagent.



Keto acid

1,6-Disubstituted naphthalene

By proper combinations of these modifications, a wide variety of substituted naphthalenes can be prepared.

Problem 30.18 Outline all steps in the synthesis of the following compounds, starting from benzene and using any necessary aliphatic and inorganic reagents:

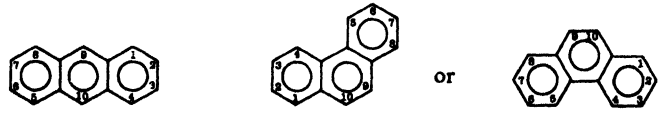
(a) 2-methylnaphthalene
(b) 1-methylnaphthalene
(c) 1,4-dimethylnaphthalene
(d) 1,7-dimethylnaphthalene
(e) 1,6-dimethylnaphthalene
(f) 1,4,6-trimethylnaphthalene
(g) 1-ethyl-4-methylnaphthalene
(h) 7-bromo-1-ethylnaphthalene
(i) 1-phenylnaphthalene

Problem 30.19 Outline the Haworth sequence of reactions, starting with naphthalene and succinic anhydride. What is the final hydrocarbon or hydrocarbons? (Remember the orientation rules for naphthalene.) Check your answer in Sec. 30.19.

ANTHRACENE AND PHENANTHRENE

30.15 Nomenclature of anthracene and phenanthrene derivatives

The positions in anthracene and phenanthrene are designated by numbers as shown:



Anthracene Phenanthrene

Examples are found in the various reactions that follow.

30.16 Structure of anthracene and phenanthrene

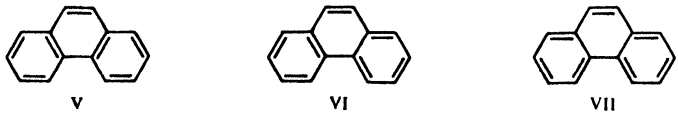
Like naphthalene, anthracene and phenanthrene are classified as aromatic on the basis of their properties. Consideration of atomic orbitals follows the same pattern as for naphthalene, and leads to the same kind of picture: a flat structure with partially overlapping π clouds lying above and below the plane of the molecule.

In terms of valence bonds, anthracene is considered to be a hybrid of structures I–IV,

I II III IV

Anthracene

and phenanthrene, a hybrid of structures V–IX. Heats of combustion indicate



V VI VII

VIII IX

Phenanthrene

that anthracene has a resonance energy of 84 kcal/mole, and that phenanthrene has a resonance energy of 92 kcal/mole.

For convenience we shall represent anthracene as the single structure X, and phenanthrene as XI, in which the circles can be thought of as representing partially overlapping aromatic sextets.

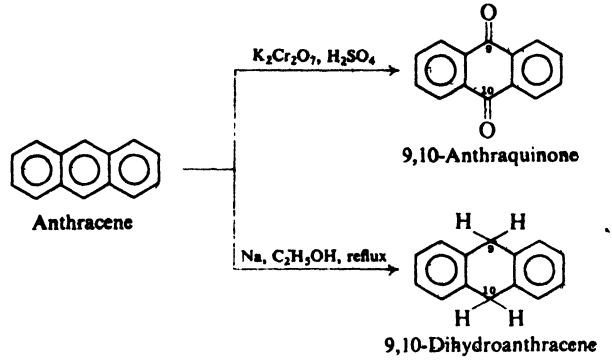
X XI

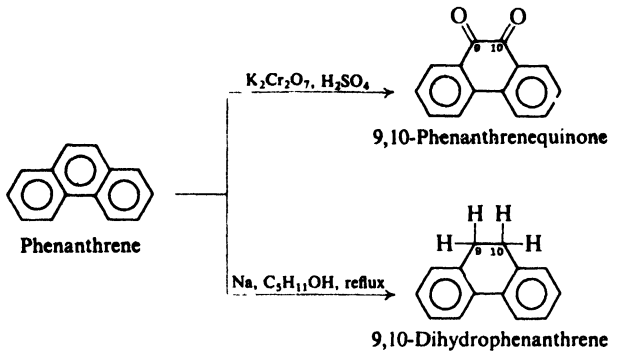
Anthracene Phenanthrene

30.17 Reactions of anthracene and phenanthrene

Anthracene and phenanthrene are even less resistant toward oxidation or reduction than naphthalene. Both hydrocarbons are oxidized to the 9,10-quinones and reduced to the 9,10-dihydro compounds. Both the orientation of these reactions and the comparative ease with which they take place are understandable on the basis of the structures involved. Attack at the 9- and 10-positions leaves two

benzene rings intact; thus there is a sacrifice of only 12 kcal of resonance energy (84 − 2 × 36) for anthracene, and 20 kcal (92 − 2 × 36) for phenanthrene.





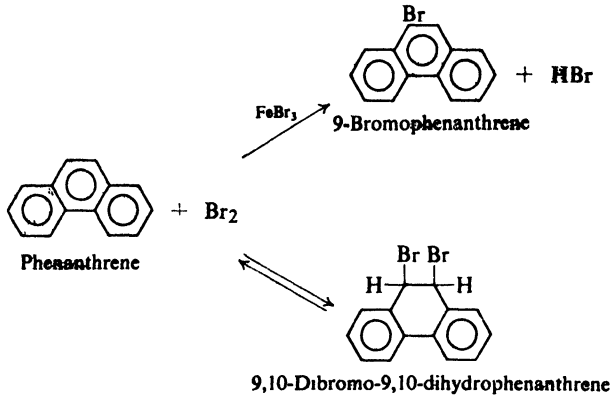
(In the case of phenanthrene, the two remaining rings are conjugated; to the extent that this conjugation stabilizes the product—estimated at anywhere from 0 to 8 kcal/mole—the sacrifice is even less than 20 kcal.)

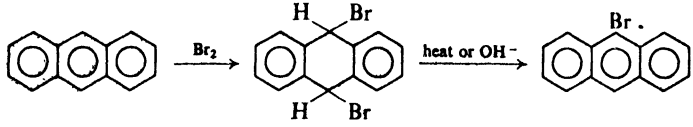
Problem 30.20 How much resonance energy would be sacrificed by oxidation or reduction of one of the outer rings of anthracene? Of phenanthrene?

Both anthracene and phenanthrene undergo electrophilic substitution. With a few exceptions, however, these reactions are of little value in synthesis because of the formation of mixtures and polysubstitution products. Derivatives of these two hydrocarbons are usually obtained in other ways: by electrophilic substitution in 9,10-anthraquinone or 9,10-dihydrophenanthrene, for example, or by ring closure methods (Secs. 30.18 and 30.19).

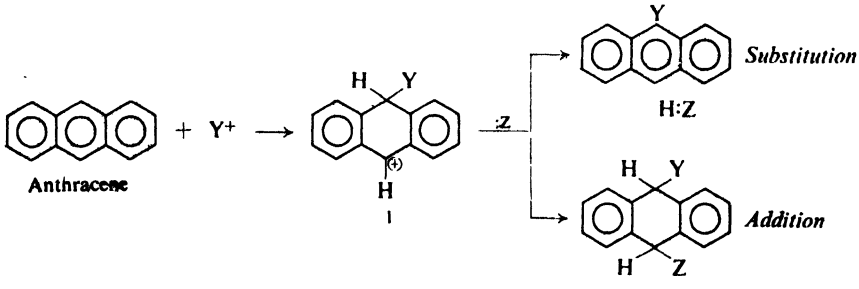
Bromination of anthracene or phenanthrene takes place at the 9-position. (9-Bromophenanthrene is a useful intermediate for the preparation of certain 9-substituted phenanthrenes.) In both cases, especially for anthracene, there is a

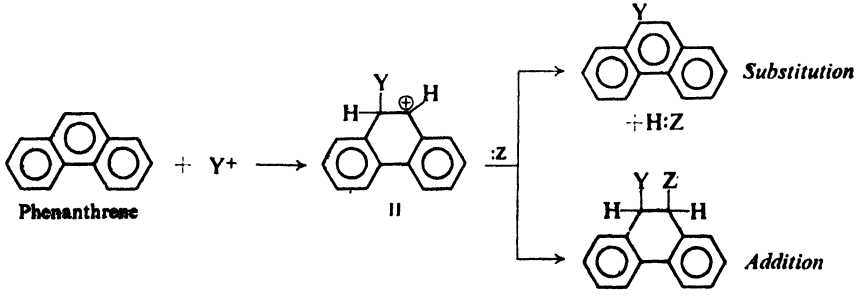
tendency for addition to take place with the formation of the 9,10-dibromo-9,10-dihydro derivatives.





This reactivity of the 9- and 10-positions toward electrophilic attack is understandable, whether reaction eventually leads to substitution or addition. The carbonium ion initially formed is the most stable one, I or II, in which aromatic

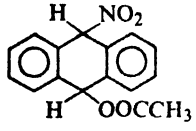




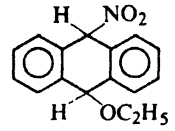
sextets are preserved in two of the three rings. This carbonium ion can then either (a) give up a proton to yield the substitution product, or (b) accept a base to yield the addition product. The tendency for these compounds to undergo addition is undoubtedly due to the comparatively small sacrifice in resonance energy that this entails (12 kcal/mole for anthracene, 20 kcal/mole or less for phenanthrene).

Problem 30.21 Nitric acid converts anthracene into any of a number of products, III–VI, depending upon the exact conditions. How could each be accounted for?

(a) Nitric acid and acetic acid yields III
(b) Nitric acid and ethyl alcohol yields IV
(c) Excess nitric acid yields V
(d) Nitric acid and acetic anhydride yields 9-nitroanthracene (VI)



III



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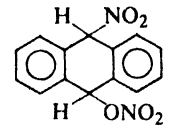

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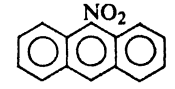


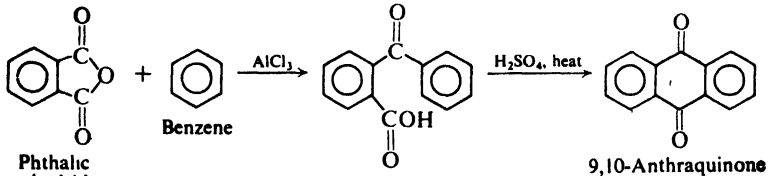
VI

Problem 30.22 Account for the following observations: (a) Upon treatment with hydrogen and nickel, 9,10-dihydroanthracene yields 1,2,3,4-tetrahydroanthracene. (b) In contrast to bromination, sulfonation of anthracene yields the 1-sulfonic acid.

30.18 Preparation of anthracene derivatives by ring closure. Anthraquinones

Derivatives of anthracene are seldom prepared from anthracene itself, but rather by ring-closure methods. As in the case of naphthalene, the most important method of ring closure involves adaptation of Friedel-Crafts acylation. The products initially obtained are **anthraquinones**, which can be converted into corresponding anthracenes by reduction with zinc and alkali. This last step is seldom carried out, since the quinones are by far the more important class of compounds.

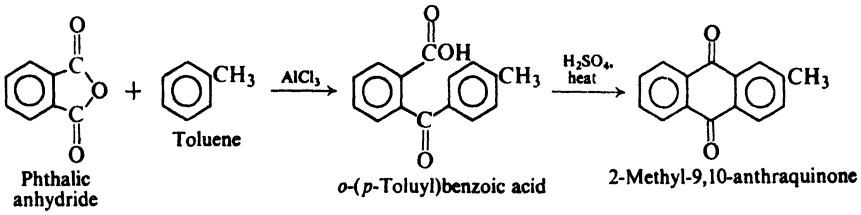
The following reaction sequence shows the basic scheme. (Large amounts of anthraquinones are manufactured for the dye industry in this way.)



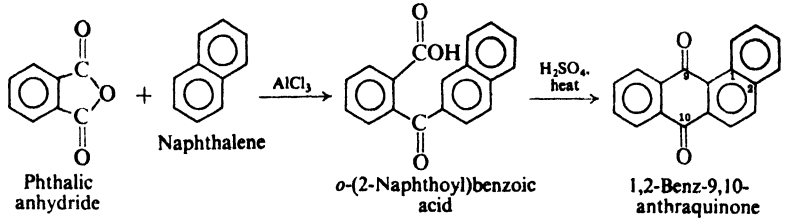
The basic scheme can be modified in a number of ways.

(a) A monosubstituted benzene can be used in place of benzene, and a

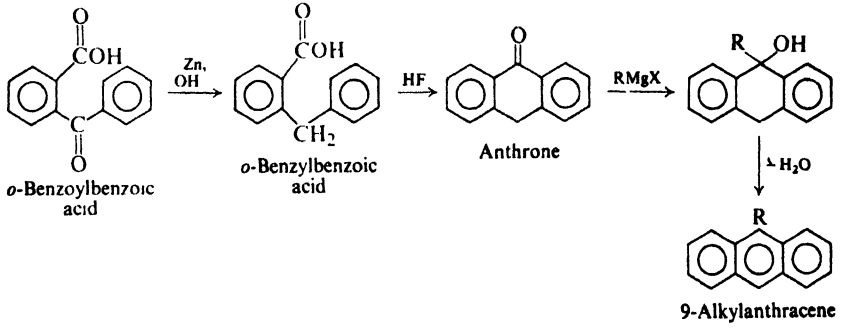
2-substituted anthraquinone obtained. (The initial acylation goes chiefly *para*. If the *para* position is blocked, *ortho* acylation is possible.) For example:



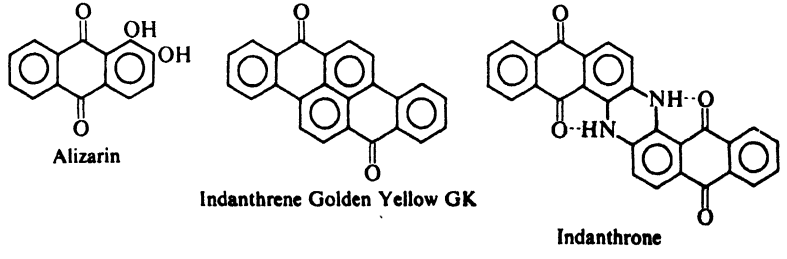
(b) A polynuclear compound can be used in place of benzene, and a product having more than three rings obtained. For example:



(c) The intermediate *o*-aroylbenzoic acid can be reduced before ring closure, and 9-substituted anthracenes obtained via Grignard reactions.



Anthraquinoid dyes are of enormous technological importance, and much work has been done in devising syntheses of large ring systems embodying the quinone structure. Several examples of anthraquinoid dyes are:



Problem 30.23 Outline the synthesis of the following, starting from compounds having fewer rings:

(a) 1,4-dimethylanthraquinone
(b) 1,2-dimethylanthraquinone
(c) 1,3-dimethylanthraquinone
(d) 2,9-dimethylanthracene
(e) 9-methyl-1,2-benzanthracene (a potent cancer-producing hydrocarbon)

Problem 30.24 What anthraquinone or anthraquinones would be expected from a sequence starting with 3-nitrophthalic anhydride and (a) benzene, (b) toluene?

30.19 Preparation of phenanthrene derivatives by ring closure

Starting from naphthalene instead of benzene, the Haworth succinic anhydride synthesis (Sec. 30.14) provides an excellent route to substituted phenanthrenes.

The basic scheme is outlined in Fig. 30.3. Naphthalene is acylated by succinic anhydride at both the 1- and 2-positions; the two products are separable, and either can be converted into phenanthrene. We notice that γ-(2-naphthyl)butyric acid undergoes ring closure at the 1-position to yield phenanthrene rather than at the 3-position to yield anthracene; the electron-releasing side chain at the 2-position directs further substitution to the 1-position (Sec. 30.13).

Substituted phenanthrenes are obtained by modifying the basic scheme in the ways already described for the Haworth method (Sec. 30.14).

Problem 30.25 Apply the Haworth method to the synthesis of the following, starting from naphthalene or a monosubstituted naphthalene:

(a) 9-methylphenanthrene
(b) 4-methylphenanthrene
(c) 1-methylphenanthrene
(d) 1,9-dimethylphenanthrene
(e) 4,9-dimethylphenanthrene
(f) 1,4-dimethylphenanthrene
(g) 1,4,9-trimethylphenanthrene
(h) 2-methoxyphenanthrene (*Hint:* See Problem 30.15, p. 984.)

Problem 30.26 Give structural formulas for all intermediates in the following synthesis of 2-methylphenanthrene. Tell what kind of reaction each step involves.

$$\text{Naphthalene} + CH_3CH_2COCl + AlCl_3 \xrightarrow{C_6H_5NO_2} A\ (C_{13}H_{12}O)$$
$$A + Br_2 \longrightarrow B\ (C_{13}H_{11}OBr)$$
$$B + CH(COOC_2H_5)_2^-Na^+ \longrightarrow C\ (C_{20}H_{22}O_5)$$
$$C \xrightarrow{\text{aq. KOH, heat}} D \xrightarrow{HCl} E \xrightarrow{\text{heat}} F\ (C_{15}H_{14}O_3) + CO_2$$
$$F + Zn(Hg) + HCl \longrightarrow G\ (C_{15}H_{16}O_2)$$
$$G \xrightarrow{\text{polyphosphoric acid}} H\ (C_{15}H_{14}O)$$
$$H + Zn(Hg) + HCl \longrightarrow I\ (C_{15}H_{16})$$
$$I \xrightarrow{\text{Pd, heat}} \text{2-methylphenanthrene}$$

Problem 30.27 Follow the instructions for Problem 30.26 for the following synthesis of phenanthrene (the **Bogert-Cook synthesis**).

$$\beta\text{-Phenylethyl bromide} + Mg \longrightarrow A\ (C_8H_9MgBr)$$
$$A + \text{cyclohexanone} \longrightarrow B \xrightarrow{H_2O} C\ (C_{14}H_{20}O)$$
$$C \xrightarrow{H_2SO_4} D\ (C_{14}H_{18})$$
$$D \xrightarrow{H_2SO_4} E\ (C_{14}H_{18})$$
$$E \xrightarrow{Se,\ \text{heat}} \text{phenanthrene}$$

How could β-phenylethyl bromide be made from benzene?

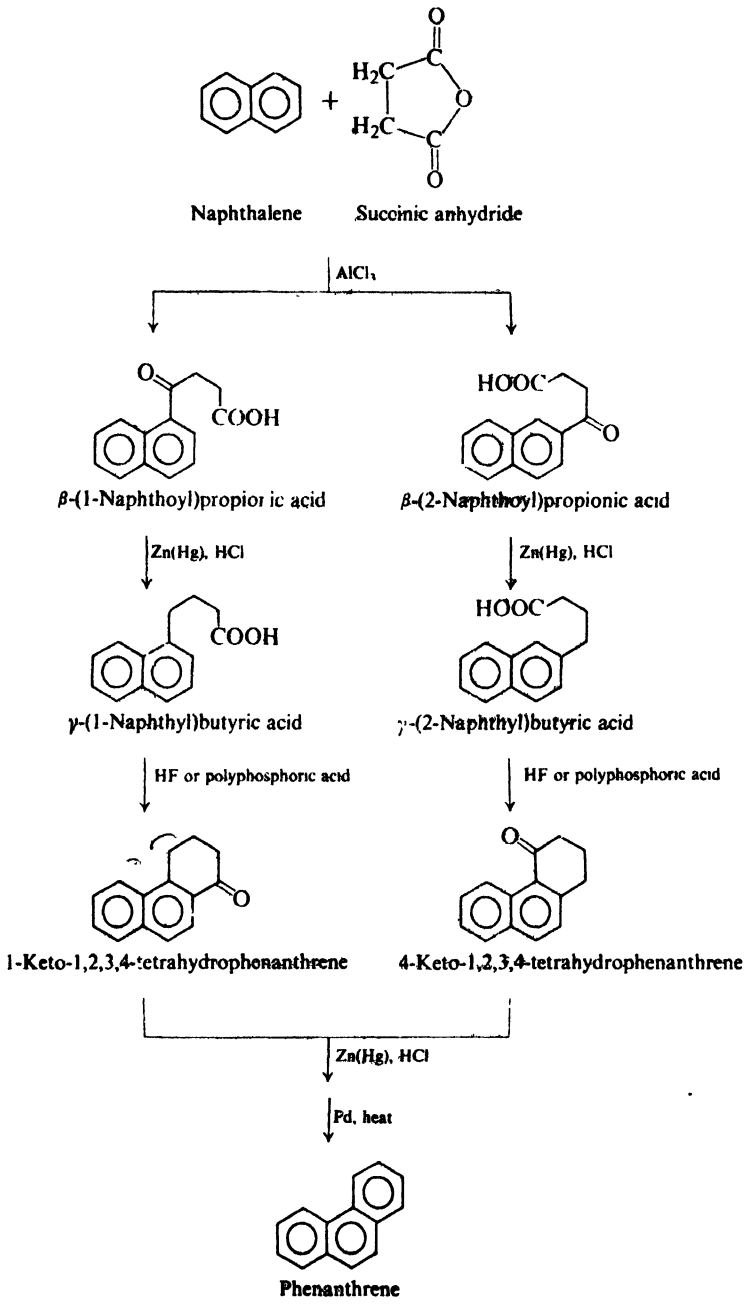


Figure 30.3. Haworth synthesis of phenanthrene derivatives.

Problem 30.28 Follow the instruction for Problem 30.26 for the following synthesis of phenanthrene (the **Bardhan-Sengupta synthesis**).

Potassium + ethyl 2-keto-1-cyclohexanecarboxylate $\longrightarrow$ A ($C_9H_{13}O_3K$)

A + β-phenylethyl bromide $\longrightarrow$ B ($C_{17}H_{22}O_3$)

B $\xrightarrow{\text{aq. KOH, heat}}$ C $\xrightarrow{HCl}$ D ($C_{14}H_{18}O$)

D + Na + moist ether $\longrightarrow$ E ($C_{14}H_{20}O$)

E $\xrightarrow{P_2O_5}$ [F ($C_{14}H_{18}$)] $\xrightarrow{P_2O_5}$ G ($C_{14}H_{18}$)

G $\xrightarrow{Se, \text{ heat}}$ phenanthrene

Problem 30.29 Follow the instructions for Problem 30.26 for the following synthesis of *pyrene*:

4-Keto-1,2,3,4-tetrahydrophenanthrene ($C_{14}H_{12}O$)

$$+ BrCH_2COOC_2H_5 + Zn \xrightarrow{\text{ether}} A \xrightarrow{H_2O,\, H^+} B\ (C_{18}H_{20}O_3)$$

B + acid + heat $\longrightarrow$ C ($C_{18}H_{18}O_2$)

C + aq. NaOH + heat $\longrightarrow$ D $\xrightarrow{HCl}$ E ($C_{16}H_{14}O_2$)

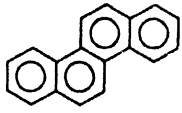
E $\xrightarrow{HF}$ F ($C_{16}H_{12}O$)

F + Zn(Hg) + HCl $\longrightarrow$ G ($C_{16}H_{14}$)

G $\xrightarrow{Pd, \text{ heat}}$ pyrene ($C_{16}H_{10}$)

How could you make the starting material?

Problem 30.30 Outline a possible synthesis of *chrysene* by the Bogert-Cook method (Problem 30.27, p. 944), starting from naphthalene and using any aliphatic or inorganic reagents. (*Hint:* See Problem 30.7(g), p. 977.)

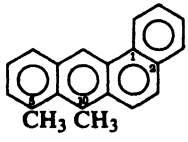


Chrysene

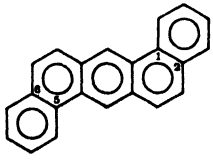
Problem 30.31 Outline an alternative synthesis of chrysene by the Bogert-Cook method, starting from benzene and using any aliphatic or inorganic reagents.

30.20 Carcinogenic hydrocarbons

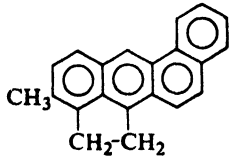
Much of the interest in complex polynuclear hydrocarbons has arisen because a considerable number of them have cancer-producing properties. Some of the most powerful carcinogens are derivatives of 1,2-benzanthracene:



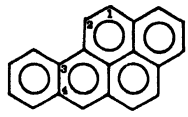
5,10-Dimethyl-1,2-benzanthracene



1,2,5,6-Dibenzanthracene



Methylcholanthrene



3,4-Benzpyrene

The relationship between carcinogenic activity and chemical properties is far from clear, but the possibility of uncovering this relationship has inspired a tremendous amount of research in the fields of synthesis and of structure and reactivity.

PROBLEMS

1. Give the structures and names of the principal products of the reaction (if any) of naphthalene with:

(a) CrO_3, CH_3COOH
(b) O_2, V_2O_5
(c) Na, C_2H_5OH
(d) Na, $C_5H_{11}OH$
(e) H_2, Ni
(f) HNO_3, H_2SO_4
(g) Br_2
(h) conc. H_2SO_4, 80°
(i) conc. H_2SO_4, 160°
(j) CH_3COCl, $AlCl_3$, CS_2
(k) CH_3COCl, $AlCl_3$, $C_6H_5NO_2$
(l) succinic anhydride, $AlCl_3$, $C_6H_5NO_2$

2. Give the structures and names of the principal products of the reaction of HNO_3/H_2SO_4 with:

(a) 1-methylnaphthalene
(b) 2-methylnaphthalene
(c) 1-nitronaphthalene
(d) 2-nitronaphthalene
(e) 1-naphthalenesulfonic acid
(f) 2-naphthalenesulfonic acid
(g) N-(1-naphthyl)acetamide
(h) N-(2-naphthyl)acetamide
(i) α-naphthol
(j) β-naphthol
(k) anthracene

3. When 2-methylnaphthalene is nitrated, three isomeric mononitro derivatives are obtained. Upon vigorous oxidation one of these yields 3-nitro-1,2,4-benzenetricarboxylic acid, and the other two both yield 3-nitrophthalic acid. Give the names and structures of the original three isomeric nitro compounds.

4. Outline all steps in a possible synthesis of each of the following from naphthalene, using any needed organic and inorganic reagents:

(a) α-naphthol
(b) β-naphthol
(c) α-naphthylamine
(d) β-naphthylamine
(e) 1-iodonaphthalene
(f) 2-iodonaphthalene
(g) 1-nitronaphthalene
(h) 2-nitronaphthalene
(i) α-naphthoic acid
(j) β-naphthoic acid
(k) 4-(1-naphthyl)butanoic acid
(l) α-naphthaldehyde
(m) β-naphthaldehyde
(n) 1-phenylazo-2-naphthol
(o) 1-amino-2-naphthol (*Hint:* Use product of (n).)
(p) 4-amino-1-naphthol
(q) 1-bromo-2-methoxynaphthalene
(r) 1,5-diaminonaphthalene
(s) 4,8-dibromo-1,5-diiodonaphthalene
(t) 5-nitro-2-naphthalenesulfonic acid
(u) 1,2-diaminonaphthalene
(v) 1,3-diaminonaphthalene
(w) *o*-aminobenzoic acid
(x) phenanthrene
(y) 9,10-anthraquinone
(z) anthracene

5. Naphthalene was transformed into another hydrocarbon by the following sequence of reactions:

naphthalene + Na, $C_5H_{11}OH$ $\longrightarrow$ A ($C_{10}H_{12}$)
A + succinic anhydride, $AlCl_3$ $\longrightarrow$ B ($C_{14}H_{16}O_3$)
B + Zn(Hg) + HCl $\longrightarrow$ C ($C_{14}H_{18}O_2$)
C + anhydrous HF $\longrightarrow$ D ($C_{14}H_{16}O$)
D + Zn(Hg) + HCl $\longrightarrow$ E ($C_{14}H_{18}$)
E + Pd/C + heat $\longrightarrow$ F ($C_{14}H_{10}$, m.p. 100–101°) + $4H_2$

What was F?

6. Outline all steps in a possible synthesis of each of the following from hydrocarbons containing fewer rings.

(a) 6-methoxy-4-phenyl-1-methylnaphthalene
(b) 1,2-benzanthracene
(c) 9-phenylanthracene
(d) 1-phenylphenanthrene
(e) 1,9-diphenylphenanthrene

7. Acylation of phenanthrene by succinic anhydride takes place at the 2- and 3-positions. The sequence of reduction, ring closure, and aromatization converts the 2-isomer into G and H, and converts the 3-isomer into G.

What is the structure and name of G? Of H?

8. When 4-phenyl-3-butenoic acid is refluxed there is formed a product, $C_{10}H_8O$, which is soluble in aqueous NaOH but not in aqueous $NaHCO_3$, and which reacts with benzenediazonium chloride to yield a red-orange solid. What is the product, and by what series of steps is it probably formed?

9. Anthracene reacts readily with maleic anhydride to give I, $C_{18}H_{12}O_3$, which can be hydrolyzed to J, a dicarboxylic acid of formula $C_{18}H_{14}O_4$. (a) What reaction do you think is involved in the formation of I? (b) What is the most probable structure of I? Of J?

Anthracene reacts with methyl fumarate to give a product that on hydrolysis yields K, a dicarboxylic acid of formula $C_{18}H_{14}O_4$. (c) Compare the structures of J and K. (*Hint:* See Problem 8, p. 880.)

Anthracene reacts with *p*-benzoquinone to yield L, $C_{20}H_{14}O_2$. In acid, L undergoes rearrangement to a hydroquinone M, $C_{20}H_{14}O_2$. Oxidation of M gives a new quinone N, $C_{20}H_{12}O_2$. Reductive amination of N gives a diamine O, $C_{20}H_{16}N_2$. Deamination of O by the usual method gives the hydrocarbon *triptycene*, $C_{20}H_{14}$. (d) What is a likely structure for triptycene?

10. Reduction of aromatic rings by the action of Li metal in ammonia generally gives 1,4-addition and yields a dihydro compound. Thus from naphthalene, $C_{10}H_8$, one can obtain $C_{10}H_{10}$. (a) Draw the structure of this dihydro compound.

Similar reduction is possible for 2-methoxynaphthalene (methyl 2-naphthyl ether). (b) Draw the structure of this dihydro compound. (c) If this dihydro ether is cleaved by acid, what is the structure of the initial product? (d) What further change will this initial product undoubtedly undergo, and what will be the final product?

11. Reduction of naphthalene by Li metal in $C_2H_5NH_2$ gives a 52% yield of 1,2,3,4,5,6,7,8-octahydronaphthalene. (a) What will this compound yield upon ozonolysis?

Treatment of the ozonolysis product ($C_{10}H_{16}O_2$) with base yields an unsaturated ketone ($C_{10}H_{14}O$). (b) What is its structure? (c) Show how this ketone can be transformed into *azulene*, $C_{10}H_8$, a blue hydrocarbon that is isomeric with naphthalene.

I

Azulene

12. (a) Azulene (preceding problem) is a planar molecule, and has a heat of combustion about 40 kcal/mole lower than that calculated by the method of Problem 10.2 (p. 323). It couples with diazonium salts and undergoes nitration and Friedel-Crafts acylation. Using both valence-bond and orbital structures, account for these properties of azulene. What might be a better representation of azulene than the formula 1?

(b) The dipole moment of azulene is 1.08 D; that of 1-chloroazulene is 2.69 D. What is the direction of the dipole of azulene? Is this consistent with the structure you arrived at in (a)?

13. (a) In CF_3COOH solution, azulene gives the following nmr spectrum:

a singlet, δ 4 4, 2H
b doublet, δ 7.8, 1H
c doublet, δ 8.1, 1H
d multiplet, δ 9, 5H

and in CF_3COOD solution, the following spectrum:

a singlet, δ 8.1, 1H
b multiplet, δ 9, 5H

What compound gives rise to the spectrum in CF_3COOH? in CF_3COOD? Identify all nmr signals.

(b) In light of your structure for azulene (preceding problem), how do you account for what happens in CF_3COOH solution? What would you expect to obtain on neutralization of this solution?

(c) Show in detail just how the compound giving rise to the spectrum observed in CF_3COOD must have been formed. What would you expect to obtain on neutralization of this solution?

(d) At which position or positions in azulene would you expect nitration, Friedel-Crafts acylation, and diazonium coupling to occur?

14. Azulene reacts with *n*-butyllithium to yield, after hydrolysis and dehydrogenation, an *n*-butylazulene, and similarly with sodamide to yield an aminoazulene. To what class of reactions do these substitutions belong? In which ring would you expect such substitution to have occurred? At which position?

15. The structure of *eudalene*, $C_{14}H_{16}$, a degradation product of eudesmol (a terpene found in eucalyptus oil), was first established by the following synthesis:

p-isopropylbenzaldehyde + ethyl bromoacetate, Zn; then H_2O $\longrightarrow$ P ($C_{14}H_{20}O_3$)
P + acid, heat $\longrightarrow$ Q ($C_{14}H_{18}O_2$)
Q + Na, ethyl alcohol $\longrightarrow$ R ($C_{12}H_{18}O$)
R $\xrightarrow{HBr}$ $\xrightarrow{KCN}$ $\xrightarrow{H_2O,\ H^+}$ $\xrightarrow{SOCl_2}$ S ($C_{13}H_{17}OCl$)
S + $AlCl_3$, warm $\longrightarrow$ T ($C_{13}H_{16}O$)
T + CH_3MgBr, then H_2O $\longrightarrow$ U ($C_{14}H_{20}O$)
U + acid, heat $\longrightarrow$ V ($C_{14}H_{18}$)
V + sulfur, heat $\longrightarrow$ eudalene ($C_{14}H_{16}$)

What is the structure and systematic name of eudalene?

16. Many polynuclear aromatic compounds do not contain fused ring systems, e.g., biphenyl and triphenylmethane. Give structures and names of compounds W through II, formed in the following syntheses of such polynuclear compounds.

(a) 1,2,4,5-tetrachlorobenzene + H_2O, heat $\longrightarrow$ W ($C_6H_3OCl_3$)
W + HCHO + H_2SO_4 $\longrightarrow$ [X, $C_7H_5O_2Cl_3$] $\longrightarrow$ Y ($C_{13}H_6O_2Cl_6$), "Hexachlorophene," soluble in base

(b) *m*-bromotoluene + Mg, ether $\longrightarrow$ Z (C_7H_7MgBr)
Z + 4-methylcyclohexanone, then H_2O $\longrightarrow$ AA ($C_{14}H_{20}O$)
AA + H^+, heat $\longrightarrow$ BB ($C_{14}H_{18}$)
BB + Pd/C, heat $\longrightarrow$ CC ($C_{14}H_{14}$)

(c) ethyl benzoate + C_6H_5MgBr, then H_2O $\longrightarrow$ DD ($C_{19}H_{16}O$)
DD + conc. HBr $\longrightarrow$ EE ($C_{19}H_{15}Br$)
EE + Ag $\longrightarrow$ FF ($C_{38}H_{30}$)
(d) $(C_6H_5)_3COH$ + $C_6H_5NH_2$ + acid $\longrightarrow$ GG ($C_{25}H_{21}N$)
GG + $NaNO_2$ + HCl; then H_3PO_2 $\longrightarrow$ HH ($C_{25}H_{20}$)
(e) $C_6H_5COCH_3$ + acid + heat $\longrightarrow$ II ($C_{24}H_{18}$) (*Hint:* Acids catalyze aldol condensations.)

17. When 1-nitro-2-aminonaphthalene is treated with sodium nitrite and HCl, and then with warm water, there is obtained not only 1-nitro-2-naphthol, but also 1-chloro-2-naphthol. How do you account for the formation of the chloronaphthol? Consider carefully the stage at which chlorine is introduced into the molecule.

18. Treatment of phenanthrene with diazomethane yields a product JJ for which mass spectrometry indicates a molecular weight of 192. The infrared spectrum of JJ resembles that of 9,10-dihydrophenanthrene; its nmr spectrum shows two signals of one proton each at δ −0.12 and δ 1.48.

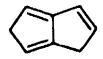
(a) What is a likely structure for JJ, and how is it probably formed? How do you account for the formation of JJ rather than one of its isomers?

(b) When a solution of JJ in *n*-pentane was irradiated with ultraviolet light, there were obtained phenanthrene, 2-methylpentane, 3-methylpentane, and *n*-hexane; the alkanes were obtained in the ratio 34:17:49. What happened in this reaction? What is the driving force?

(c) The irradiation of JJ in cyclohexene gave four products of formula C_7H_{12}. What would you expect these products to be?

(d) What would you expect to obtain from the irradiation of JJ in *cis*-4-methyl-2-pentene? In *trans*-4-methyl-2-pentene?

19. When *dihydropentalene* is treated with a little more than two moles of *n*-butyl-



Dihydropentalene

lithium, a stable white crystalline material KK is obtained. In contrast to the rather complicated nmr spectrum of dihydropentalene, the nmr spectrum of KK is simple:

a doublet, δ 4.98, J = 3 cps
b triplet, δ 5.73, J = 3 cps
peak area ratio $a:b$ = 2:1

What is a likely structure for KK? Of what theoretical significance is its formation and stability?

20. (a) When *either* 1-chloronaphthalene *or* 2-chloronaphthalene is treated with lithium piperidide and piperidine (Sec. 31.12) dissolved in ether, the *same* mixture of products is obtained: I and II of Problem 30.8 (p. 977) in the ratio 31:69. Show all steps in a mechanism that accounts for these observations. In particular, show why 2-chloronaphthalene yields the same mixture as 1-chloronaphthalene.

(b) Under the conditions of (a), 1-bromonaphthalene and 1-iodonaphthalene give I and II in the same ratio as 1-chloronaphthalene does. With 1-fluoronaphthalene, however, the ratio of products depends on the concentration of piperidine. At high piperidine concentration, I makes up as much as 84% of the product; at low piperidine concentrations, the product ratio levels off at the 31:69 value.

Account in detail for these facts. Tell what is happening to change the product ratio, why the ratio is affected by piperidine concentration, and why the fluoride should behave differently from the other halides.

21. Give structural formulas for LL through UU. Account in detail for the properties of compound UU.

3,5-dibromo-4-methylanisole + CuCN $\longrightarrow$ LL ($C_{10}H_8ON_2$)
LL + KOH, then CH_3OH, H^+ $\longrightarrow$ MM ($C_{12}H_{14}O_5$)
MM + $LiAlH_4$ $\longrightarrow$ NN ($C_{10}H_{14}O_3$)
NN + PBr_3 $\longrightarrow$ OO ($C_{10}H_{12}OBr_2$)
OO + Na $\longrightarrow$ PP ($C_{20}H_{24}O_2$)
PP + CrO_3 $\longrightarrow$ QQ ($C_{18}H_{18}O_2$), a pale yellow solid (*Hint:* A carbon–carbon bond is formed.)
QQ + 2NaOH $\longrightarrow$ RR ($C_{18}H_{16}O_2Na_2$), soluble in water
RR + O_2 $\longrightarrow$ SS ($C_{18}H_{14}O_2$), a yellow solid
SS + $LiAlH_4$ $\longrightarrow$ TT ($C_{18}H_{18}$)
TT + 2,3-dichloro-5,6-dicyanoquinone ("D.D.Q.") $\longrightarrow$ UU ($C_{18}H_{16}$)

Compound UU undergoes nitration, bromination, and Friedel-Crafts acylation. X-ray analysis shows that (except for the two methyl groups) UU is flat or nearly flat. Ten carbon–carbon bonds are between 1.386 A and 1.401 A long. The nmr spectrum shows peaks for 10H downfield, and for 6H *far upfield*:

a singlet, δ −4.25 (τ 14.25), 6H
b triplet, δ 8.11, 2H
c doublet, δ 8.62, 4H
d singlet, δ 8.67, 4H