Chapter 11 Electrophilic Aromatic Substitution

11.1 Introduction

We have already seen that the characteristic reactions of benzene involve substitution, in which the resonance-stabilized ring system is preserved. What kind of reagents bring about this substitution? What is the mechanism by which these reactions take place?

Above and below the plane of the benzene ring there is a cloud of π electrons. Because of resonance, these π electrons are more involved in holding together carbon nuclei than are the π electrons of a carbon–carbon double bond. Still, in comparison with σ electrons, these π electrons are loosely held and are available to a reagent that is seeking electrons.

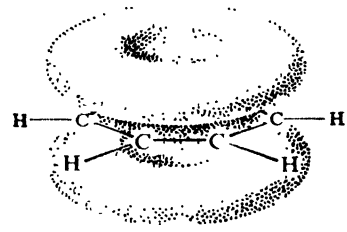


Figure 11.1. Benzene ring: π cloud is source of electrons.

It is not surprising that *in its typical reactions the benzene ring serves as a* **source of electrons**, that is, as a **base**. The compounds with which it reacts are deficient in electrons, that is, are electrophilic reagents or acids. Just as the typical reactions of the alkenes are electrophilic addition reactions, so *the typical reactions of the benzene ring are* **electrophilic substitution reactions.**

These reactions are characteristic not only of benzene itself, but of the benzene ring wherever it is found—and, indeed, of many aromatic rings, benzenoid and non-benzenoid.

Electrophilic aromatic substitution includes a wide variety of reactions: nitration, halogenation, sulfonation, and Friedel-Crafts reactions, undergone by nearly all aromatic rings; reactions like nitrosation and diazo coupling, undergone only by rings of high reactivity; and reactions like desulfonation, isotopic exchange, and many ring closures which, although apparently unrelated, are found on closer examination to be properly and profitably viewed as reactions of this kind. In synthetic importance electrophilic aromatic substitution is probably unequaled by any other class of organic reactions. It is the initial route of access to nearly all aromatic compounds: it permits the direct introduction of certain substituent groups which can then be converted, by replacement or by transformation, into other substituents, including even additional aromatic rings.

ELECTROPHILIC AROMATIC SUBSTITUTION

Ar = *aryl*, any aromatic group with attachment directly to ring carbon

1. **Nitration.** Discussed in Sec. 11.8.

$$ArH + HONO_2 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$$

A nitro compound

2. **Sulfonation.** Discussed in Sec. 11.9.

$$ArH + HOSO_3H \xrightarrow{SO_3} ArSO_3H + H_2O$$

A sulfonic acid

3. **Halogenation.** Discussed in Sec. 11.11.

$$ArH + Cl_2 \xrightarrow{Fe} ArCl + HCl$$

An aryl chloride

$$ArH + Br_2 \xrightarrow{Fe} ArBr + HBr$$

An aryl bromide

4. **Friedel-Crafts alkylation.** Discussed in Sec. 11.10.

$$ArH + RCl \xrightarrow{AlCl_3} ArR + HCl$$

An alkylbenzene

5. **Friedel-Crafts acylation.** Discussed in Sec. 19.6.

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR + HCl$$

An acyl chloride — A ketone

6. **Protonation.** Discussed in Sec. 11.12.

$$ArSO_3H + H^+ \xrightarrow{H_2O} ArH + H_2SO_4$$ *Desulfonation*

$$ArH + D^+ \longrightarrow ArD + H^+$$ *Hydrogen exchange*

7. **Thallation.** Discussed in Sec. 11.13.

$$\underset{\text{Thallium trifluoroacetate}}{ArH + Tl(OOCCF_3)_3} \xrightarrow{CF_3COOH} \underset{\text{An arylthallium ditrifluoroacetate}}{ArTl(OOCCF_3)_2} + CF_3COOH$$

8. **Nitrosation.** Discussed in Secs. 23.11 and 24.10.

$$ArH + HONO \longrightarrow \underset{\text{A nitroso compound}}{ArN{=}O} + H_2O$$

Only for highly reactive ArH

9. **Diazo coupling.** Discussed in Sec. 23.17.

$$\underset{\text{A diazonium salt}}{ArH + Ar'N_2{}^+X^-} \longrightarrow \underset{\text{An azo compound}}{ArN{=}NAr'} + HX$$

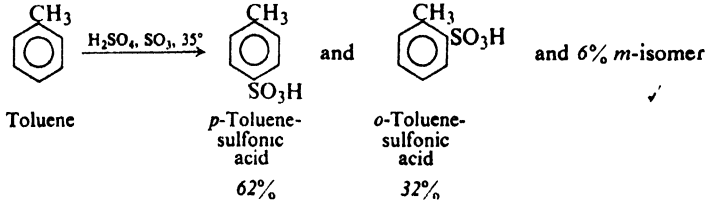
Only for highly reactive ArH

10. **Kolbe reaction.** Discussed in Sec. 24.11. *Only for phenols.*

11. **Reimer-Tiemann reaction.** Discussed in Sec. 24.12. *Only for phenols.*

11.2 Effect of substituent groups

Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation, for example. Although there are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the *o*- and *p*-isomers.



Benzene and toluene are insoluble in sulfuric acid, whereas the sulfonic acids are readily soluble; completion of reaction is indicated simply by disappearance of the hydrocarbon layer. When shaken with fuming sulfuric acid at room temperature, benzene reacts completely within 20 to 30 minutes, whereas toluene is found to react within only a minute or two.

Studies of nitration, halogenation, and Friedel-Crafts alkylation of toluene give analogous results. In some way the methyl group makes the ring more reactive than unsubstituted benzene, and *directs* the attacking reagent to the *ortho* and *para* positions of the ring.

On the other hand, nitrobenzene, to take a different example, has been found to undergo substitution more slowly than benzene, and to yield chiefly the *meta isomer.*

Like methyl or nitro, any group attached to a benzene ring affects the **reactivity** of the ring and determines the **orientation** of substitution. When an electrophilic reagent attacks an aromatic ring, it is the group already attached to the ring that determines *how readily* the attack occurs and *where* it occurs.

A group that makes the ring more reactive than benzene is called an **activating group.** A group that makes the ring less reactive than benzene is called a **deactivating group.**

A group that causes attack to occur chiefly at positions **ortho** and **para** to it is called an **ortho,para director.** A group that causes attack to occur chiefly at positions **meta** to it is called a **meta director.**

In this chapter we shall examine the methods that are used to measure these effects on reactivity and orientation, the results of these measurements, and a theory that accounts for these results. The theory is, of course, based on the most likely mechanism for electrophilic aromatic substitution; we shall see what this mechanism is, and some of the evidence supporting it. First let us look at the facts.

11.3 Determination of orientation

To determine the effect of a group on orientation is, in principle, quite simple: the compound containing this group attached to benzene is allowed to undergo substitution and the product is analyzed for the proportions of the three isomers. Identification of each isomer as *ortho*, *meta*, or *para* generally involves comparison with an authentic sample of that isomer prepared by some other method from a compound whose structure is known. In the last analysis, of course, all these identifications go back to absolute determinations of the Körner type (Problem 10.8, p. 332).

In this way it has been found that every group can be put into one of two classes: *ortho,para* directors or *meta* directors. Table 11.1 summarizes the orientation of nitration in a number of substituted benzenes. Of the five positions open to attack, three (60%) are *ortho* and *para* to the substituent group, and two (40%) are *meta* to the group; if there were no selectivity in the substitution reaction, we

Table 11.1 ORIENTATION OF NITRATION OF C_6H_5Y

Y	*Ortho*	*Para*	*Ortho* plus *para*	*Meta*
—OH	50–55	45–50	100	trace
—$NHCOCH_3$	19	79	98	2
—CH_3	58	38	96	4
—F	12	88	100	trace
—Cl	30	70	100	trace
—Br	37	62	99	1
—I	38	60	98	2
—NO_2	6.4	0.3	6.7	93.3
—$N(CH_3)_3^+$	0	11	11	89
—CN	—	—	19	81
—COOH	19	1	20	80
—SO_3H	21	7	28	72
—CHO	—	—	28	72

would expect the *ortho* and *para* isomers to make up 60% of the product, and the *meta* isomer to make up 40%. We see that seven of the groups direct 96–100% of nitration to the *ortho* and *para* positions; the other six direct 72–94% to the *meta* positions.

A given group causes the same general kind of orientation—predominantly *ortho,para* or predominantly *meta*—whatever the electrophilic reagent involved. The actual distribution of isomers may vary, however, from reaction to reaction. In Table 11.2, for example, compare the distribution of isomers obtained from toluene by sulfonation or bromination with that obtained by nitration.

Table 11.2 ORIENTATION OF SUBSTITUTION IN TOLUENE

	Ortho	*Meta*	*Para*
Nitration	58	4	38
Sulfonation	32	6	62
Bromination	33	—	67

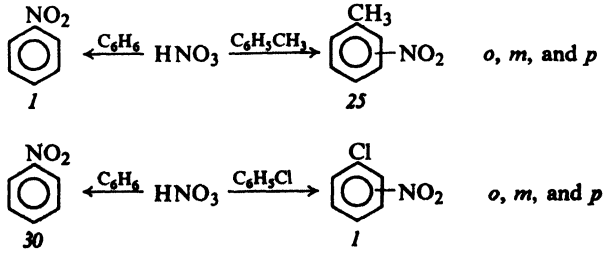
11.4 Determination of relative reactivity

A group is classified as *activating* if the ring it is attached to is more reactive than benzene, and is classified as *deactivating* if the ring it is attached to is less reactive than benzene. The reactivities of benzene and a substituted benzene are compared in one of the following ways.

The **time required** for reactions to occur under identical conditions can be measured. Thus, as we just saw, toluene is found to react with fuming sulfuric acid in about one-tenth to one-twentieth the time required by benzene. Toluene is more reactive than benzene, and $-CH_3$ is therefore an activating group.

The **severity of conditions** required for comparable reaction to occur within the same period of time can be observed. For example, benzene is nitrated in less than an hour at 60° by a mixture of concentrated sulfuric acid and concentrated nitric acid; comparable nitration of nitrobenzene requires treatment at 90° with fuming nitric acid and concentrated sulfuric acid. Nitrobenzene is evidently less reactive than benzene, and the nitro group, $-NO_2$, is a deactivating group.

For an exact, quantitative comparison under identical reaction conditions, **competitive reactions** can be carried out, in which the compounds to be compared are allowed to compete for a limited amount of a reagent (Sec. 3.22). For example, if equimolar amounts of benzene and toluene are treated with a small amount of nitric acid (in a solvent like nitromethane or acetic acid, which will dissolve both



organic and inorganic reactants), about 25 times as much nitrotoluene as nitrobenzene is obtained, showing that toluene is 25 times as reactive as benzene. On the other hand, a mixture of benzene and chlorobenzene yields a product in which nitrobenzene exceeds the nitrochlorobenzenes by 30:1, showing that chlorobenzene is only one-thirtieth as reactive as benzene. The chloro group is therefore classified as deactivating, the methyl group as activating. The activation or deactivation caused by some groups is extremely powerful: aniline, $C_6H_5NH_2$, is roughly one million times as reactive as benzene, and nitrobenzene, $C_6H_5NO_2$, is roughly one-millionth as reactive as benzene.

11.5 Classification of substituent groups

The methods described in the last two sections have been used to determine the effects of a great number of groups on electrophilic substitution. As shown in Table 11.3, nearly all groups fall into one of two classes: activating and *ortho,para*-directing, or deactivating and *meta*-directing. The halogens are in a class by themselves, being deactivating but *ortho,para*-directing.

Table 11.3 EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

Activating: *Ortho,para* Directors	**Deactivating: *Meta* Directors**
Strongly activating	$-NO_2$
$-NH_2$ ($-NHR$, $-NR_2$)	$-N(CH_3)_3^+$
$-OH$	$-CN$
	$-COOH$ ($-COOR$)
Moderately activating	$-SO_3H$
$-OCH_3$ ($-OC_2H_5$, etc.)	$-CHO$, $-COR$
$-NHCOCH_3$	
	Deactivating: *Ortho,para* Directors
Weakly activating	$-F$, $-Cl$, $-Br$, $-I$
$-C_6H_5$	
$-CH_3$ ($-C_2H_5$, etc.)	

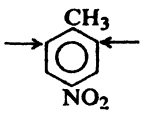
Just by knowing the effects summarized in these short lists, we can now predict fairly accurately the course of hundreds of aromatic substitution reactions. We now know, for example, that bromination of nitrobenzene will yield chiefly the *m*-isomer and that the reaction will go more slowly than the bromination of benzene itself; indeed, it will probably require severe conditions to go at all. We now know that nitration of $C_6H_5NHCOCH_3$ (*acetanilide*) will yield chiefly the *o*- and *p*-isomers and will take place more rapidly than nitration of benzene.

Although, as we shall see, it is possible to account for these effects in a reasonable way, it is necessary for the student to memorize the classifications in Table 11.3 so that he may deal rapidly with synthetic problems involving aromatic compounds.

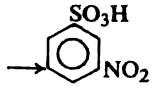
11.6 Orientation in disubstituted benzenes

The presence of two substituents on a ring makes the problem of orientation more complicated, but even here we can frequently make very definite predictions. First of all, the two substituents may be located so that the directive influence of

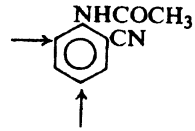
e *reinforces* that of the other; for example, in I, II, and III the orientation clearly ıst be that indicated by the arrows.



I



II



III

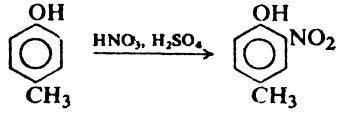
On the other hand, when the directive effect of one group *opposes* that of the ıer, it may be difficult to predict the major product; in such cases complicated xtures of several products are often obtained.

Even where there are opposing effects, however, it is still possible in certain ıes to make predictions in accordance with the following generalizations.

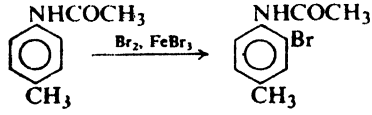
(a) *Strongly activating groups generally win out over deactivating or weakly tivating groups.* The differences in directive power in the sequence

$$-NH_2, -OH > -OCH_3, -NHCOCH_3 > -C_6H_5, -CH_3 > \textit{meta}\text{ directors}$$

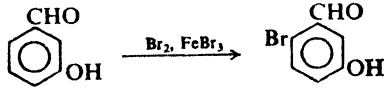
: great enough to be used in planning feasible syntheses. For example:



Sole product

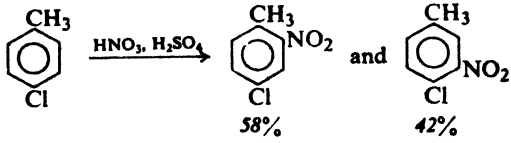


Chief product



Chief product

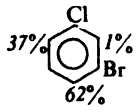
ere must be, however, a fairly large difference in the effects of the two groups for ar-cut results; otherwise one gets results like these:



58% *42%*

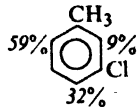
(b) *There is often little substitution between two groups that are meta to each er.* In many cases it seems as though there just is not enough room between

two groups located *meta* to each other for appreciable substitution to occur there, as illustrated by IV and V:



Nitration

IV



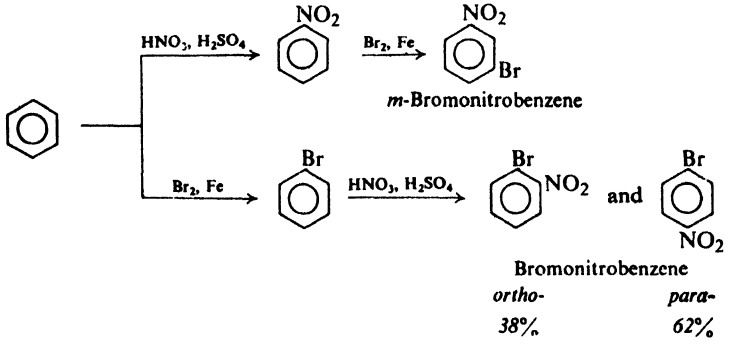
Nitration

V

11.7. Orientation and synthesis

As we discussed earlier (Sec. 3.14), a laboratory synthesis is generally aimed at obtaining a single, pure compound. Whenever possible we should avoid use of a reaction that produces a mixture, since this lowers the yield of the compound we want and causes difficult problems of purification. With this in mind, let us see some of the ways in which we can apply our knowledge of orientation to the synthesis of pure aromatic compounds.

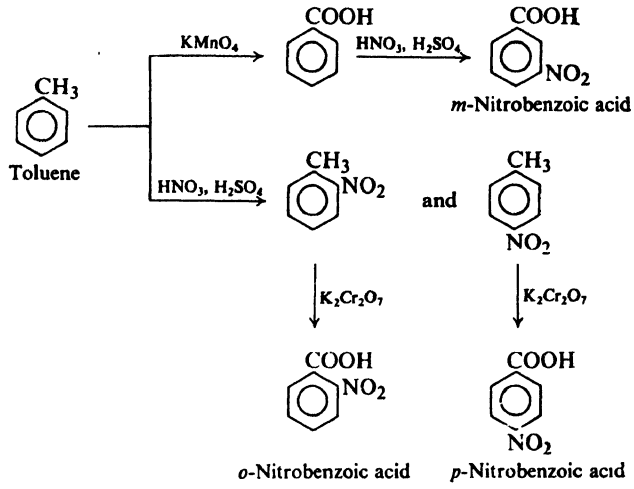
First of all, *we must consider the order in which we introduce these various substituents into the ring.* In the preparation of the bromonitrobenzenes, for example, it is obvious that if we nitrate first and then brominate, we will obtain the *m*-isomer; whereas if we brominate first and then nitrate, we will obtain a mixture of the *o*- and *p*-isomers. The order in which we decide to carry out the two steps, then, depends upon which isomer we want.



Next, if our synthesis involves conversion of one group into another, *we must consider the proper time for this conversion.* For example, oxidation of a methyl group yields a carboxyl group (Sec. 12.10). In the preparation of nitrobenzoic acids from toluene, the particular product obtained depends upon whether oxidation or nitration is carried out first.

Substitution controlled by an activating group yields a mixture of *ortho* and *para* isomers; nevertheless, we must often make use of such reactions, as in the examples just shown. It is usually possible to obtain the pure *para* isomer from the mixture by fractional crystallization. As the more symmetrical isomer, it is the less soluble (Sec. 12.3), and crystallizes while the solvent still retains the soluble

ortho isomer. Some *para* isomer, of course, remains in solution to contaminate the *ortho* isomer, which is therefore difficult to purify. As we shall see, special approaches are often used to prepare *ortho* isomers.



In the special case of nitro compounds, the difference in boiling points is often large enough that both *ortho* and *para* isomers can be obtained pure by fractional distillation. As a result, many aromatic compounds are best prepared not by direct substitution but by conversion of one group into another, in the last analysis starting from an original nitro compound; we shall take up these methods of conversion later.

A goal of aromatic synthesis is control of orientation: the preparation, at will and from the same substrate, of a pure *ortho*, a pure *meta*, or a pure *para* isomer. Steps toward this goal have been taken very recently by Edward C. Taylor (Princeton University) and Alexander McKillop (University of East Anglia), chiefly through the chemistry of *thallium*: thallium as the cation in organic salts; thallium salts as Lewis acids; arylthallium compounds (Sec. 11.13) as reactive organometallic intermediates. One approach to regiospecific substitution involves complexing—attachment through a Lewis acid–base reaction—of the attacking reagent by some other molecule. Complexing of the reagent by the substituent group prior to reaction tends to favor attack at the *nearest* position: *ortho*. Complexing of the reagent by a bulky molecule tends to favor attack at the *least crowded* position: *para*. If reaction can be carried out so that orientation is governed, not by relative rates of reaction—as it usually is—but by position of equilibrium, then the *most stable* isomer is favored: often the *meta* isomer. We shall see examples of all these ways of controlling orientation.

11.8 Mechanism of nitration

Now that we have seen the effects that substituent groups exert on orientation and reactivity in electrophilic aromatic substitution, let us see how we can account

for these effects. The first step in doing this is to examine the mechanism for the reaction. Let us begin with nitration, using benzene as the aromatic substrate.

The commonly accepted mechanism for nitration with a mixture of nitric and sulfuric acids (the widely used "mixed acid" of the organic chemist) involves the following sequence of reactions:

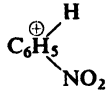
(1) $HONO_2 + 2H_2SO_4 \rightleftharpoons H_3O^+ + 2HSO_4^- + {}^{\oplus}NO_2$ (Nitronium ion)

(2) ${}^{\oplus}NO_2 + C_6H_6 \longrightarrow C_6H_5(H)(NO_2)$ *Slow*

(3) $C_6H_5(H)(NO_2) + HSO_4^- \longrightarrow C_6H_5NO_2 + H_2SO_4$ *Fast*

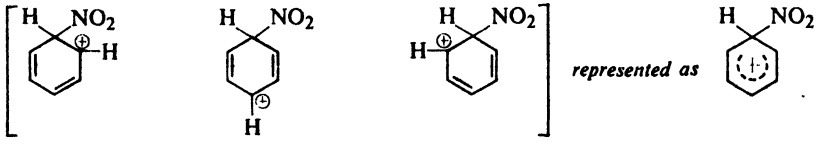
Step (1) generates the **nitronium ion**, ${}^{\oplus}NO_2$, which is the electrophilic particle that actually attacks the benzene ring. This reaction is simply an acid–base equilibrium in which sulfuric acid serves as the acid and the much weaker nitric acid serves as a base. We may consider that the very strong acid, sulfuric acid, causes nitric acid to ionize in the sense, $HO^- \ldots {}^+NO_2$, rather than in the usual way, $H^+ \ldots {}^-ONO_2$. The nitronium ion is well known, existing in salts such as nitronium perchlorate, $NO_2^+ClO_4^-$, and nitronium fluoborate, $NO_2^+BF_4^-$. Indeed, solutions of these stable nitronium salts in solvents like nitromethane or acetic acid have been found by George Olah (of Case Western Reserve University) to nitrate aromatic compounds smoothly and in high yield at room temperature.

Needing electrons, the nitronium ion finds them particularly available in the π cloud of the benzene ring, and so in step (2) attaches itself to one of the carbon atoms by a covalent bond. This forms the carbonium ion,



often called a *benzenonium ion.*

Just what is the structure of this carbonium ion? We find that we can represent it by three structures (I, II, and III) that differ from each other only in position of double bonds and positive charge. The actual ion must then be a resonance hybrid of these three structures.



I II III IV

This means, of course, that the positive charge is not localized on one carbon atom, but is distributed over the molecule, being particularly strong on the carbon

atoms *ortho* and *para* to the carbon bearing the $-NO_2$ group. (As we shall see later, this *ortho,para* distribution is significant.) The dispersal of the positive charge over the molecule by resonance makes this ion more stable than an ion with a localized positive charge. It is probably because of this stabilization that the carbonium ion forms at all, in view of the stability of the original benzene itself. Sometimes the hybrid carbonium ion is represented as IV, where the broken line stands for the fractional bonds due to the delocalized π electrons.

Thus far the reaction is like addition to alkenes: an electrophilic particle, attracted by the π electrons, attaches itself to the molecule to form a carbonium ion. But the fate of this carbonium ion is different from the fate of the ion formed from an alkene. Attachment of a basic group to the benzenonium ion to yield the addition product would destroy the aromatic character of the ring. Instead, the basic ion, HSO_4^-, abstracts a hydrogen ion (step 3) to yield the substitution product, which retains the resonance-stabilized ring. Loss of a hydrogen ion, as we have seen, is one of the reactions typical of a carbonium ion (Sec. 5.20); it is the *preferred* reaction in this case.

As with other carbonium ion reactions we have studied, it is the *formation* of the carbonium ion (step 2) that is the more difficult step; once formed, the carbonium ion rapidly loses a hydrogen ion (step 3) to form the products. (We shall see proof of this in Sec. 11.16.)

Electrophilic substitution, then, like electrophilic addition, is a stepwise process involving an intermediate carbonium ion. The two reactions differ, however, in the fate of the carbonium ion. While the mechanism of nitration is, perhaps, better established than the mechanisms for other aromatic substitution reactions, it seems clear that all these reactions follow the same course.

Problem 11.1 Nitration by nitric acid alone is believed to proceed by essentially the same mechanism as nitration in the presence of sulfuric acid. Write an equation for the generation of NO_2^+ from nitric acid alone.

11.9 Mechanism of sulfonation

Sulfonation of many aromatic compounds involves the following steps:

(1) $$2H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- + SO_3$$

(2) $$SO_3 + C_6H_6 \rightleftharpoons C_6H_5(H)^{\oplus}SO_3^-$$ *Slow*

(3) $$C_6H_5(H)^{\oplus}SO_3^- + HSO_4^- \rightleftharpoons C_6H_5SO_3^- + H_2SO_4$$ *Fast*

(4) $$C_6H_5SO_3^- + H_3O^+ \rightleftharpoons C_6H_5SO_3H + H_2O$$ *Equilibrium far to the left*

Again the first step, which generates the electrophilic sulfur trioxide, is simply an acid–base equilibrium, this time between molecules of sulfuric acid. For

sulfonation we commonly use sulfuric acid containing an excess of SO_3; even if this is not done, it appears that SO_3 formed in step (1) can be the electrophile.

In step (2) the electrophilic reagent, SO_3, attaches itself to the benzene ring to form the intermediate carbonium ion. Although sulfur trioxide is not positively charged, it is electron-deficient, and hence an acid, nevertheless.

Step (3) is the loss of a hydrogen ion to form the resonance-stabilized substitution product, this time the anion of benzenesulfonic acid which, being a strong acid, is highly dissociated (step 4).

With some aromatic substrates and at certain acidities, the electrophile may be HSO_3^+ or molecules that can readily transfer SO_3 or HSO_3^+ to the aromatic ring.

Problem 11.2 Write an equation for the formation from H_2SO_4 of each of the following sulfonating electrophiles: (a) $H_3SO_4^+$; (b) HSO_3^+; (c) $H_2S_2O_7$.

11.10 Mechanism of Friedel-Crafts alkylation

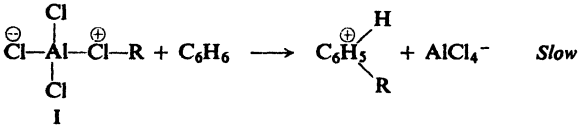
In Friedel-Crafts alkylation, the electrophile is typically a carbonium ion. It, too, is formed in an acid-base equilibrium, this time in the Lewis sense:

(1) $$RCl + AlCl_3 \rightleftharpoons AlCl_4^- + R^{\oplus}$$

(2) $$R^{\oplus} + C_6H_6 \rightleftharpoons C_6H_5^{\oplus}(H)(R) \qquad \textit{Slow}$$

(3) $$C_6H_5^{\oplus}(H)(R) + AlCl_4^- \rightleftharpoons C_6H_5R + HCl + AlCl_3 \qquad \textit{Fast}$$

In certain cases, there is no free carbonium ion involved. Instead, the alkyl group is transferred—without a pair of electrons—directly to the aromatic ring from the polar complex, I, between $AlCl_3$ and the alkyl halide:



The electrophile is thus either (a) R^+ or (b) a molecule like I that can readily *transfer* R^+ to the aromatic ring. *This duality of mechanism is common in electrophilic aromatic substitution.* In either case, the Lewis acid R^+ is displaced from RCl by the other Lewis acid, $AlCl_3$.

We speak of the Friedel-Crafts reaction as electrophilic substitution and, from the viewpoint of the aromatic ring, it is. But, just as an acid reacts with a base, so an electrophile reacts with a *nucleophile* (nucleus-lover), a molecule which can provide the electrons that the electrophile seeks. From the opposite point of view, then, this reaction involves

nucleophilic attack by the aromatic ring on the alkyl group of complex I. The $AlCl_4^-$ ion is a better leaving group than Cl^- would be; the Lewis acid, $AlCl_3$, serves the same purpose here that a Lowry-Brønsted acid does in protonation of an alcohol (Sec. 5.20).

As we shall find out when we take up the Friedel-Crafts reaction as a synthetic tool (Sec. 12.6), the Friedel-Crafts reaction in its widest sense involves reactants other than alkyl halides and Lewis acids other than aluminium chloride: BF_3, $SnCl_4$, HF, and even H^+.

Problem 11.3 How do you account for the fact that benzene in the presence of $AlCl_3$ reacts: (a) with *n*-propyl bromide to give isopropylbenzene; (b) with isobutyl bromide to yield *tert*-butylbenzene; (c) with neopentyl bromide to yield *tert*-pentylbenzene? (d) By which of the alternative mechanisms for the Friedel-Crafts reaction are these products probably formed?

Problem 11.4 Write all steps in the most likely mechanism for the reaction of benzene: (a) with *tert*-butyl alcohol in the presence of H_2SO_4 to yield *tert*-butylbenzene; (b) with propylene in the presence of H_3PO_4 to form isopropylbenzene.

11.11 Mechanism of halogenation

Aromatic halogenation, illustrated for chlorination, involves the following steps.

(1) $$Cl_2 + FeCl_3 \rightleftharpoons \underset{\text{II}}{Cl_3\overset{\ominus}{Fe}{-}\overset{\oplus}{Cl}{-}Cl}$$

(2) $$\underset{\text{II}}{Cl_3\overset{\ominus}{Fe}{-}\overset{\oplus}{Cl}{-}Cl} + C_6H_6 \longrightarrow \overset{\oplus}{C_6H_5}\begin{smallmatrix}H\\Cl\end{smallmatrix} + FeCl_4^- \qquad \textit{Slow}$$

(3) $$\overset{\oplus}{C_6H_5}\begin{smallmatrix}H\\Cl\end{smallmatrix} + FeCl_4^- \longrightarrow C_6H_5Cl + HCl + FeCl_3 \qquad \textit{Fast}$$

The key step (2) is the attachment of positive chlorine to the aromatic ring. It seems unlikely, though, that an actually free Cl^+ ion is involved. Instead, ferric chloride combines with Cl_2 to form complex II, from which chlorine is transferred, without its electrons, directly to the ring.

Addition of halogens to alkenes, we have seen (Sec. 6.13), similarly involves attack by positive halogen to form an intermediate carbonium ion. The loosely held π electrons of an alkene make it more reactive, however, and positive halogen is transferred from the halogen molecule itself, X_2, with loss of Cl^-. The less reactive benzene molecule needs the assistance of a Lewis acid; reaction occurs with the loss of the better leaving group, $FeCl_4^-$. Indeed, more highly reactive aromatic compounds, i.e., those whose π electrons are more available, do react with halogens in the absence of any added Lewis acid.

Problem 11.5 Certain activated benzene rings can be chlorinated by hypochlorous acid, HOCl, and this reaction is catalyzed by H^+. In light of the above discussion, can you suggest a possible function of H^+?

Problem 11.6 Aromatic bromination catalyzed by the Lewis acid thallium acetate, $Tl(OOCCH_3)_3$, gives only the *para* isomer. Suggest an explanation for this regiospecificity. (*Hint:* See Sec. 11.7.)

11.12 Desulfonation. Mechanism of protonation

When an aromatic sulfonic acid is heated to 100–175° with aqueous acid, it is converted into sulfuric acid and an aromatic hydrocarbon. This *desulfonation* is the exact reverse of the sulfonation process by which the sulfonic acid was originally made.

$$\underset{\substack{\text{Hydrocarbon}\\ \textit{Volatile}}}{C_6H_6} + H_2SO_4 \overset{H^+}{\rightleftharpoons} \underset{\substack{\text{Sulfonic acid}\\ \textit{Non-volatile}}}{C_6H_5SO_3H} + H_2O$$

By applying the usual equilibrium principles, we can select conditions that will drive the reaction in the direction we want it to go. To sulfonate we use a large excess of concentrated or fuming sulfuric acid; high concentration of sulfonating agent and low concentration of water (or its removal by reaction with SO_3) shift the equilibrium toward sulfonic acid. To desulfonate we use dilute acid and often pass superheated steam through the reaction mixture; high concentration of water and removal of the relatively volatile hydrocarbon by steam distillation shift the equilibrium toward hydrocarbon.

According to the principle of microscopic reversibility (p. 170), the mechanism of desulfonation must be the exact reverse of the mechanism of sulfonation.

(1) $$C_6H_5SO_3^- + H^+ \rightleftharpoons C_6\overset{\overset{H}{\diagup}}{\overset{\oplus}{H}}_5\diagdown SO_3^-$$

(2) $$C_6\overset{\overset{H}{\diagup}}{\overset{\oplus}{H}}_5\diagdown SO_3^- \rightleftharpoons C_6H_6 + SO_3$$

The reaction is simply another example of electrophilic aromatic substitution. The electrophile is the proton, H^+, and the reaction is *protonation* or, more specifically, *protodesulfonation.*

Sulfonation is unusual among electrophilic aromatic substitution reactions in its reversibility. It is also unusual in another way: in sulfonation, ordinary hydrogen (protium) is displaced from an aromatic ring about twice as fast as deuterium. These two facts are related to each other and, as we shall see in Sec. 11.16, give us a more detailed picture of sulfonation and of electrophilic aromatic substitution in general.

Problem 11.7 Predict the product or products of: (a) monobromination of toluene; (b) monobromination of *p*-toluenesulfonic acid followed by treatment with acid and superheated steam. (c) Using the principle of (b), and following the guidelines of Sec. 11.7, outline a synthesis from benzene of *o*-dibromobenzene; of *o*-bromochlorobenzene.

11.13 Thallation

Treatment of aromatic compounds with thallium trifluoroacetate, $Tl(OOCCF_3)_3$, dissolved in trifluoroacetic acid (CF_3COOH) gives rapidly and in

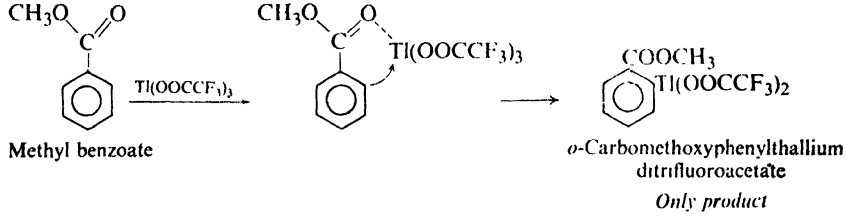
high yield arylthallium ditrifluoroacetates, stable crystalline compounds. Reaction is believed by Taylor and McKillop (p. 345) to involve electrophilic attack on the aromatic ring by the (Lewis) acidic thallium.

$$\underset{\text{Thallium trifluoroacetate}}{ArH + Tl(OOCCF_3)_3} \xrightarrow{CF_3COOH} \underset{\text{Arylthallium ditrifluoroacetate}}{ArTl(OOCCF_3)_2} + CF_3COOH$$

Thallium compounds are very poisonous, and must be handled with extreme care.

Although substituent groups affect the reactivity of the aromatic substrate as expected for electrophilic substitution, orientation is unusual in a number of ways, and it is here that much of the usefulness of thallation lies. Thallation is almost exclusively *para* to —R, —Cl, and —OCH_3, and this is attributed to the bulk of the electrophile, thallium trifluoroacetate, which seeks out the uncrowded *para* position.

Thallation is almost exclusively *ortho* to certain substituents like —COOH, —$COOCH_3$, and —CH_2OCH_3 (even though some of these are normally *meta*-directing), and this is attributed to prior complexing of the electrophile with the substituent; thallium is held at just the right distance for easy intramolecular delivery to the *ortho* position. For example:



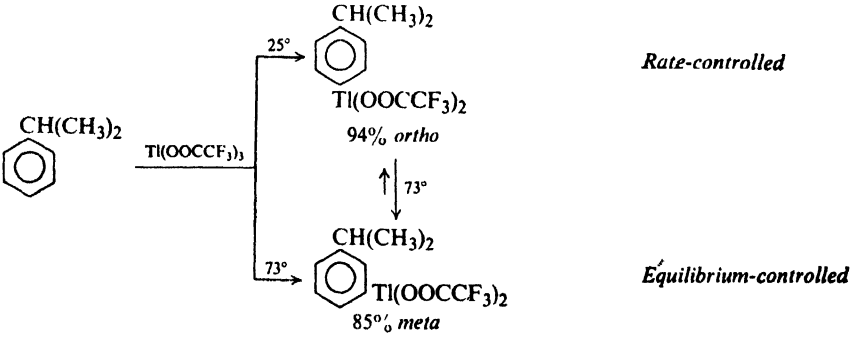
Methyl benzoate

o-Carbomethoxyphenylthallium ditrifluoroacetate

Only product

(In $C_6H_5CH_2CH_2COOH$, however, it is evidently held too far from the ring, and must *leave* the substituent before attacking the ring intermolecularly—at the *para* position.)

Thallation is *reversible*, and when carried out at a higher temperature (73° instead of room temperature) yields the *more stable* isomer: usually the *meta* (compare 1,2- and 1,4-addition, Sec. 8.22). For example:



Now, these arylthallium compounds are useful, not in themselves, but as intermediates in the synthesis of a variety of other aromatic compounds. Thallium can be replaced by other atoms or groups which cannot themselves be introduced directly into the aromatic ring – or at least not with the same regiospecificity. In this way one can prepare phenols (ArOH, Sec. 24.5) and aryl iodides (Sec. 25.3). Direct iodination of most aromatic rings does not work very well, but the process of thallation followed by treatment with iodide ion gives aryl iodides in high yields.

$$ArH + Tl(OOCCF_3)_3 \xrightarrow{CF_3COOH} ArTl(OOCCF_3)_2 \xrightarrow{KI} ArI$$

11.14 Mechanism of electrophilic aromatic substitution: a summary

Electrophilic aromatic substitution reactions seem, then, to proceed by a single mechanism, whatever the particular reagent involved. This can be summarized for the reagent YZ as follows:

(1) $$C_6H_6 + Y^+ \longrightarrow C_6H_5\overset{H}{\underset{Y}{}} \qquad \textit{Slow}$$

(2) $$C_6H_5\overset{H}{\underset{Y}{}} + :Z^- \longrightarrow C_6H_5Y + H:Z \qquad \textit{Fast}$$

Two essential steps are involved: (1) attack by an electrophilic reagent upon the ring to form a carbonium ion, $C_6H_5\overset{H}{\underset{Y}{}}$, and (2) abstraction of a hydrogen ion from this carbonium ion by some base. In each case there is a preliminary acid–base reaction which generates the attacking particle; the actual substitution, however, is contained in these two steps.

Most of the support for this mechanism comes from evidence about the nature of the attacking particle in each of these reactions: evidence, that is, that substitution is *electrophilic*. This evidence, in turn, comes largely from kinetics, augmented by various other observations: the nitrating power of preformed nitronium salts (Sec. 11.8), for example, or carbonium ion-like rearrangements in some Friedel-Crafts alkylations (Problem 11.3 above). The electrophilic nature of these reactions is supported in a very broad way by the fact that other reactions which show the same reactivity and orientation features also fit into the same mechanistic pattern.

Problem 11.8 In each of the following reactions, groups on the ring under attack exert the kinds of effects summarized in Sec. 11.5. Suggest a likely electrophile in each case, and write a likely mechanism.

(a) $$ArH + R{-}\underset{\underset{O}{\|}}{C}{-}Cl \xrightarrow{AlCl_3} Ar{-}\underset{\underset{O}{\|}}{C}{-}R$$

(b) $$ArH + Ar'N_2^+Cl^- \longrightarrow Ar{-}N{=}N{-}Ar'$$

(c) $$ArH + HONO \xrightarrow{H^+} Ar{-}NO + H_2O$$

Problem 11.9 When phenol is treated with D_2SO_4 in D_2O (deuterium sulfate in heavy water), there is formed phenol containing deuterium instead of hydrogen at positions *ortho* and *para* to the —OH group. Benzene undergoes similar exchange but at a much lower rate; under the same conditions benzenesulfonic acid does not undergo exchange at all. (a) Outline the most probable mechanism for hydrogen–deuterium exchange in aromatic compounds. (b) What is the attacking reagent in each case, and to what general class does this reaction belong?

But this is only part of the mechanism. Granting that substitution is electrophilic, how do we know that it involves *two* steps, as we have shown, and not just *one*? And how do we know that, of the two steps, the first is much slower than the second? To understand the answer to these questions, we must first learn something about *isotope effects*.

11.15 Isotope effects

Different isotopes of the same element have, by definition, the same electronic configuration, and hence similar chemical properties. This similarity is the basis of the isotopic tracer technique (Sec. 3.29): one isotope does pretty much what another will do, but, from its radioactivity or unusual mass, can be traced through a chemical sequence.

Yet different isotopes have, also by definition, different masses, and because of this their chemical properties are *not identical*: the same reactions can occur but at somewhat different rates (or, for reversible reactions, with different positions of equilibrium). *A difference in rate (or position of equilibrium) due to a difference in the isotope present in the reaction system is called an* **isotope effect.**

Theoretical considerations, which we cannot go into, supported by much experimental evidence, lead to the conclusion: *if a particular atom is less tightly bound in the transition state of a reaction than in the reactant, the reaction involving the heavier isotope of that atom will go more slowly*. The hydrogen isotopes have the greatest proportional differences in mass: deuterium (D) is twice as heavy as protium (H), and tritium (T) is three times as heavy. As a result, hydrogen isotope effects are the biggest, the easiest to measure, and—because of the special importance of hydrogen in organic chemistry—the most often studied. (If you doubt the importance of hydrogen, look at the structure of almost any compound in this book.)

One kind of reaction in which an atom is less tightly bound in the transition state than in the reactant is a reaction in which a bond to that atom is being broken. Isotope effects due to the breaking of a bond to the isotopic atom are called *primary isotope effects*. They are in general the biggest effects observed for a particular set of isotopes.

In this book we shall be concerned with **primary hydrogen isotope effects**, which amount to this: *a bond to protium (H) is broken faster than a bond to deuterium (D)*. For many reactions of this kind,

(1) $$\sim C{-}H + Z \xrightarrow{k^H} [\sim C\cdots H\cdots Z] \longrightarrow \sim C + H{-}Z$$

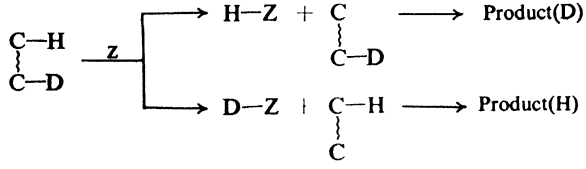
(2) $$\sim C{-}D + Z \xrightarrow{k^D} [\sim C\cdots D\cdots Z] \longrightarrow \sim C + D{-}Z$$

in which hydrogen is abstracted as an atom, positive ion, or negative ion, deuterium isotope effects (k^H/k^D) in the range 5 to 8 (at room temperature) have been observed; that is to say, the reaction is 5 to 8 times as fast for ordinary hydrogen as for deuterium. (Tritium isotope effects, k^H/k^T, are about twice as large as deuterium isotope effects.)

These differences in rate can be measured in a variety of ways. In some cases, the rates of the two individual reactions (1) and (2) can be measured directly and the results compared. Usually, however, it is more feasible, as well as more satisfactory, to use our familiar method of competition (Sec. 3.22) in either of two ways.

In *intermolecular* competition, a mixture of labeled and unlabeled reactants compete for a limited amount of reagent; reactions (1) and (2) thus go on in the same mixture, and we measure the relative amounts of H—Z and D—Z produced. (Sometimes, larger amounts of the reagent Z are used, and the relative amounts of the two reactants—ordinary and labeled—left *unconsumed* are measured; the less reactive will have been used up more slowly and will predominate. The relative rates of reaction can be calculated without much difficulty.)

In *intramolecular* competition, a single reactant is used which contains several equivalent positions, some labeled and some not:

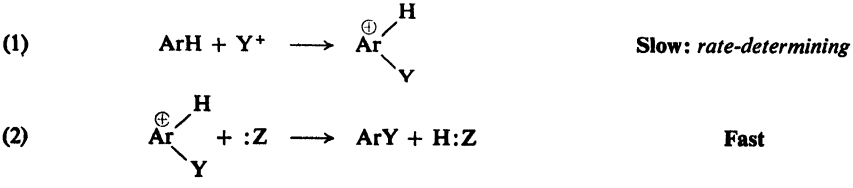


One can then measure either the relative amounts of H—Z and D—Z, or the relative amounts of the D-containing product formed by reaction (3) and the H-containing product formed by reaction (4).

Problem 11.10 (a) When excess toluene-α-d ($C_6H_5CH_2D$) was photochemically monochlorinated at 80° with 0.1 mole of chlorine, there were obtained 0.0212 mole DCl and 0.0868 mole HCl. What is the value of the isotope effect k^H/k^D (*per hydrogen atom*, of course)? (b) What relative amounts of DCl and HCl would you expect to get from $C_6H_5CHD_2$?

11.16 Mechanism of electrophilic aromatic substitution: the two steps

Now that we know what isotope effects are and, in a general way, how they arise, we are ready to see why they are of interest to the organic chemist. Let us return to the questions we asked before: how do we know that electrophilic aromatic substitution involves *two* steps,



instead of just *one*,

(1a) $$ArH + Y^+ \longrightarrow \left[\begin{array}{c} H \\ Ar \\ Y \end{array}\right]^+ \longrightarrow ArY + H^+$$

and how do we know that, of these two steps, the first is much slower than the second?

The answer is found in a series of studies begun by Lars Melander (of the Nobel Institute of Chemistry, Stockholm) and extended by many other workers. A variety of aromatic compounds labeled with deuterium or tritium were subjected to nitration, bromination, and Friedel-Crafts alkylation. It was found that in these reactions deuterium or tritium is replaced at the *same* rate as protium; *there is no significant isotope effect.*

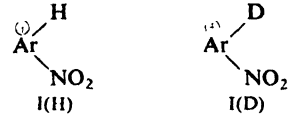
We have seen that a carbon–deuterium bond is broken more slowly than a carbon–protium bond, and a carbon–tritium bond more slowly yet. How then, are we to interpret the fact that there is no isotope effect here? If the rates of replacement of the various hydrogen isotopes are the same, it can only mean that the reactions *whose rates we are comparing* do not involve the breaking of a carbon–hydrogen bond.

This interpretation is consistent with our mechanism. The rate of the overall substitution is determined by the slow attachment of the electrophilic reagent to the aromatic ring to form the carbonium ion. Once formed, the carbonium ion rapidly loses hydrogen ion to form the products. Step (1) is thus the *rate-determining step.* Since it does not involve the breaking of a carbon–hydrogen bond, its rate– and hence the rate of the overall reaction– is independent of the particular hydrogen isotope that is present.

If substitution involved a *single* step, as in (1a), this step would necessarily be the rate-determining step and, since it involves breaking of the carbon hydrogen bond, an isotope effect would be observed. Or, if step (2) of the two-step sequence were slow enough relative to step (1) to affect the overall rate, again we would expect an isotope effect. (Indeed, sulfonation *does* show a small isotope effect and, as we shall see, for just this reason. Even in sulfonation, however, the overall rate is controlled chiefly by step (1).)

Thus the absence of isotope effects establishes not only the two-step nature of electrophilic aromatic substitution, but also the relative speeds of the steps. Attachment of the electrophile to a carbon atom of the ring is the difficult step (see Fig. 11.2); but it is equally difficult whether the carbon carries protium or deuterium. The next step, loss of hydrogen ion, is easy. Although it occurs more slowly for deuterium than for protium, this really makes no difference; slightly faster or slightly slower, its speed has no effect on the overall rate.

Let us look at this matter more closely (Fig. 11.2, insert). Every carbonium ion formed, whether I(H) or I(D), goes on to product, since the energy barrier to



the right (ahead of the carbonium ion)—whether slightly higher for deuterium or slightly lower for protium—is still considerably lower than the barrier to the left (behind the carbonium ion). But the barrier behind the carbonium ion is the E_{act} for the *reverse* of step (1). It is this reverse reaction that must be much slower than step (2) if step (1) is to be truly rate-determining (see Sec. 14.12). Summarized in terms of the *rate constants*, k, for the various steps, we have:

$$ArH + {}^{+}NO_2 \underset{k_{-1}}{\overset{(1)\ k_1}{\rightleftharpoons}} \underset{I}{\overset{H}{\overset{\oplus}{Ar}}\!\!<_{NO_2}} \xrightarrow[(2)]{k_2} ArNO_2 + H^+ \qquad k_2 \gg k_{-1}$$

We can see why nitration and reactions like it are not reversible. In the reverse of nitration, nitrobenzene is protonated (the reverse of reaction 2) to form carbonium ion I; but this is, of course, no different from the ion I formed in the nitration process, and it does the same thing: (re)forms nitrobenzene.

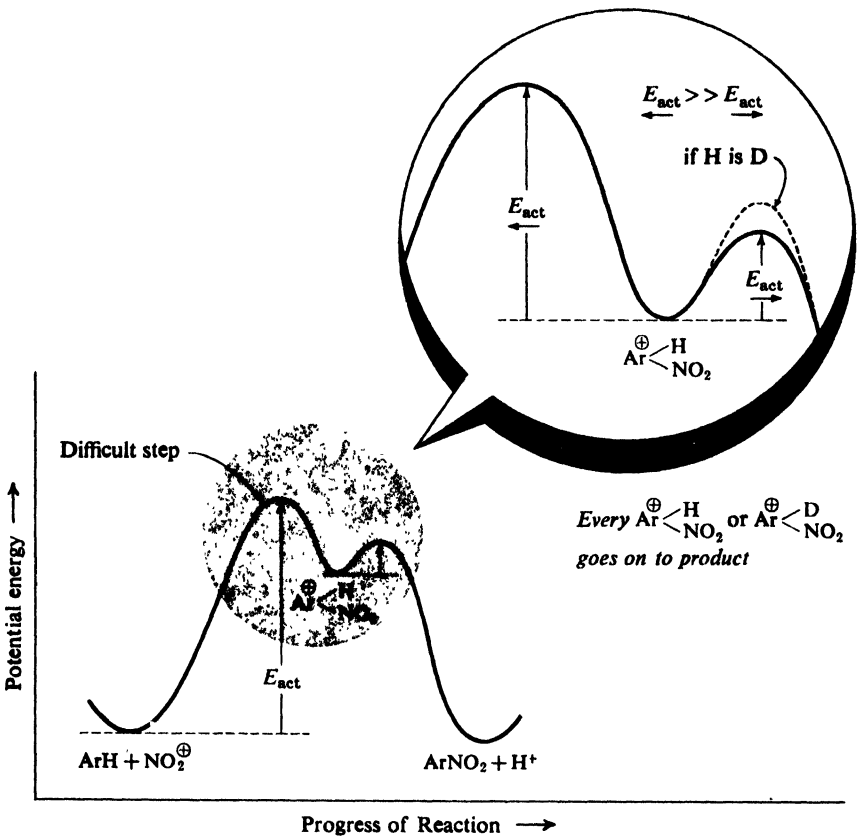


Figure 11.2. Nitration. Formation of carbonium ion is rate-controlling step; occurs equally rapidly whether protium (H) or deuterium (D) at point of attack. All carbonium ions go on to product. There is no isotope effect, and nitration is irreversible.

Unlike most other electrophilic substitution reactions, sulfonation shows a moderate isotope effect: ordinary hydrogen (protium) is displaced from an aromatic ring about twice as fast as deuterium. Does this mean that sulfonation takes place by a different mechanism than nitration, one involving a single step? Almost certainly not.

$$ArH + SO_3 \underset{k_{-1}}{\overset{(1)\ k_1}{\rightleftharpoons}} \overset{\oplus}{Ar}\!\!<\!\!\begin{matrix}H\\ SO_3^-\end{matrix} \quad (II) \xrightarrow{(2)\ k_2} ArSO_3^- + H^+ \qquad k_2 \sim k_{-1}$$

Unlike most other electrophilic substitution reactions, sulfonation is reversible, and this fact gives us our clue. Reversibility means that carbonium ion II can lose SO_3 to form the hydrocarbon. Evidently here reaction (2) is *not* much

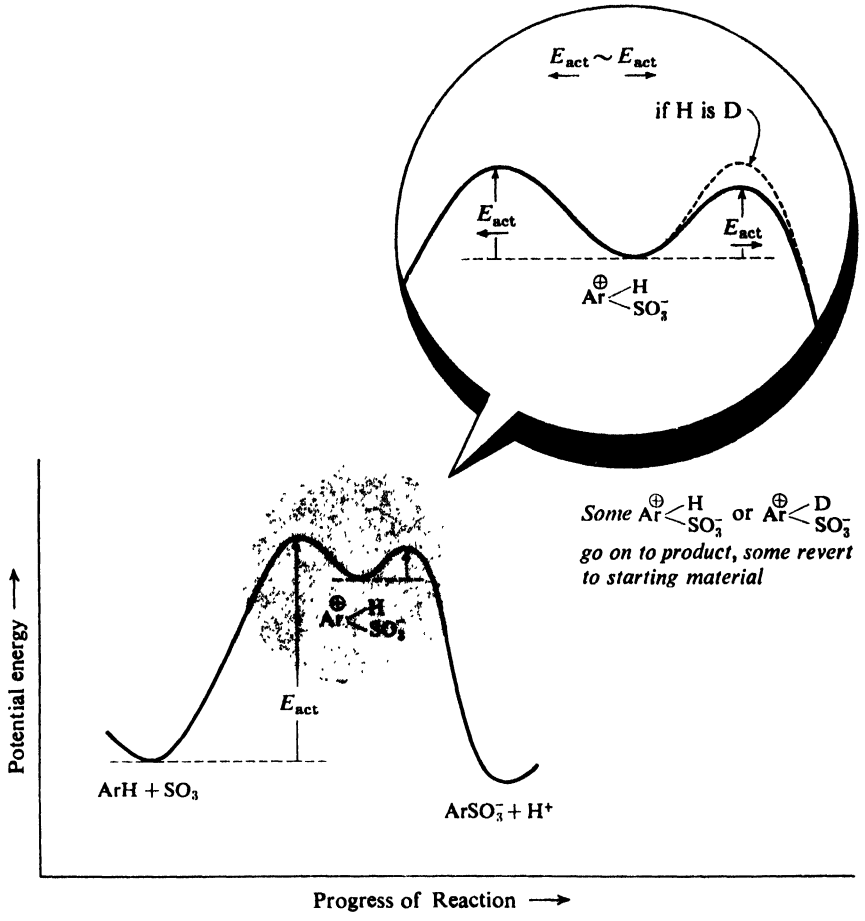


Figure 11.3 Sulfonation. Some carbonium ions go on to product, some revert to starting material. There is an isotope effect, and sulfonation is reversible.

faster than the reverse of reaction (1). In sulfonation, the energy barriers on either side of the carbonium ion II must be roughly the same height; some ions go one way, some go the other (Fig. 11.3). Now, whether the carbonium ion is II(D) or II(H), the barrier to the left (behind it) is the same height. But to climb the barrier to the right (ahead), a carbon–hydrogen bond must be broken, so this barrier is higher for carbonium ion II(D) than for carbonium ion II(H). More deuterated ions than ordinary ions revert to starting material, and so overall sulfonation is slower for the deuterated benzene. Thus, the particular shape of potential energy curve that makes sulfonation reversible also permits an isotope effect to be observed.

By use of especially selected aromatic substrates—highly hindered ones—isotope effects can be detected in other kinds of electrophilic aromatic substitution, even in nitration. In certain reactions the *size* of the isotope can be deliberately varied by changes in experimental conditions—and in a way that shows dependence on the relative rates of (2) and the reverse of (1). There can be little doubt that all these reactions follow the same two-step mechanism, but with differences in the shape of potential energy curves. In isotope effects the chemist has an exceedingly delicate probe for the examination of organic reaction mechanisms.

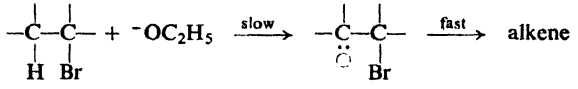
Problem 11.11 From the reaction of mesitylene (1,3,5-trimethylbenzene) with HF and BF_3, Olah (see p. 346) isolated at low temperatures a bright-yellow solid whose elemental composition corresponds to mesitylene:HF:BF_3 in the ratio 1:1:1. The compound was poorly soluble in organic solvents and, when melted, conducted an electric current; chemical analysis showed the presence of the BF_4^- ion. When heated, the compound evolved BF_3 and regenerated mesitylene.

What is a likely structure for the yellow compound? The isolation of this and related compounds is considered to be strong support for the mechanism of electrophilic aromatic substitution. Why should this be so?

Problem 11.12 Dehydrobromination by $C_2H_5O^-Na^+$ of ordinary isopropyl bromide and of labeled isopropyl bromide, $(CD_3)_2CHBr$, at 25° has been studied, and the rates found to be in the ratio 1.76:0.26. (a) What is the value of the isotope effect? (b) Is this isotope effect consistent with the mechanism for dehydrohalogenation given in Sec. 5.13? (c) With the following two-step mechanism involving a carbonium ion?

$$RBr \xrightarrow{\text{slow}} R^+Br^- \xrightarrow{\text{fast}} \text{alkene}$$

(d) With the following two-step mechanism involving a carbanion?



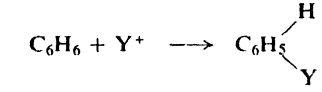
11.17 Reactivity and orientation

We have seen that certain groups activate the benzene ring and direct substitution to *ortho* and *para* positions, and that other groups deactivate the ring and (except halogens) direct substitution to *meta* positions. Let us see if we can account for these effects on the basis of principles we have already learned.

First of all, we must remember that reactivity and orientation are both matters of relative rates of reaction. Methyl is said to activate the ring because it makes

the ring react *faster* than benzene; it causes *ortho,para* orientation because it makes the *ortho* and *para* positions react *faster* than the *meta* positions.

Now, we know that, whatever the specific reagent involved, the rate of electrophilic aromatic substitution is determined by the same slow step –attack of the electrophile on the ring to form a carbonium ion:

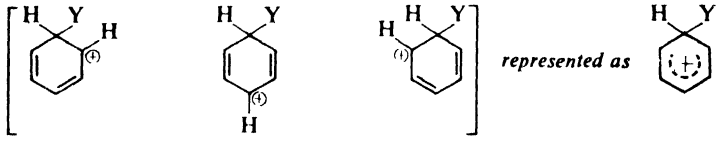


Slow: *rate-determining*

Any differences in rate of substitution must therefore be due to differences in the rate of this step.

For closely related reactions, a difference in rate of formation of carbonium ions is largely determined by a difference in E_{act}, that is, by a difference in stability of transition states. As with other carbonium ion reactions we have studied, factors that stabilize the ion by dispersing the positive charge should for the same reason stabilize the incipient carbonium ion of the transition state. Here again we expect the more stable carbonium ion to be formed more rapidly. We shall therefore concentrate on the relative stabilities of the carbonium ions.

In electrophilic aromatic substitution the intermediate carbonium ion is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest as the positions *ortho* and *para* to the carbon atom being attacked.

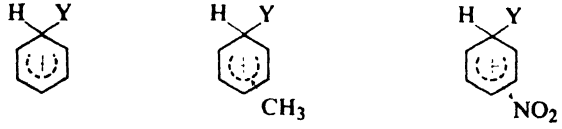


I II III IV

A group already attached to the benzene ring should affect the stability of the carbonium ion by dispersing or intensifying the positive charge, depending upon its electron-releasing or electron-withdrawing nature. It is evident from the structure of the ion (I–III) that this stabilizing or destabilizing effect should be especially important when the group is attached *ortho* or *para* to the carbon being attacked.

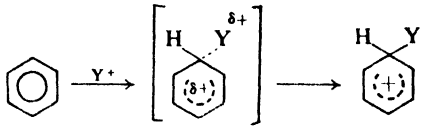
11.18 Theory of reactivity

To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbonium ions formed from the three compounds:



I II III

By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbonium ion. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to a faster reaction.



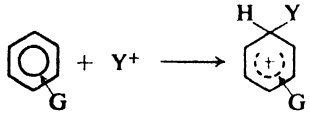
Transition state. *developing positive charge*

Carbonium ion: *full positive charge*

The $-NO_2$ group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbonium ion, and thus causes a slower reaction.

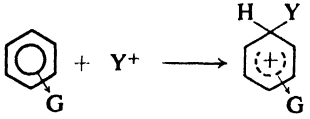
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. **A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.**

Electrophilic Aromatic Substitution



G releases electrons, stabilizes carbonium ion, activates

G = $-NH_2$, $-OH$, $-OCH_3$, $-NHCOCH_3$, $-C_6H_5$, $-CH_3$



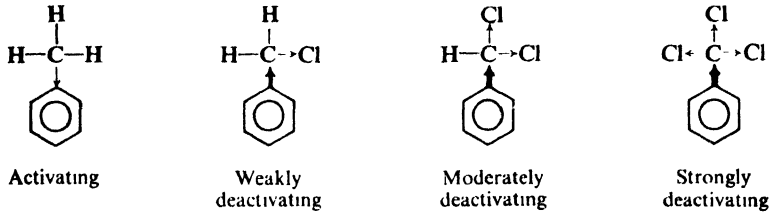
G withdraws electrons; destabilizes carbonium ion, deactivates

G = $-N(CH_3)_3^+$, $-NO_2$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$, $-X$

Like $-CH_3$, other alkyl groups release electrons, and like $-CH_3$ they activate the ring. For example, *tert*-butylbenzene is 16 times as reactive as benzene toward nitration. Electron release by $-NH_2$ and $-OH$, and by their derivatives $-OCH_3$ and $-NHCOCH_3$, is due not to their inductive effect but to resonance, and is discussed later (Sec. 11.20).

We are already familiar with the electron-withdrawing effect of the halogens (Sec. 6.11). The full-fledged positive charge of the $-N(CH_3)_3^+$ group has, of course, a powerful attraction for electrons. In the other deactivating groups (e.g., $-NO_2$, $-CN$, $-COOH$), the atom next to the ring is attached by a multiple bond to oxygen or nitrogen. These electronegative atoms attract the mobile π electrons, making the atom next to the ring electron-deficient; to make up this deficiency, the atom next to the ring withdraws electrons from the ring.

We might expect replacement of hydrogen in $-CH_3$ by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group. This is found to be the case. Toward nitration,



toluene is 25 times as reactive as benzene; benzyl chloride is only one-third as reactive as benzene. The $-CH_2Cl$ group is thus weakly deactivating. Further replacement of hydrogen by halogen to yield the $-CHCl_2$ and the $-CCl_3$ groups results in stronger deactivation.

11.19 Theory of orientation

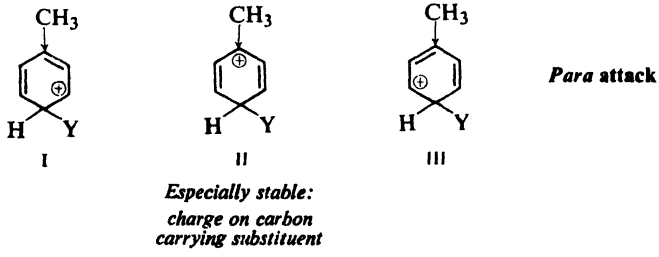
Before we try to account for orientation in electrophilic substitution, let us look more closely at the facts.

An activating group activates all positions of the benzene ring; even the positions *meta* to it are more reactive than any single position in benzene itself. It directs *ortho* and *para* simply because it activates the *ortho* and *para* positions much *more* than it does the *meta*.

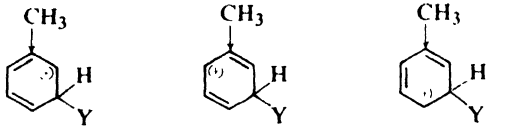
A deactivating group deactivates all positions in the ring, even the positions *meta* to it. It directs *meta* simply because it deactivates the *ortho* and *para* positions even *more* than it does the *meta*.

Thus both *ortho,para* orientation and *meta* orientation arise in the same way: **the effect of any group—whether activating or deactivating—is strongest at the *ortho* and *para* positions.**

To see if this is what we would expect, let us compare, for example, the carbonium ions formed by attack at the *para* and *meta* positions of toluene, a compound that contains an activating group. Each of these is a hybrid of three structures, I–III for *para*, IV–VI for *meta*. In one of these six structures, II, the positive charge is located on the carbon atom to which $-CH_3$ is attached. Although $-CH_3$ releases electrons to all positions of the ring, it does so most strongly to the car-



bon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbonium ion resulting from

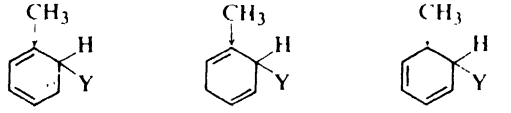


IV V VI

Meta attack

attack at the *para* position is more stable than the carbonium ion resulting from attack at a *meta* position. *Para* substitution, therefore, occurs faster than *meta* substitution.

In the same way, it can be seen that attack at an *ortho* position (VII–IX)



VII VIII IX

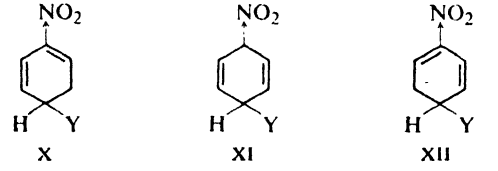
Ortho attack

Especially stable: charge on carbon carrying substituent

also yields a more stable carbonium ion, through contribution from IX, than attack at a *meta* position.

In toluene, *ortho,para* substitution is thus faster than *meta* substitution because electron release by $-CH_3$ is more effective during attack at the positions *ortho* and *para* to it.

Next, let us compare the carbonium ions formed by attack at the *para* and *meta* positions of nitrobenzene, a compound that contains a deactivating group. Each of these is a hybrid of three structures, X–XII for *para* attack, XIII–XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the



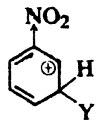
X XI XII

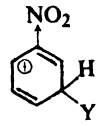
Para attack

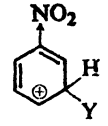
Especially unstable: charge on carbon carrying substituent

carbon atom to which $-NO_2$ is attached. Although $-NO_2$ withdraws electrons from all positions, it does so most from the carbon atom nearest it, and hence this carbon atom, already positive, has little tendency to accommodate the positive charge of the carbonium ion. Structure XI is thus a particularly unstable one and does little to help stabilize the ion resulting from attack at the *para* position. The ion for *para* attack is virtually a hybrid of only two structures, X and XII; the

positive charge is mainly restricted to only *two* carbon atoms. It is less stable than the ion resulting from attack at a *meta* position, which is a hybrid of three structures, and in which the positive charge is accommodated by *three* carbon atoms. *Para* substitution, therefore, occurs more slowly than *meta* substitution.

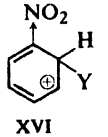

XIII

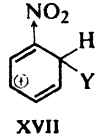

XIV

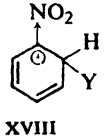

XV

***Meta* attack**

In the same way it can be seen that attack at an *ortho* position (XVI–XVIII) yields a less stable carbonium ion, because of the instability of XVIII, than attack at a *meta* position.


XVI


XVII


XVIII

Especially unstable: charge on carbon carrying substituent

***Ortho* attack**

In nitrobenzene, *ortho,para* substitution is thus slower than *meta* substitution because electron withdrawal by $-NO_2$ is more effective during attack at the positions *ortho* and *para* to it.

Thus we see that both *ortho,para* orientation by activating groups and *meta* orientation by deactivating groups follow logically from the structure of the intermediate carbonium ion. The charge of the carbonium ion is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest effect, whether activating or deactivating.

The unusual behavior of the halogens, which direct *ortho* and *para* although deactivating, results from a combination of two opposing factors, and will be taken up in Sec. 11.21.

11.20 Electron release via resonance

We have seen that a substituent group affects both reactivity and orientation in electrophilic aromatic substitution by its tendency to release or withdraw electrons. So far, we have considered electron release and electron withdrawal only as inductive effects, that is, as effects due to the electronegativity of the group concerned.

But certain groups ($-NH_2$ and $-OH$, and their derivatives) act as powerful activators toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to have electron-withdrawing inductive effects. If our approach to the problem is correct, these groups must release electrons in some other way than through their inductive effects; they are

believed to do this by a resonance effect. But before we discuss this, let us review a little of what we know about nitrogen and oxygen.

Although electronegative, the nitrogen of the $-NH_2$ group is basic and tends to share its last pair of electrons and acquire a positive charge. Just as ammonia accepts a hydrogen ion to form the ammonium (NH_4^+) ion, so organic compounds related to ammonia accept hydrogen ions to form substituted ammonium ions.

$$\ddot{N}H_3 + H^+ \longrightarrow NH_4^+ \qquad R\ddot{N}H_2 + H^+ \longrightarrow RNH_3^+$$

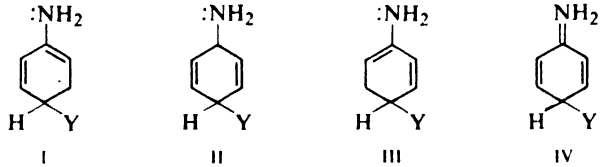
$$R_2\ddot{N}H + H^+ \longrightarrow R_2NH_2^+ \qquad R_3\ddot{N} + H^+ \longrightarrow R_3NH^+$$

The —OH group shows similar but weaker basicity; we are already familiar with oxonium ions, ROH_2^+.

$$H_2\ddot{O} + H^+ \longrightarrow H_3O^+ \qquad R\ddot{O}H + H^+ \longrightarrow ROH_2^+$$

The effects of $-NH_2$ and —OH on electrophilic aromatic substitution can be accounted for by assuming that nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge.

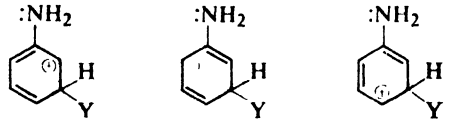
The carbonium ion formed by attack *para* to the $-NH_2$ group of aniline, for example, is considered to be a hybrid not only of structures I, II, and III, with positive charges located on carbons of the ring, but also of structure IV in which the



I II III IV

Para attack

Especially stable: every atom has octet

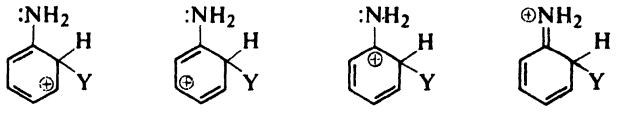


V VI VII

Meta attack

positive charge is carried by nitrogen. Structure IV is especially stable, since in it *every atom* (except hydrogen, of course) *has a complete octet of electrons.* This carbonium ion is much more stable than the one obtained by attack on benzene itself, or the one obtained (V–VII) from attack *meta* to the $-NH_2$ group of aniline; in neither of these cases is a structure like IV possible. (Compare, for example, the stabilities of the ions NH_4^+ and CH_3^+. Here it is not a matter of which atom, nitrogen or carbon, can better accommodate a positive charge; it is a matter of which atom has a complete octet of electrons.)

Examination of the corresponding structures (VIII–XI) shows that *ortho* attack is much like *para* attack:



VIII IX X XI

Ortho attack

Especially stable: every atom has octet

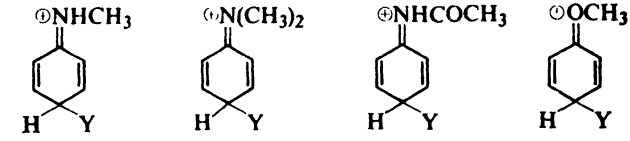
Thus substitution in aniline occurs faster than substitution in benzene, and occurs predominantly at the positions *ortho* and *para* to $-NH_2$.

In the same way activation and *ortho,para* orientation by the —OH group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:

XII XIII

Para attack *Ortho* attack

The similar effects of the derivatives of $-NH_2$ and —OH are accounted for by similar structures (shown only for *para* attack):



$-NHCH_3$ $-N(CH_3)_2$ $-NHCOCH_3$ $-OCH_3$

The tendency of oxygen and nitrogen in groups like these to share more than a pair of electrons with an aromatic ring is shown in a number of other ways, which will be discussed later (Sec. 23.2 and Sec. 24.7).

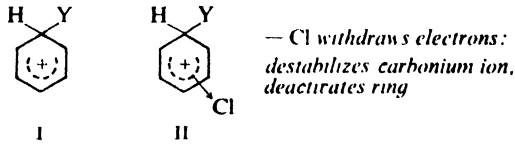
11.21 Effect of halogen on electrophilic aromatic substitution

Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet *ortho,para*-directing. Deactivation is characteristic of electron withdrawal, whereas *ortho,para* orientation is characteristic of electron release. Can halogen both withdraw and release electrons?

The answer is *yes*. Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect. So, presumably, can the $-NH_2$ and —OH groups, but there the much stronger resonance effect greatly

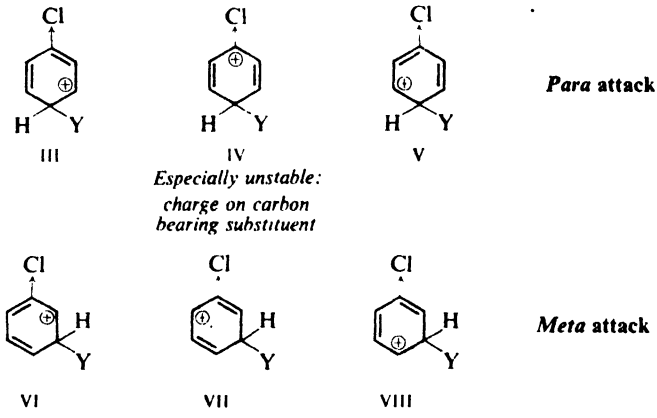
outweighs the other. For halogen, the two effects are more evenly balanced, and we observe the operation of both.

Let us first consider **reactivity.** Electrophilic attack on benzene yields car-



bonium ion I, attack on chlorobenzene yields carbonium ion II. The electron-withdrawing inductive effect of chlorine intensifies the positive charge in carbonium ion II, makes the ion less stable, and causes a slower reaction.

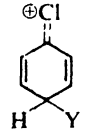
Next, to understand **orientation**, let us compare the structures of the carbonium ions formed by attack at the *para* and *meta* positions of chlorobenzene. Each of



these is a hybrid of three structures, III–V for *para*, VI–VIII for *meta*. In one of these six structures, IV, the positive charge is located on the carbon atom to which chlorine is attached. Through its inductive effect chlorine withdraws electrons most from the carbon to which it is joined, and thus makes structure IV especially unstable. As before, we expect IV to make little contribution to the hybrid, which should therefore be less stable than the hybrid ion resulting from attack at the *meta* positions. If only the inductive effect were involved, then, we would expect not only deactivation but also *meta* orientation.

But the existence of halonium ions (Sec. 7.12) has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. If we apply that idea to the present problem, what do we find? The ion resulting from *para* attack is a hybrid not only of structures III–V, but also of structure IX, in which chlorine bears a positive charge and is joined to the ring by a double bond. This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a *complete octet of electrons.* (Structure IX is exactly analogous to those proposed to account for activation and *ortho,para* direction by $—NH_2$ and —OH.) No such structure is possible for the ion resulting from

meta attack. To the extent that structure IX contributes to the hybrid, it makes the ion resulting from *para* attack more stable than the ion resulting from *meta* attack.



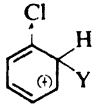
IX

Comparatively stable: every atom has octet

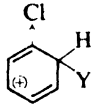
***Para* attack**

Although we could not have predicted the relative importance of the two factors — the instability of IV and the stabilization by IX —the result indicates that the contribution from IX is the more important.

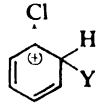
In the same way it can be seen that attack at an *ortho* position also yields an ion (X–XIII) that can be stabilized by accommodation of the positive charge by chlorine.



X

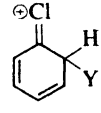


XI



XII

Especially unstable: charge on carbon bearing substituent



XIII

Comparatively stable: every atom has octet

***Ortho* attack**

Through its inductive effect halogen tends to withdraw electrons and thus to destabilize the intermediate carbonium ion. This effect is felt for attack at all positions, but particularly for attack at the positions *ortho* and *para* to the halogen.

Through its resonance effect halogen tends to release electrons and thus to stabilize the intermediate carbonium ion. This electron release is effective only for attack at the positions *ortho* and *para* to the halogen.

The inductive effect is stronger than the resonance effect and causes net electron withdrawal—and hence deactivation—for attack at all positions. The resonance effect tends to oppose the inductive effect for attack at the *ortho* and *para* positions, and hence makes the deactivation less for *ortho,para* attack than for *meta*.

Reactivity is thus controlled by the stronger inductive effect, and orientation is controlled by the resonance effect, which, although weaker, seems to be more selective.

Problem 11.13 Hydrogen iodide adds to vinyl chloride more slowly than to ethylene, and yields 1-chloro-1-iodoethane. (a) Draw the formula of the carbonium ion formed in the initial step of the addition to vinyl chloride. (b) Of addition to ethylene. (c) Judging from the relative rates of reaction, which would appear to be the more stable carbonium ion? (d) Account for the difference in stability.

(e) Draw the formula for the carbonium ion that would be formed if vinyl chloride were to yield 1-chloro-2-iodoethane. (f) Judging from the actual orientation of addition, which carbonium ion from vinyl chloride is the more stable, (a) or (e)? (g) Account for the difference in stability.

(h) Which effect, inductive or resonance, controls reactivity in electrophilic addition to vinyl halides? (i) Which effect controls orientation?

Thus we find that a single structural concept—partial double-bond formation between halogen and carbon—helps to account for unusual chemical properties of such seemingly different compounds as aryl halides and vinyl halides. The structures involving doubly-bonded halogen, which probably make important contribution not only to benzenonium ions but to the parent aryl halides as well (Sec. 25.6), certainly do not seem to meet our usual standard of reasonableness (Sec. 6.27). The sheer weight of evidence forces us to accept the idea that certain carbon–halogen bonds possess double-bond character. If this idea at first appears strange to us, it simply shows how little, after all, we really know about molecular structure.

11.22 Relation to other carbonium ion reactions

In summary, we can say that both reactivity and orientation in electrophilic aromatic substitution are determined by the rates of formation of the intermediate carbonium ions concerned. These rates parallel the stabilities of the carbonium ions, which are determined by the electron-releasing or electron-withdrawing tendencies of the substituent groups.

A group may release or withdraw electrons by an inductive effect, a resonance effect, or both. These effects oppose each other only for the $-NH_2$ and $-OH$ groups (and their derivatives) and for the halogens, $-X$. For $-NH_2$ and $-OH$ the resonance effect is much the more important; for $-X$ the effects are more evenly matched. It is because of this that the halogens occupy the unusual position of being deactivating groups but *ortho,para* directors.

We have accounted for the facts of electrophilic aromatic substitution in exactly the way that we accounted for the relative ease of dehydration of alcohols, and for reactivity and orientation in electrophilic addition to alkenes: the more stable the carbonium ion, the faster it is formed; the faster the carbonium ion is formed, the faster the reaction goes.

In all this we have estimated the stability of a carbonium ion on the same basis: **the dispersal or concentration of the charge** due to electron release or electron withdrawal by the substituent groups. As we shall see, the approach that has worked so well for elimination, for addition, and for electrophilic aromatic substitution works for still another important class of organic reactions in which a positive charge develops: *nucleophilic aliphatic substitution by the S_N1 mechanism* (Sec. 14.14). It works equally well for *nucleophilic aromatic substitution* (Sec. 25.9), in which a negative charge develops. Finally, we shall find that this approach will help us to understand *acidity* or *basicity* of such compounds as carboxylic acids, sulfonic acids, amines, and phenols.

PROBLEMS

1. Give structures and names of the principal products expected from the ring monobromination of each of the following compounds. In each case, tell whether bromination will occur faster or slower than with benzene itself.

(a) acetanilide ($C_6H_5NHCOCH_3$)
(b) iodobenzene
(c) *sec*-butylbenzene
(d) N-methylaniline ($C_6H_5NHCH_3$)
(e) ethyl benzoate ($C_6H_5COOC_2H_5$)
(f) acetophenone ($C_6H_5COCH_3$)

(g) phenetole ($C_6H_5OC_2H_5$)
(h) diphenylmethane ($C_6H_5CH_2C_6H_5$)
(i) benzonitrile (C_6H_5CN)
(j) benzotrifluoride ($C_6H_5CF_3$)
(k) biphenyl ($C_6H_5—C_6H_5$)

2. Give structures and names of the principal organic products expected from mononitration of:

(a) *o*-nitrotoluene
(b) *m*-dibromobenzene
(c) *p*-nitroacetanilide (p-$O_2NC_6H_4NHCOCH_3$)
(d) *m*-dinitrobenzene
(e) *m*-cresol (m-$CH_3C_6H_4OH$)
(f) *o*-cresol
(g) *p*-cresol
(h) *m*-nitrotoluene
(i) *p*-xylene (p-$C_6H_4(CH_3)_2$)
(j) terephthalic acid (p-$C_6H_4(COOH)_2$)
(k) anilinium hydrogen sulfate ($C_6H_5NH_3^+HSO_4^-$)

3. Give structures and names of the principal organic products expected from the monosulfonation of :

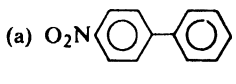
(a) cyclohexylbenzene
(b) nitrobenzene
(c) anisole ($C_6H_5OCH_3$)
(d) benzenesulfonic acid
(e) salicylaldehyde (o-HOC_6H_4CHO)
(f) *m*-nitrophenol
(g) *o*-fluoroanisole
(h) *o*-nitroacetanilide (o-$O_2NC_6H_4NHCOCH_3$)
(i) *o*-xylene
(j) *m*-xylene
(k) *p*-xylene

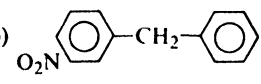
4. Arrange the following in order of reactivity toward ring nitration, listing by structure the most reactive at the top, the least reactive at the bottom.

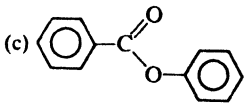
(a) benzene, mesitylene ($1,3,5$-$C_6H_3(CH_3)_3$), toluene, *m*-xylene, *p*-xylene
(b) benzene, bromobenzene, nitrobenzene, toluene
(c) acetanilide ($C_6H_5NHCOCH_3$), acetophenone ($C_6H_5COCH_3$), aniline, benzene
(d) terephthalic acid, toluene, *p*-toluic acid (p-$CH_3C_6H_4COOH$), *p*-xylene
(e) chlorobenzene, *p*-chloronitrobenzene, 2,4-dinitrochlorobenzene
(f) 2,4-dinitrochlorobenzene, 2,4-dinitrophenol
(g) *m*-dinitrobenzene, 2,4-dinitrotoluene

5. Even though 1,3,5-trinitrobenzene (TNB) has more shattering power (more *brisance*) and is no more dangerous to handle, 2,4,6-trinitrotoluene (TNT) has always been the high explosive in more general use. Can you suggest a reason (connected with manufacture) for the popularity of TNT? (Benzene and toluene are both readily available materials; for many years benzene was cheaper.)

6. For each of the following compounds, indicate which ring you would expect to be attacked in nitration, and give structures of the principal products.

(a) 
p-Nitrobiphenyl

(b) 
m-Nitrodiphenylmethane

(c) 
Phenyl benzoate

7. Arrange the compounds of each set in order of reactivity toward electrophilic substitution. Indicate in each set which would yield the highest percentage of *meta* isomer, and which would yield the lowest.

(a) $C_6H_5N(CH_3)_3^+$, $C_6H_5CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2CH_2N(CH_3)_3^+$
(b) $C_6H_5NO_2$, $C_6H_5CH_2NO_2$, $C_6H_5CH_2CH_2NO_2$
(c) $C_6H_5CH_3$, $C_6H_5CH_2COOC_2H_5$, $C_6H_5CH(COOC_2H_5)_2$, $C_6H_5C(COOC_2H_5)_3$

8. There is evidence that the phenyl group, C_6H_5–, has an electron-withdrawing inductive effect. Yet each ring of biphenyl, C_6H_5–C_6H_5, is more reactive than benzene

toward electrophilic substitution, and the chief products are *ortho* and *para* isomers. Show how reactivity and orientation can be accounted for on the basis of resonance.

9. When β-phenylethyl alcohol, $C_6H_5CH_2CH_2OH$, is treated with thallium trifluoroacetate followed by potassium iodide, there is obtained predominantly one aryl iodide, the particular isomer depending upon the conditions of thallation: (a) 25°, *ortho*; (b) 75°, *meta*; (c) prior conversion to the ester, $C_6H_5CH_2CH_2OCOCH_3$, then 25°, *para*. Suggest an explanation for each case of regiospecificity.

10. There is evidence that the reaction between HNO_3 and H_2SO_4 to generate $^+NO_2$ (which we have summarized in one equation, Sec. 11.8) actually involves three steps, the second of which is the slowest one and the one that actually produces $^+NO_2$. Can you suggest a reasonable sequence of reactions? (*Hint:* See Sec. 5.20.)

11. Treatment of *sulfanilic acid* (p-$H_2NC_6H_4SO_3H$) with 3 moles of bromine yields 2,4,6-tribromoaniline. Treatment of 4-hydroxy-1,3-benzenedisulfonic acid with nitric acid yields picric acid, 2,4,6-trinitrophenol. (a) Outline the most probable mechanism for the replacement of $-SO_3H$ by $-Br$ and by $-NO_2$. (b) To what general class of organic reactions do those reactions belong?

12. Using only individual steps with which you are already familiar, outline a likely mechanism for the following reaction.

$$C_6H_5C(CH_3)_3 + Br_2(AlBr_3) \longrightarrow C_6H_5Br + HBr + (CH_3)_2C{=}CH_2$$

13. In light of what you have learned in this chapter, predict the major products of each of the following reactions.

(a) $(CH_3)_3\overset{+}{N}CH{=}CH_2 + HI$
(b) $CH_2{=}CHCF_3 + HBr(AlBr_3)$
(c) What is the function of $AlBr_3$ in (b)? Why is it needed here?

14. You are trying to find out whether or not there is an isotope effect in a particular kind of substitution in which the electrophile Y replaces a hydrogen of an aromatic ring. In each of the following cases, tell what you would *do*, and what you would *expect to observe* if there were an isotope effect. (You can quantitatively analyze mixtures of isomers. Your mass spectrometer will tell you what percentage of the hydrogen in a compound is deuterium, but not the location of deuterium in a molecule.)

(a) C_6H_6 and C_6D_6 are allowed to react separately but under identical conditions.
(b) A 50:50 mixture of C_6H_6 and C_6D_6 is allowed to react with a limited amount of the reagent.
(c) Anisole and anisole-4-d are allowed to react separately. (Both your watch and your mass spectrometer are under repair when this particular experiment is carried out.)
(d) Benzene-1,3,5-d_3 (1,3,5-trideuteriobenzene) is allowed to react.

15. Outline all steps in the laboratory synthesis of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents. (Review the general instructions on p. 224. Assume that a pure *para* isomer can be separated from an *ortho,para* mixture.)

(a) *p*-nitrotoluene
(b) *p*-bromonitrobenzene
(c) *p*-dichlorobenzene
(d) *m*-bromobenzenesulfonic acid
(e) *p*-bromobenzenesulfonic acid
(f) *p*-bromobenzoic acid
(g) *m*-bromobenzoic acid
(h) *o*-iodobenzoic acid
(i) 1,3,5-trinitrobenzene
(j) 2-bromo-4-nitrotoluene
(k) 2-bromo-4-nitrobenzoic acid
(l) 4-bromo-3-nitrobenzoic acid
(m) 3,5-dinitrobenzoic acid
(n) 4-nitro-1,2-dibromobenzene
(o) 2-nitro-1,4-dichlorobenzene
(p) *m*-iodotoluene

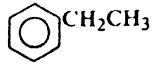
16. Outline all steps in the following laboratory syntheses, using any needed aliphatic or inorganic reagents. (Follow the other instructions in Problem 15).

(a) 4-nitro-2,6-dibromoanisole from anisole ($C_6H_5OCH_3$)
(b) 4-bromo-2-nitrobenzoic acid from *o*-nitrotoluene
(c) 2,4,6-tribromoaniline from aniline
(d) 2,4-dinitroacetanilide from acetanilide ($C_6H_5NHCOCH_3$)
(e) 5-nitroisophthalic acid from *m*-xylene
(f) 4-nitroisophthalic acid from *m*-xylene
(g) 2-nitroterephthalic acid from *p*-xylene (two ways)
(h) Which way in (g) is preferable? Why?

Chapter 12 Arenes

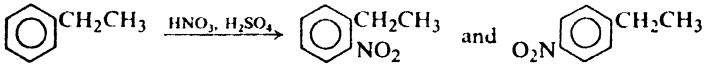
12.1 Aliphatic-aromatic hydrocarbons

From our study so far we know what kind of chemical properties to expect of an aliphatic hydrocarbon, that is, of an alkane, alkene, or alkyne. We know what kind of chemical behavior to expect of the parent aromatic hydrocarbon, benzene. Many important compounds are not just aliphatic or just aromatic, however, but contain both aliphatic and aromatic units; hydrocarbons of this kind are known collectively as **arenes**. *Ethylbenzene*, for example, contains a benzene ring and an aliphatic side chain.



Ethylbenzene

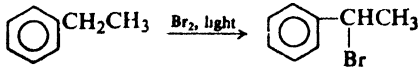
What kind of chemical properties might we expect of one of these mixed aliphatic-aromatic hydrocarbons? First, we might expect it to show *two* sets of chemical properties. The ring of ethylbenzene should undergo the electrophilic



More readily than for benzene

o-Nitroethylbenzene *p*-Nitroethylbenzene

Chief products



More readily than for ethane

1-Bromo-1-phenylethane
(α-Phenylethyl bromide)
Only product

substitution characteristic of benzene, and the side chain should undergo the free-radical substitution characteristic of ethane. Second, the properties of each portion of the molecule should be modified by the presence of the other portion. The ethyl group should modify the aromatic properties of the ring, and the ring should modify the aliphatic properties of the side chain.

These predictions are correct. Treatment of ethylbenzene with nitric acid and sulfuric acid, for instance, introduces a nitro group into the ring; treatment with bromine in the presence of light introduces a bromine atom into the side chain. But because of the ethyl group, nitration takes place more readily than with benzene itself, and occurs chiefly at the positions *ortho* and *para* to the ethyl group; and because of the ring, bromination takes place more readily than with ethane, and occurs exclusively on the carbon nearer the ring. Thus *each portion of the molecule affects the* **reactivity** *of the other portion and determines the* **orientation** *of attack.*

In the same way we may have a molecule that is part aromatic and part alkene, or part aromatic and part alkyne. Again each portion of such a molecule shows the properties characteristic of its particular structure, although these properties are modified by the other portion of the molecule.

We shall examine most closely the compounds made up of aromatic and alkane units, the **alkylbenzenes**. We shall look much more briefly at the aromatic-alkene compounds (**alkenylbenzenes**) and aromatic-alkyne compounds (**alkynylbenzenes**).

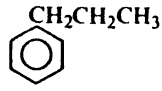
We shall encounter the *benzyl* free radical and the *benzyl* carbonium ion, which pretty much complete our lists of these reactive particles, and shall see how their relative stabilities can be accounted for.

12.2 Structure and nomenclature

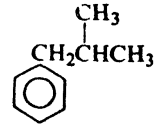
The simplest of the alkylbenzenes, methylbenzene, is given the special name of **toluene**. Compounds containing longer side chains are named by prefixing the name of the alkyl group to the word *-benzene*, as, for example, in *ethylbenzene*, *n-propylbenzene*, and *isobutylbenzene*.

Toluene

Ethylbenzene

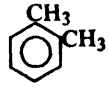


n-Propylbenzene

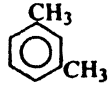


Isobutylbenzene

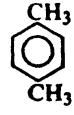
The simplest of the dialkylbenzenes, the dimethylbenzenes, are given the special names of **xylenes**; we have, then, *o-xylene*, *m-xylene*, and *p-xylene*. Dialkylbenzenes containing one methyl group are named as derivatives of toluene, while others are named by prefixing the names of both alkyl groups to the word *-benzene*. A compound containing a very complicated side chain might be named as a



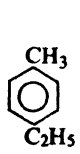
o-Xylene



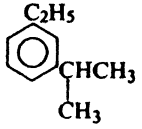
m-Xylene



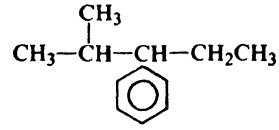
p-Xylene



p-Ethyltoluene

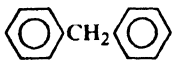


m-Ethylisopropylbenzene

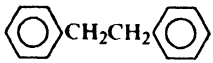


2-Methyl-3-phenylpentane

phenylalkane (C_6H_5 = **phenyl**). Compounds containing more than one benzene ring are nearly always named as derivatives of alkanes.

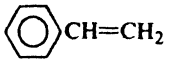


Diphenylmethane

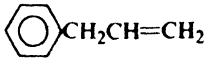


1,2-Diphenylethane

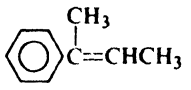
The simplest alkenylbenzene has the special name **styrene**. Others are generally named as substituted alkenes, occasionally as substituted benzenes. Alkynylbenzenes are named as substituted alkynes.



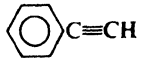
Styrene
(Vinylbenzene)
(Phenylethylene)



Allylbenzene
(3-Phenylpropene)



2-Phenyl-2-butene



Phenylacetylene

12.3 Physical properties

As compounds of low polarity, the alkylbenzenes possess physical properties that are essentially the same as those of the hydrocarbons we have already studied. They are insoluble in water, but quite soluble in non-polar solvents like ether, carbon tetrachloride, or ligroin. They are almost always less dense than water. As we can see from Table 12.1, boiling points rise with increasing molecular weight, the boiling point increment being the usual 20–30° for each carbon atom.

Since melting points depend not only on molecular weight but also on molecular shape, their relationship to structure is a very complicated one. One important general relationship does exist, however, between melting point and structure of aromatic compounds: *among isomeric disubstituted benzenes, the para isomer generally melts considerably higher than the other two.* The xylenes, for example, boil within six degrees of one another; yet they differ widely in melting point, the *o*- and *m*-isomers melting at −25° and −48°, and the *p*-isomer melting at +13°. Since dissolution, like melting, involves overcoming the intermolecular forces of the crystal, it is not surprising to find that *generally the para isomer is also the least soluble in a given solvent.*

The higher melting point and lower solubility of a *para* isomer is only a special example of the general effect of molecular symmetry on intracrystalline forces. The more symmetrical a compound, the better it fits into a crystal lattice and hence the higher the melting point and the lower the solubility. *Para* isomers are simply the most symmetrical of disubstituted benzenes. We can see (Table 12.1) that

Table 12.1 ALIPHATIC-AROMATIC HYDROCARBONS

Name	Formula	M.p., °C	B.p., °C	Density (20°C)
Benzene	C_6H_6	5.5	80	0.879
Toluene	$C_6H_5CH_3$	− 95	111	.866
o-Xylene	$1,2\text{-}C_6H_4(CH_3)_2$	− 25	144	.880
m-Xylene	$1,3\text{-}C_6H_4(CH_3)_2$	− 48	139	.864
p-Xylene	$1,4\text{-}C_6H_4(CH_3)_2$	13	138	.861
Hemimellitene	$1,2,3\text{-}C_6H_3(CH_3)_3$	− 25	176	.895
Pseudocumene	$1,2,4\text{-}C_6H_3(CH_3)_3$	− 44	169	.876
Mesitylene	$1,3,5\text{-}C_6H_3(CH_3)_3$	− 45	165	.864
Prehnitene	$1,2,3,4\text{-}C_6H_2(CH_3)_4$	− 6.5	205	.902
Isodurene	$1,2,3,5\text{-}C_6H_2(CH_3)_4$	− 24	197	
Durene	$1,2,4,5\text{-}C_6H_2(CH_3)_4$	80	195	
Pentamethylbenzene	$C_6H(CH_3)_5$	53	231	
Hexamethylbenzene	$C_6(CH_3)_6$	165	264	
Ethylbenzene	$C_6H_5C_2H_5$	− 95	136	.867
n-Propylbenzene	$C_6H_5CH_2CH_2CH_3$	− 99	159	.862
Cumene	$C_6H_5CH(CH_3)_2$	− 96	152	.862
n-Butylbenzene	$C_6H_5(CH_2)_3CH_3$	− 81	183	.860
Isobutylbenzene	$C_6H_5CH_2CH(CH_3)_2$		171	.867
sec-Butylbenzene	$C_6H_5CH(CH_3)C_2H_5$	− 83	173.5	.864
tert-Butylbenzene	$C_6H_5C(CH_3)_3$	− 58	169	.867
p-Cymene	$1,4\text{-}CH_3C_6H_4CH(CH_3)_2$	− 70	177	.857
Biphenyl	$C_6H_5C_6H_5$	70	255	
Diphenylmethane	$C_6H_5CH_2C_6H_5$	26	263	
Triphenylmethane	$(C_6H_5)_3CH$	93	360	
1,2-Diphenylethane	$C_6H_5CH_2CH_2C_6H_5$	52	284	
Styrene	$C_6H_5CH{=}CH_2$	− 31	145	.907
trans-Stilbene	*trans*-$C_6H_5CH{=}CHC_6H_5$	124	307	
cis-Stilbene	*cis*-$C_6H_5CH{=}CHC_6H_5$	6		
unsym-Diphenylethylene	$(C_6H_5)_2C{=}CH_2$	9	277	1.02
Triphenylethylene	$(C_6H_5)_2C{=}CHC_6H_5$	73		
Tetraphenylethylene	$(C_6H_5)_2C{=}C(C_6H_5)_2$	227	425	
Phenylacetylene	$C_6H_5C{\equiv}CH$	− 45	142	0.930
Diphenylacetylene	$C_6H_5C{\equiv}CC_6H_5$	62.5	300	

1,2,4,5-tetramethylbenzene melts 85° to 100° higher than the less symmetrical 1,2,3,5- and 1,2,3,4-isomers. A particularly striking example of the effect of symmetry on melting point is that of benzene and toluene. The introduction of a single methyl group into the extremely symmetrical benzene molecule lowers the melting point from 5° to −95°.

12.4 Industrial source of alkylbenzenes

It would be hard to exaggerate the importance to the chemical industry and to our entire economy of the large-scale production of benzene and the alkylbenzenes. Just as the alkanes obtained from petroleum are ultimately the source of nearly all our aliphatic compounds, so benzene and the alkylbenzenes are ultimately the source of nearly all our aromatic compounds. When a chemist wishes to make a

complicated aromatic compound, whether in the laboratory or in industry, he does not make a benzene ring; he takes a simpler compound already containing a benzene ring and then adds to it, piece by piece, until he has built the structure he wants.

Just where do the enormous quantities of simple aromatic compounds come from? There are two large reservoirs of organic material, **coal** and **petroleum**, and aromatic compounds are obtained from both. Aromatic compounds are separated as such from coal tar, and are synthesized from the alkanes of petroleum.

By far the larger portion of coal that is mined today is converted into coke, which is needed for the smelting of iron to steel. When coal is heated in the absence of air, it is partly broken down into simpler, volatile compounds which are driven out; the residue is *coke*. The volatile materials consist of *coal gas* and a liquid known as **coal tar**.

From coal tar by distillation there are obtained a number of aromatic compounds. Upon coking, a ton of soft coal may yield about 120 pounds of coal tar. From this 120 pounds the following aromatic compounds can be separated: benzene, 2 pounds; toluene, 0.5 pound; xylenes, 0.1 pound; phenol, 0.5 pound; cresols, 2 pounds; naphthalene, 5 pounds. Two pounds of benzene from a ton of coal does not represent a very high percentage yield, yet so much coal is coked every year that the annual production of benzene from coal tar is enormous.

Still larger quantities of aromatic hydrocarbons are needed, and these are synthesized from alkanes through the process of **catalytic reforming** (Sec. 9.3). This can bring about not only *dehydrogenation*, as in the formation of toluene from methylcyclohexane, but also *cyclization* and *isomerization*, as in the formation of toluene from *n*-heptane or 1,2-dimethylcyclopentane. In an analogous way, benzene is obtained from cyclohexane and methylcyclopentane, as well as from the *hydrodealkylation* of toluene.

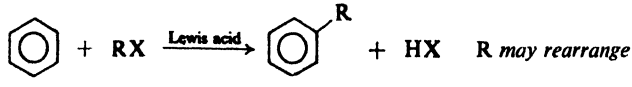
Today, petroleum is the *chief* source of the enormous quantities of benzene, toluene, and the xylenes required for chemicals and fuels. Half of the toluene and xylenes are utilized in high-test gasoline where, in a sense, they replace the aliphatic compounds—inferior as fuels—from which they were made. (A considerable fraction even of naphthalene, the major component of coal tar distillate, is now being produced from petroleum hydrocarbons.)

12.5 Preparation of alkylbenzenes

Although a number of the simpler alkylbenzenes are available from industrial sources, the more complicated compounds must be synthesized in one of the ways outlined below.

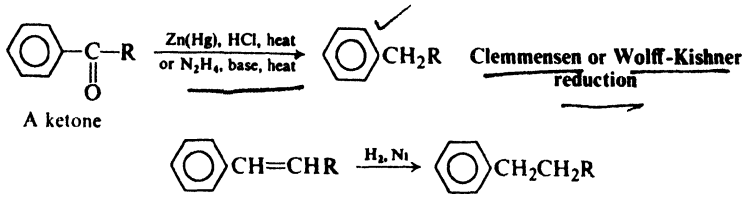
PREPARATION OF ALKYLBENZENES

1. Attachment of alkyl group: Friedel-Crafts alkylation. Discussed in Secs. 12.6–12.8.



Lewis acid: $AlCl_3$, BF_3, HF, etc.
Ar-X *cannot be used in place of* R-X

2. Conversion of side chain. Discussed in Sec. 19.10.



Friedel-Crafts alkylation is extremely useful since it permits the direct attachment of an alkyl group to the aromatic ring. There are, however, a number of limitations to its use (Sec. 12.8), including the fact that the alkyl group that becomes attached to the ring is not always the same as the alkyl group of the parent halide; this **rearrangement** of the alkyl group is discussed in Sec. 12.7.

There are frequently available aromatic compounds containing aliphatic side chains that are not simple alkyl groups. An alkylbenzene can be prepared from one of these compounds by converting the side chain into an alkyl group. Although there is an aromatic ring in the molecule, this conversion is essentially the preparation of an alkane from some other aliphatic compound. The methods used are those that we have already learned for the preparation of alkanes: hydrogenation of a carbon-carbon double bond in a side chain, for example. Many problems of the alkylbenzenes are solved by a consideration of simple alkane chemistry.

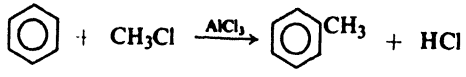
The most important side-chain conversion involves **reduction of ketones** either by amalgamated zinc and HCl (*Clemmensen reduction*) or by hydrazine and strong base (*Wolff-Kishner reduction*). This method is important because the necessary ketones are readily available through a modification of the Friedel-Crafts reaction that involves acid chlorides (see Sec. 19.6). Unlike alkylation by the Friedel-Crafts reaction, this method does not involve rearrangement.

Problem 12.1 How might you prepare ethylbenzene from: (a) benzene and ethyl alcohol; (b) acetophenone, $C_6H_5COCH_3$; (c) styrene, $C_6H_5CH{=}CH_2$; (d) α-phenylethyl alcohol, $C_6H_5CHOHCH_3$; and (e) β-phenylethyl chloride, $C_6H_5CH_2CH_2Cl$?

Problem 12.2 How might you prepare 2,3-diphenylbutane from α-phenylethyl alcohol, $C_6H_5CHOHCH_3$?

12.6 Friedel-Crafts alkylation

If a small amount of anhydrous aluminum chloride is added to a mixture of benzene and methyl chloride, a vigorous reaction occurs, hydrogen chloride gas is



Toluene

evolved, and toluene can be isolated from the reaction mixture. This is the simplest example of the reaction discovered in 1877 at the University of Paris by the French-American team of chemists, Charles Friedel and James Crafts. *Considered in its various modifications, the Friedel-Crafts reaction is by far the most important method for attaching alkyl side chains to aromatic rings.*

Each of the components of the simple example just given can be varied. The alkyl halide may contain an alkyl group more complicated than methyl, and a halogen atom other than chlorine; in some cases alcohols are used or—especially in industry—alkenes. Substituted alkyl halides, like benzyl chloride, $C_6H_5CH_2Cl$, also can be used. Because of the low reactivity of halogen attached to an aromatic ring (Sec. 25.5), aryl halides (Ar—X, e.g., bromo- or chlorobenzene) *cannot* be used in place of alkyl halides.

The aromatic ring to which the side chain becomes attached may be that of benzene itself, certain substituted benzenes (chiefly alkylbenzenes and halobenzenes), or more complicated aromatic ring systems like naphthalene and anthracene (Chap. 30).

In place of aluminum chloride, other Lewis acids can be used, in particular BF_3, HF, and phosphoric acid.

The reaction is carried out by simply mixing together the three components; usually the only problems are those of moderating the reaction by cooling and of trapping the hydrogen halide gas. Since the attachment of an alkyl side chain makes the ring more susceptible to further attack (Sec. 11.5), steps must be taken to limit substitution to *mono*alkylation. As in halogenation of alkanes (Sec. 2.8), this is accomplished by using an *excess* of the hydrocarbon. In this way an alkyl carbonium ion seeking an aromatic ring is more likely to encounter an unsubstituted ring than a substituted one. Frequently the aromatic compound does double duty, serving as solvent as well as reactant.

From polyhalogenated alkanes it is possible to prepare compounds containing more than one aromatic ring:

$$2C_6H_6 + CH_2Cl_2 \xrightarrow{AlCl_3} C_6H_5CH_2C_6H_5 + 2HCl$$

Diphenylmethane

$$2C_6H_6 + ClCH_2CH_2Cl \xrightarrow{AlCl_3} C_6H_5CH_2CH_2C_6H_5 + 2HCl$$

1,2-Diphenylethane

$$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} C_6H_5{-}\underset{\displaystyle H}{\overset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}{-}C_6H_5 + 3HCl$$

Triphenylmethane

$$3C_6H_6 + CCl_4 \xrightarrow{AlCl_3} C_6H_5{-}\underset{\displaystyle Cl}{\overset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}{-}C_6H_5 + 3HCl$$

Triphenylchloromethane

12.7 Mechanism of Friedel-Crafts alkylation

In Sec. 11.10 we said that two mechanisms are possible for Friedel-Crafts alkylation. Both involve electrophilic aromatic substitution, but they differ as to the nature of the electrophile.

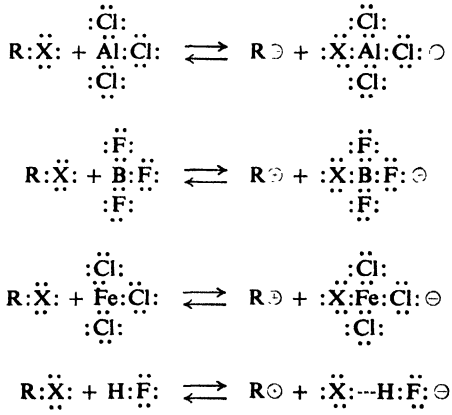
One mechanism for Friedel-Crafts alkylation involves the following steps,

(1) $$RCl + AlCl_3 \rightleftharpoons AlCl_4^- + R^{\oplus}$$

(2) $$R^{\oplus} + C_6H_6 \rightleftharpoons C_6H_5(R)H$$

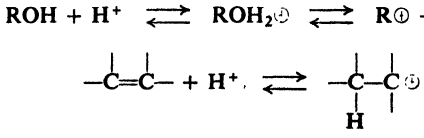
(3) $$C_6H_5(R)H + AlCl_4^- \rightleftharpoons C_6H_5R + HCl + AlCl_3$$

in which the electrophile is an alkyl carbonium ion. The function of the aluminum chloride is to generate this carbonium ion by abstracting the halogen from the alkyl halide. It is not surprising that other Lewis acids can function in the same way and thus take the place of aluminum chloride:



Carbonium ions from alkyl halides

Judging from the mechanism just described, we might expect the benzene ring to be attacked by carbonium ions generated in other ways: by the action of acid on alcohols (Sec. 5.20) and on alkenes (Sec. 6.10).



Carbonium ions from alcohols and from alkenes

This expectation is correct: alcohols and alkenes, in the presence of acids, alkylate

aromatic rings in what we may consider to be a modification of the Friedel-Crafts reaction.

$$C_6H_6 + (CH_3)_3COH \xrightarrow{H_2SO_4} C_6H_5{-}C(CH_3)_3$$

tert-Butyl alcohol — *tert*-Butylbenzene

$$C_6H_6 + (CH_3)_2C{=}CH_2 \xrightarrow{H_2SO_4} C_6H_5{-}C(CH_3)_3$$

Isobutylene — *tert*-Butylbenzene

Also judging from the mechanism, we might expect Friedel-Crafts alkylation to be accompanied by the kind of rearrangement that is characteristic of carbonium ion reactions (Sec. 5.22). This expectation, too, is correct. As the following examples show, alkylbenzenes containing rearranged alkyl groups are not only formed but are sometimes the sole products. In each case, we see that the particular kind of rearrangement corresponds to what we would expect if a less stable (1°) carbonium ion were to rearrange by a 1,2-shift to a more stable (2° or 3°) carbonium ion.

$$C_6H_6 + CH_3CH_2CH_2Cl \xrightarrow[-18° \text{ to } 80°]{AlCl_3} C_6H_5CH_2CH_2CH_3 \text{ and } C_6H_5CH(CH_3)_2$$

n-Propyl chloride — *n*-Propylbenzene, *35–31%* — Isopropylbenzene, *65–69%*

$$C_6H_6 + CH_3CH_2\overset{\delta}{C}H_2CH_2Cl \xrightarrow[0°]{AlCl_3} C_6H_5CH_2CH_2CH_2CH_3 \text{ and } C_6H_5CH(CH_3)CH_2CH_3$$

n-Butyl chloride — *n*-Butylbenzene, *34%* — *sec*-Butylbenzene, *66%*

$$C_6H_6 + CH_3CH(CH_3)CH_2Cl \xrightarrow[-18° \text{ to } 80°]{AlCl_3} C_6H_5C(CH_3)_3$$

Isobutyl chloride — *tert*-Butylbenzene, *Only product*

$$C_6H_6 + CH_3C(CH_3)_2CH_2OH \xrightarrow[60°]{BF_3} C_6H_5C(CH_3)_2CH_2CH_3$$

Neopentyl alcohol — *tert*-Pentylbenzene, *Only product*

We can now make another addition to our list of carbonium ion reactions (Sec. 6.16). **A carbonium ion may:**

(a) eliminate a hydrogen ion to form an alkene;
(b) rearrange to a more stable carbonium ion;
(c) combine with a negative ion or other basic molecule;
(d) add to an alkene to form a larger carbonium ion;
(e) abstract a hydride ion from an alkane;
(f) alkylate an aromatic ring.

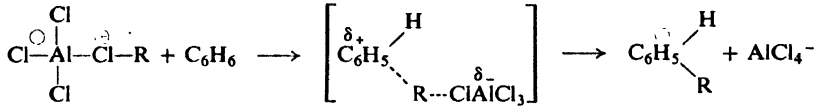
A carbonium ion formed by (b) or (d) can subsequently undergo any of the reactions.

In alkylation, as in its other reactions, the carbonium ion gains a pair of electrons to complete the octet of the electron-deficient carbon—this time from the π cloud of an aromatic ring.

Problem 12.3 *tert*-Pentylbenzene is the major product of the reaction of benzene in the presence of BF_3 with each of the following alcohols: (a) 2-methyl-1-butanol, (b) 3-methyl-2-butanol, (c) 3-methyl-1-butanol, and (d) neopentyl alcohol. Account for its formation in each case.

In some of the examples given above, we see that *part* of the product is made up of *unrearranged* alkylbenzenes. Must we conclude that part of the reaction does not go by way of carbonium ions? Not *necessarily*. Attack on an aromatic ring is probably one of the most difficult jobs a carbonium ion is called on to do; that is to say, toward carbonium ions an aromatic ring is a reagent of low reactivity and hence high selectivity. Although there may be present a higher concentration of the more stable, rearranged carbonium ions, the aromatic ring may tend to seek out the scarce unrearranged ions because of their higher reactivity. In some cases, it is quite possible that some of the carbonium ions react with the aromatic ring before they have time to rearrange; the same low stability that makes primary carbonium ions, for example, prone to rearrangement also makes them highly reactive.

On the other hand, there is additional evidence (of a kind we cannot go into here) that makes it very likely that there *is* a second mechanism for Friedel-Crafts alkylation. In this mechanism, the electrophile is not an alkyl carbonium ion, but an acid–base complex of alkyl halide and Lewis acid, from which the alkyl group is transferred *in one step* from halogen to the aromatic ring.



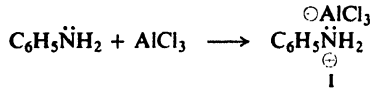
This duality of mechanism does not reflect exceptional behavior, but is usual for electrophilic aromatic substitution. It also fits into the usual pattern for *nucleophilic aliphatic substitution* (Sec. 14.16), which—from the standpoint of the alkyl halide—is the kind of reaction taking place. Furthermore, the particular halides (1° and methyl) which appear to react by this second mechanism are just the ones that would have been *expected* to do so.

12.8 Limitations of Friedel-Crafts alkylation

We have encountered three limitations to the use of Friedel-Crafts alkylation: (a) the danger of polysubstitution; (b) the possibility that the alkyl group will rearrange; and (c) the fact that aryl halides cannot take the place of alkyl halides. Besides these, there are several other limitations.

(d) An aromatic ring less reactive than that of the halobenzenes does not undergo the Friedel-Crafts reaction; evidently the carbonium ion, R^+, is a less powerful nucleophile than NO_2^+ and the other electron-deficient reagents that bring about electrophilic aromatic substitution.

Next, (e) aromatic rings containing the $-NH_2$, $-NHR$, or $-NR_2$ group do not undergo Friedel-Crafts alkylation, partly because the strongly basic nitrogen ties up the Lewis acid needed for ionization of the alkyl halide:



Problem 12.4 Tying up of the acidic catalyst by the basic nitrogen is not the only factor that prevents alkylation, since even when excess catalyst is used, reaction does not occur. Looking at the structure of the complex (I) shown for aniline, can you suggest another factor? (*Hint:* See Sec. 11.18.)

Despite these numerous limitations, the Friedel-Crafts reaction, in its various modifications (for example, acylation, Sec. 19.6), is an extremely useful synthetic tool.

12.9 Reactions of alkylbenzenes

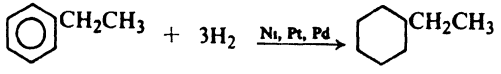
The most important reactions of the alkylbenzenes are outlined below, with toluene and ethylbenzene as specific examples; essentially the same behavior is shown by compounds bearing other side chains. Except for hydrogenation and oxidation, these reactions involve either **electrophilic substitution in the aromatic ring** or **free-radical substitution in the aliphatic side chain.**

In following sections we shall be mostly concerned with (a) how experimental conditions determine which portion of the molecule—aromatic or aliphatic—is attacked, and (b) how each portion of the molecule modifies the reactions of the other portion.

REACTIONS OF ALKYLBENZENES

1. Hydrogenation.

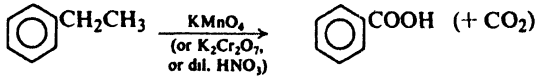
Example:



Ethylbenzene — Ethylcyclohexane

2. Oxidation. Discussed in Sec. 12.10.

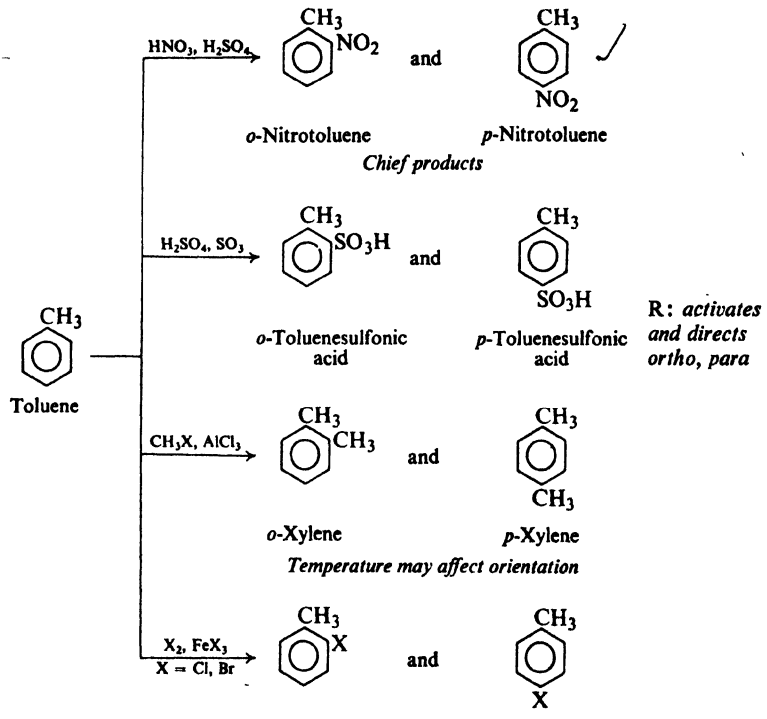
Example:



Ethylbenzene — Benzoic acid

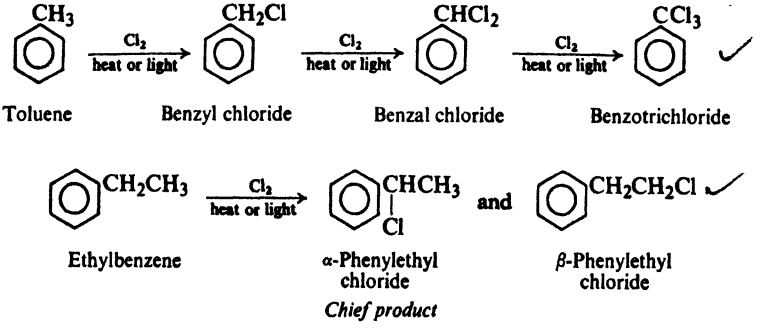
3. Substitution in the ring. Electrophilic aromatic substitution. Discussed in Sec. 12.11.

Examples:

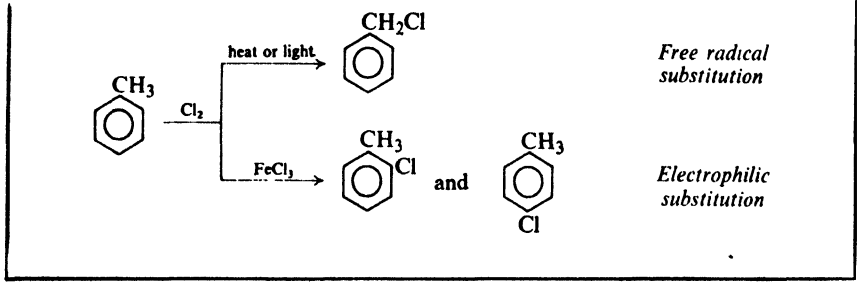


4. Substitution in the side chain. Free-radical halogenation. Discussed in Secs. 12.12–12.14.

Examples:

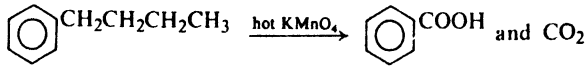


Note: Competition between ring and side chain. Discussed in Sec. 12.12.



12.10 Oxidation of alkylbenzenes

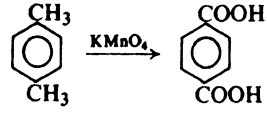
Although benzene and alkanes are quite unreactive toward the usual oxidizing agents ($KMnO_4$, $K_2Cr_2O_7$, etc.), the benzene ring renders an aliphatic side chain quite susceptible to oxidation. The side chain is oxidized down to the ring, only a carboxyl group (—COOH) remaining to indicate the position of the original side chain. Potassium permanganate is generally used for this purpose, although potassium dichromate or dilute nitric acid also can be used. (Oxidation of a side chain is more difficult, however, than oxidation of an alkene, and requires prolonged treatment with hot $KMnO_4$.)



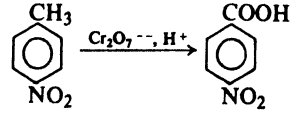
n-Butylbenzene Benzoic acid

This reaction is used for two purposes: (a) synthesis of carboxylic acids, and (b) identification of alkylbenzenes.

(a) Synthesis of carboxylic acids. One of the most useful methods of preparing an aromatic carboxylic acid involves oxidation of the proper alkylbenzene. For example:



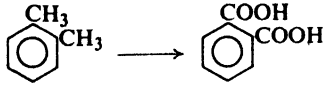
p-Xylene Terephthalic acid
(1,4-Benzenedicarboxylic acid)



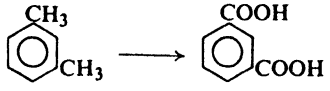
p-Nitrotoluene *p*-Nitrobenzoic acid

(b) Identification of alkylbenzenes. The number and relative positions of side chains can frequently be determined by oxidation to the corresponding acids.

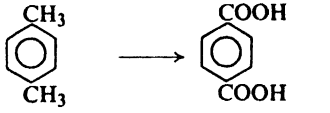
Suppose, for example, that we are trying to identify an unknown liquid of formula C_8H_{10} and boiling point 137–139° that we have shown in other ways to be an alkylbenzene (Sec. 12.22). Looking in Table 12.1 (p. 375), we find that it could be any one of four compounds: *o*-, *m*-, or *p*-xylene, or ethylbenzene. As shown below, oxidation of each of these possible hydrocarbons yields a different acid, and these acids can readily be distinguished from each other by their melting points or the melting points of derivatives.



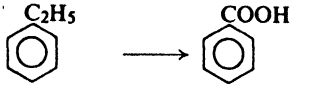
o-Xylene (b.p. 144°) — Phthalic acid, m.p. 231° (*p*-nitrobenzyl ester, m.p. 155°)



m-Xylene (b.p. 139°) — Isophthalic acid, m.p. 348° (*p*-nitrobenzyl ester, m.p. 215°)



p-Xylene (b.p. 138°) — Terephthalic acid, m.p. 300° subl. (*p*-nitrobenzyl ester, m.p. 263)



Ethylbenzene (b.p. 136) — Benzoic acid, m.p. 122° (*p*-nitrobenzyl ester, m.p. 89)

12.11 Electrophilic aromatic substitution in alkylbenzenes

Because of its electron-releasing effect, an alkyl group activates a benzene ring to which it is attached, and directs *ortho* and *para* (Secs. 11.18 and 11.19).

Problem 12.5 Treatment with methyl chloride and $AlCl_3$ at 0° converts toluene chiefly into *o*- and *p*-xylenes; at 80°, however, the chief product is *m*-xylene. Furthermore, either *o*- or *p*-xylene is readily converted into *m*-xylene by treatment with $AlCl_3$ and HCl at 80°.

How do you account for this effect of temperature on orientation? Suggest a role for the HCl.

Problem 12.6 Why is polysubstitution a complicating factor in Friedel-Crafts alkylation but not in aromatic nitration, sulfonation, or halogenation?

12.12 Halogenation of alkylbenzenes: ring *vs.* side chain

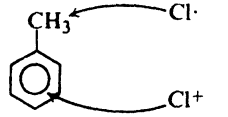
Alkylbenzenes clearly offer two main areas to attack by halogens: the ring and the side chain. We can control the position of attack simply by choosing the proper reaction conditions.

Halogenation of alkanes requires conditions under which halogen atoms are formed, that is, high temperature or light. Halogenation of benzene, on the other hand, involves transfer of positive halogen, which is promoted by acid catalysts like ferric chloride.

$$CH_4 + Cl_2 \xrightarrow{\text{heat or light}} CH_3Cl + HCl$$

$$C_6H_6 + Cl_2 \xrightarrow{FeCl_3,\ \text{cold}} C_6H_5Cl + HCl$$

We might expect, then, that the position of attack in, say, toluene would be governed by which attacking particle is involved, and therefore by the conditions employed. This is so: if chlorine is bubbled into boiling toluene that is exposed to

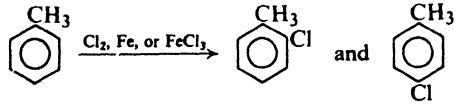


Atom: *attacks side chain*

Ion: *attacks ring*

ultraviolet light, substitution occurs almost exclusively in the side chain; in the absence of light and in the presence of ferric chloride, substitution occurs mostly in the ring. (Compare the foregoing with the problem of substitution *vs.* addition in the halogenation of alkenes (Sec. 6.21), where atoms bring about substitution and ions—or, more accurately, molecules that can transfer ions—bring about addition.)

Like nitration and sulfonation, ring halogenation yields chiefly the *o*- and

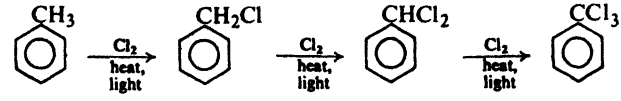


Toluene *o*-Chlorotoluene 58% *p*-Chlorotoluene 42%

p-isomers. Similar results are obtained with other alkylbenzenes, and with bromine as well as chlorine.

Side-chain halogenation, like halogenation of alkanes, may yield polyhalogenated products; even when reaction is limited to monohalogenation, it may yield a mixture of isomers.

Side-chain chlorination of toluene can yield successively the mono-, di-, and trichloro compounds. These are known as *benzyl chloride*, *benzal chloride*, and



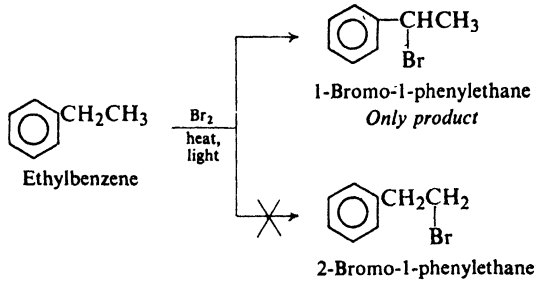
Toluene Benzyl chloride Benzal chloride Benzotrichloride

benzotrichloride; such compounds are important intermediates in the synthesis of alcohols, aldehydes, and acids.

12.13 Side-chain halogenation of alkylbenzenes

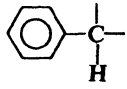
Chlorination and bromination of side chains differ from one another in orientation and reactivity in one very significant way. Let us look first at bromination, and then at chlorination.

An alkylbenzene with a side chain more complicated than methyl offers more than one position for attack, and so we must consider the likelihood of obtaining a mixture of isomers. Bromination of ethylbenzene, for example, could theoretically yield two products: 1-bromo-1-phenylethane and 2-bromo-1-phenylethane. Despite



a probability factor that favors 2-bromo-1-phenylethane by 3:2, the found is 1-bromo-1-phenylethane. Evidently abstraction of the hydrogens attached to the carbon next to the aromatic ring is greatly preferred.

Hydrogen atoms attached to carbon joined directly to an aromatic ring are called **benzylic hydrogens.**



Benzylic hydrogen:
easy to abstract

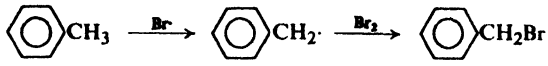
The relative ease with which benzylic hydrogens are abstracted is shown not only by orientation of bromination but also—and in a more exact way—by comparison of reactivities of different compounds. Competition experiments (Sec. 3.22) show, for example, that at 40° a benzylic hydrogen of toluene is 3.3 times as reactive toward bromine atoms as the tertiary hydrogen of an alkane—and nearly 100 million times as reactive as a hydrogen of methane!

Examination of reactions that involve attack not only by halogen atoms but by other free radicals as well has shown that this is a general rule: benzylic hydrogens are extremely easy to abstract and thus resemble allylic hydrogens. We can now expand the reactivity sequence of Sec. 6.22:

Ease of abstraction of hydrogen atoms allylic, benzylic $> 3° > 2° > 1° > CH_4$, vinylic

Side-chain halogenation of alkylbenzenes proceeds by the same mechanism as

halogenation of alkanes. Bromination of toluene, for example, would include the following steps:



Toluene Benzyl radical Benzyl bromide

The fact that benzylic hydrogens are unusually easy to abstract means that benzyl radicals are unusually easy to form.

Ease of formation of free radicals allyl, benzyl > 3° > 2° > 1° > CH_3·, vinyl

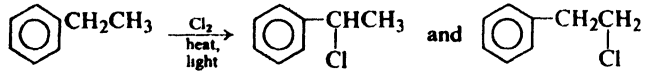
Again we ask the question: are these findings in accord with our rule that *the more stable the radical, the more rapidly it is formed*? Is the rapidly formed benzyl radical relatively stable?

The bond dissociation energies in Table 1.2 (p. 21) show that only 85 kcal is needed for formation of benzyl radicals from a mole of toluene, as compared with 91 kcal for formation of *tert*-butyl radicals and 88 kcal for formation of allyl radicals. Relative to the hydrocarbon from which each is formed, then, a benzyl radical contains less energy and is more stable than a *tert*-butyl radical.

We can now expand the sequence of radical stabilities (Sec. 6.22). Relative to the hydrocarbon from which each is formed, the relative stability of free radicals is:

Stability of free radicals allyl, benzyl > 3° > 2° > 1° > CH_3·, vinyl

Orientation of chlorination shows that chlorine atoms, like bromine atoms, preferentially attack benzylic hydrogen; but, as we see, the preference is less marked:



Ethylbenzene 1-Chloro-1-phenylethane (*Major product*, 91%) and 2-Chloro-1-phenylethane (9%)

Furthermore, competition experiments show that, under conditions where 3°, 2°, and 1° hydrogens show relative reactivities of 5.0:3.8:1.0, the relative rate per benzylic hydrogen of toluene is only 1.3. As in its attack on alkanes (Sec. 3.28), the more reactive chlorine atom is less selective than the bromine atom: less selective between hydrogens in a single molecule, and less selective between hydrogens in different molecules.

In the attack by the comparatively unreactive bromine atom, we have said (Sec. 2.23), the transition state is reached late in the reaction process: the carbon–hydrogen bond is largely broken, and the organic group has acquired a great deal of free-radical character. The factors that stabilize the benzyl free radical stabilize the incipient benzyl free radical in the transition state.

In contrast, in the attack by the highly reactive chlorine atom, the transition state is reached early in the reaction process: the carbon–hydrogen bond is only slightly broken, and the organic group has acquired little free-radical character. The factors that stabilize the benzyl radical have little effect on this transition state.

Just why benzylic hydrogens are *less* reactive toward chlorine atoms than even secondary hydrogens is not understood. It has been attributed to *polar factors* (Sec. 32.4), but this hypothesis has been questioned.

12.14 Resonance stabilization of the benzyl radical

How are we to account for the stability of the benzyl radical? Bond dissociation energies indicate that 19 kcal/mole less energy (104 − 85) is needed to form the benzyl radical from toluene than to form the methyl radical from methane.

$$\underset{\text{Toluene}}{C_6H_5CH_3} \longrightarrow \underset{\text{Benzyl radical}}{C_6H_5CH_2\cdot} + H\cdot \qquad \Delta H = +85 \text{ kcal}$$

As we did for the allyl radical (Sec. 6.24), let us examine the structures involved. Toluene contains the benzene ring and is therefore a hybrid of the two Kekulé structures, I and II:

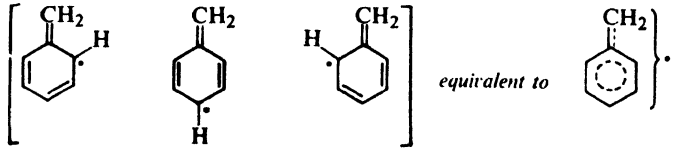
I II

Similarly, the benzyl radical is a hybrid of the two Kekulé structures, III and IV:

III IV

This resonance causes stabilization, that is, lowers the energy content. However, resonance involving Kekulé structures presumably stabilizes both molecule and radical to the same extent, and hence does not affect the *difference* in their energy contents. If there were no other factors involved, then we might reasonably expect the bond dissociation energy for a benzylic hydrogen to be about the same as that of a methane hydrogen (see Fig. 12.1).

Considering further, however, we find that we can draw three additional structures for the radical: V, VI, and VII. In these structures there is a double bond between the side chain and the ring, and the odd electron is located on the carbon atoms *ortho* and *para* to the side chain. Drawing these pictures is, of



V VI VII

course, our way of indicating that the odd electron is not localized on the side chain but is *delocalized*, being distributed about the ring. We cannot draw comparable structures for the toluene molecule.

Contribution from the three structures, V–VII, stabilizes the radical in a way that is not possible for the molecule. Resonance thus lowers the energy content of the benzyl radical more than it lowers the energy content of toluene. This extra stabilization of the radical evidently amounts to 19 kcal/mole (Fig. 12.1).

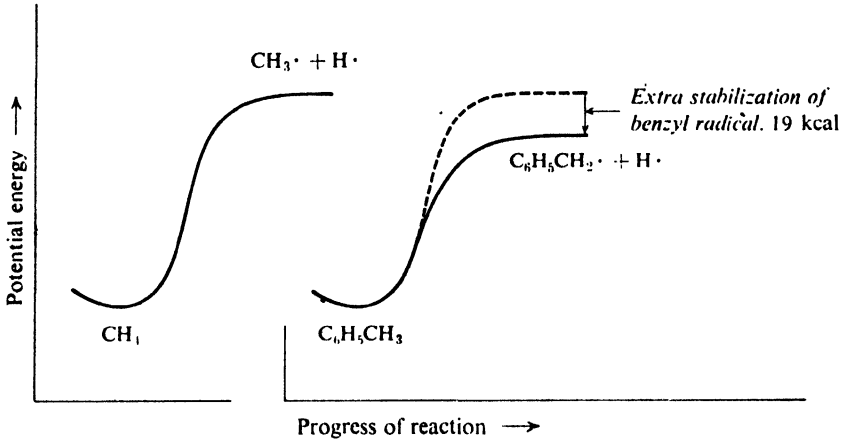


Figure 12.1. Molecular structure and rate of reaction. Resonance-stabilized benzyl radical formed faster than methyl radical. (Plots aligned with each other for easy comparison.)

We say, then, that the benzyl radical is *stabilized by resonance*. When we use this expression, we must always bear in mind that we actually mean that the benzyl radical is stabilized by resonance *to a greater extent than* the hydrocarbon from which it is formed.

In terms of orbitals, delocalization results from overlap of the p orbital occupied by the odd electron with the π cloud of the ring.

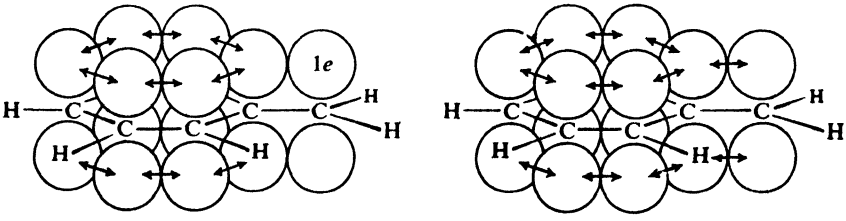


Figure 12.2. Benzyl radical. The p orbital occupied by the odd electron overlaps π cloud of ring.

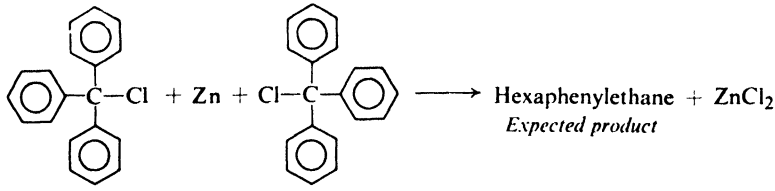
Problem 12.7 It is believed that the side-chain hydrogens of the benzyl radical lie in the same plane as the ring. Why should they?

Problem 12.8 The strength of the bond holding side-chain hydrogen in *m*-xylene is the same as in toluene; in *o*- and *p*-xylene it is 3–4 kcal lower. How do you account for these differences?

12.15 Triphenylmethyl: a stable free radical

We have said that benzyl and allyl free radicals are stabilized by resonance; but we must realize, of course, that they are stable only in comparison with simple alkyl radicals like methyl or ethyl. Benzyl and allyl free radicals are extremely reactive, unstable particles, whose fleeting existence (a few thousandths of a second) has been proposed simply because it is the best way to account for certain experimental observations. We do not find bottles on the laboratory shelf labeled "benzyl radicals" or "allyl radicals." Is there, then, any direct evidence for the existence of free radicals?

In 1900 a remarkable paper appeared in the *Journal of the American Chemical Society* and in the *Berichte der deutschen chemischen Gesellschaft*; its author was the young Russian-born chemist Moses Gomberg, who was at that time an instructor at the University of Michigan. Gomberg was interested in completely phenylated alkanes. He had prepared tetraphenylmethane (a synthesis a number of eminent chemists had previously attempted, but unsuccessfully), and he had now set himself the task of synthesizing hexaphenylethane. Having available triphenylchloromethane (Sec. 12.6), he went about the job in just the way we might today: he tried to couple together two triphenylmethyl groups by use of a metal (Sec. 9.4). Since sodium did not work very well, he used instead finely divided silver, mercury, or, best of all, zinc dust. He allowed a benzene solution of triphenylchloromethane to stand over one of these metals, and then filtered the solution free of the metal halide. When the benzene was evaporated, there was left behind a white crystalline solid which after recrystallization melted at 185°; this he thought was hexaphenylethane.



Triphenylchloromethane
2 moles

As a chemist always does with a new compound, Gomberg analyzed his product for its carbon and hydrogen content. To his surprise, the analysis showed 88% carbon and 6% hydrogen, a total of only 94%. Thinking that combustion had not been complete, he carried out the analysis again, this time more carefully and under more vigorous conditions; he obtained the same results as before. Repeated analysis of samples prepared from both triphenylchloromethane and triphenylbromomethane, and purified by recrystallization from a variety of solvents, finally convinced him that he had prepared not a hydrocarbon—not hexaphenylethane—but a compound containing 6% of some other element, probably oxygen.

Oxygen could have come from impure metals; but extremely pure samples of metals, carefully freed of oxygen, gave the same results.

Oxygen could have come from the air, although he could not see how molecular oxygen could react at room temperature with a hydrocarbon. He carried out the reaction again, this time under an atmosphere of carbon dioxide. When he filtered the solution (also under carbon dioxide) and evaporated the solvent, there was left behind not his compound of m.p. 185° but an entirely different substance, much more soluble in benzene than his first product, and having a much lower melting point. This new substance was eventually purified, and on analysis it gave the correct composition for hexaphenylethane: 93.8% carbon, 6.2% hydrogen.

Dissolved in benzene, the new substance gave a yellow solution. When a small amount of air was admitted to the container, the yellow color disappeared, and then after a few minutes reappeared. When more oxygen was admitted, the same thing happened: disappearance of the color and slow reappearance. Finally the color disappeared for good; evaporation of the solvent yielded the original compound of m.p. 185°.

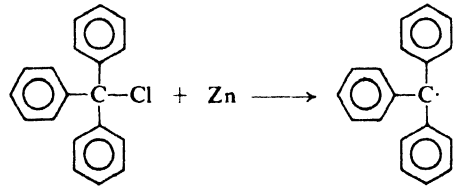
Not only oxygen but also halogens were rapidly absorbed by ice-cold solutions of this substance; even solutions of normally unreactive iodine were instantly decolorized.

The compound of m.p. 185° was the peroxide,

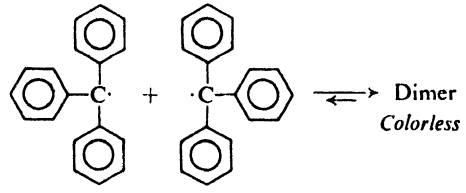
$$(C_6H_5)_3C{-}O{-}O{-}C(C_6H_5)_3$$

as Gomberg showed by preparing it in an entirely different way. The products of the halogen reactions were the triphenylhalomethanes, $(C_6H_5)_3C{-}X$.

If this new substance he had made was indeed hexaphenylethane, it was behaving very strangely. Cleavage of a carbon-carbon bond by such mild reagents as oxygen and iodine was unknown to organic chemists.



Triphenylchloromethane Triphenylmethyl



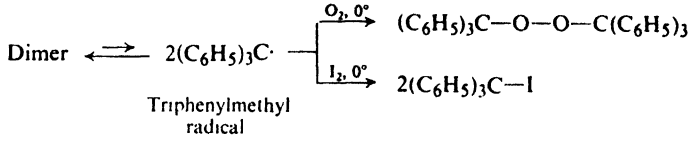
Triphenylmethyl
Yellow

"The experimental evidence presented above forces me to the conclusion that we have to deal here with a free radical, triphenylmethyl, $(C_6H_5)_3C$. On this assumption alone do the results described above become intelligible and receive

an adequate explanation." Gomberg was proposing that he had prepared a *stable* free radical.

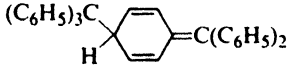
It was nearly ten years before Gomberg's proposal was generally accepted. It now seems clear that what happens is the following: the metal abstracts a chlorine atom from triphenylchloromethane to form the free radical triphenylmethyl; two of these radicals then combine to form a dimeric hydrocarbon. But the carbon–carbon bond in the dimer is a very weak one, and even at room temperature can break to regenerate the radicals. Thus an equilibrium exists between the free radicals and the hydrocarbon. Although this equilibrium tends to favor the hydrocarbon, any solution of the dimer contains an appreciable concentration of free triphenylmethyl radicals. The fraction of material existing as free radicals is about 2% in a 1 *M* solution, 10% in a 0.01 *M* solution, and nearly 100% in very dilute solutions. We could quite correctly label a bottle containing a dilute solution of this substance as "triphenylmethyl radicals."

Triphenylmethyl is yellow; both the dimer and the peroxide are colorless. A solution of the dimer is yellow because of the triphenylmethyl present in the equilibrium mixture. When oxygen is admitted, the triphenylmethyl rapidly reacts to form the peroxide, and the yellow color disappears. More dimer dissociates to restore equilibrium and the yellow color reappears. Only when all the dimer–triphenylmethyl mixture is converted into the peroxide does the yellow color fail to appear. In a similar way it is triphenylmethyl that reacts with iodine.



Thus the dimer undergoes its surprising reactions by first dissociating into triphenylmethyl, which, although unusually stable for a free radical, is nevertheless an exceedingly reactive particle.

Now, what *is* this dimer? For nearly 70 years it was believed to be hexaphenylethane. It—and dozens of analogs—were studied exhaustively, and the equilibria between them and triarylmethyl radicals were interpreted on the basis of the hexaarylethane structure. Then, in 1968, the dimer was shown to have the structure I.



I

Gomberg's original task is still unaccomplished: hexaphenylethane, it seems, has never been made.

The basic significance of Gomberg's work remains unchanged. Many dimers have been prepared, and the existence of free triarylmethyl radicals has been substantiated in a number of ways; indeed, certain of these compounds seem to exist entirely as the free radical even in the solid state. The most convincing evidence for the free-radical nature of these substances lies in properties that arise directly from the odd electron that characterizes a free radical. Two electrons

that occupy the same orbital and thus make up a pair have opposite spins (Sec. 1.6); the magnetic moments corresponding to their spins exactly cancel each other. But, by definition (Sec. 2.12), the odd electron of a free radical is not paired, and hence the effect of its spin is not canceled. This spin gives to the free radical a net magnetic moment. This magnetic moment reveals itself in two ways: (a) the compound is *paramagnetic*; that is, unlike most matter, it is attracted by a magnetic field; and (b) the compound gives a characteristic *paramagnetic resonance absorption* spectrum (or *electron spin resonance* spectrum, Sec. 13.14) which depends upon the orientation of the spin of an unpaired electron in a changing external magnetic field. This latter property permits the detection not only of stable free radicals but of low concentrations of short-lived radical intermediates in chemical reactions, and can even give information about their structure. (See, for example, Sec. 6.17).

The remarkable dissociation to form free radicals is the result of two factors. First, triphenylmethyl radicals are unusually stable because of resonance of the sort we have proposed for the benzyl radical. Here, of course, there are an even larger number of structures (36 of them) that stabilize the radical but not the hydrocarbon; the odd electron is highly delocalized, being distributed over three aromatic rings.

Second, crowding among the large aromatic rings tends to stretch and weaken the carbon–carbon bond joining the triphenylmethyl groups in the dimer. Once the radicals are formed, the bulky groups make it difficult for the carbon atoms to approach each other closely enough for bond formation: *so* difficult, in fact, that hexaphenylethane is not formed at all, but instead dimer I—even with the sacrifice of aromaticity of one ring. Even so, there is crowding in the dimer, and the total effect is to lower the dissociation energy to only 11 kcal/mole, as compared with a dissociation energy of 80–90 kcal for most carbon–carbon single bonds.

It would be hard to overestimate the importance of Gomberg's contribution to the field of free radicals and to organic chemistry as a whole. Although triphenylmethyl was isolable only because it was *not a typical* free radical, its chemical properties showed what kind of behavior to expect of free radicals *in general*; most important of all, it proved that such things as free radicals could exist.

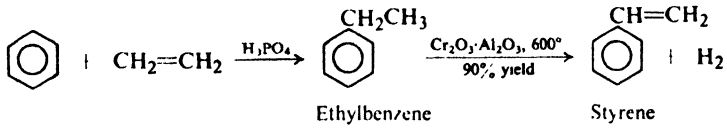
Problem 12.9 The ΔH for dissociation of the dimer I has been measured as 11 kcal/mole, the E_{act} as 19 kcal/mole. (a) Draw the potential energy curve for the reaction. (b) What is the energy of activation for the reverse reaction, combination of triphenylmethyl radicals? (c) How do you account for this unusual fact? (Compare Sec. 2.17.)

Problem 12.10 When 1.5 g of "diphenyltetra(*o*-tolyl)ethane" is dissolved in 50 g of benzene, the freezing point of the solvent is lowered 0.5° (the cryoscopic constant for benzene is 5°). Interpret these results.

12.16 Preparation of alkenylbenzenes. Conjugation with ring

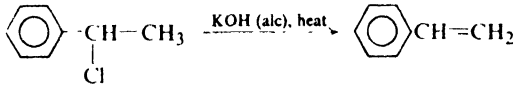
An aromatic hydrocarbon with a side chain containing a double bond can be prepared by essentially the same methods as simple alkenes (Secs. 5.12 and 5.19). In general, these methods involve elimination of atoms or groups from two adjacent carbons. The presence of the aromatic ring in the molecule may affect the orientation of elimination and the ease with which it takes place.

On an industrial scale, the elimination generally involves *dehydrogenation*. For example, **styrene**, the most important of these compounds—and perhaps the most important synthetic aromatic compound—can be prepared by simply heating ethylbenzene to about 600° in the presence of a catalyst. The ethylbenzene, in

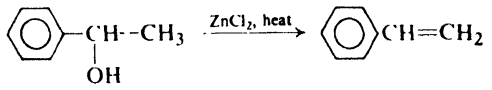


turn, is prepared by a Friedel-Crafts reaction between two simple hydrocarbons, benzene and ethylene.

In the laboratory, however, we are most likely to use dehydrohalogenation or dehydration.

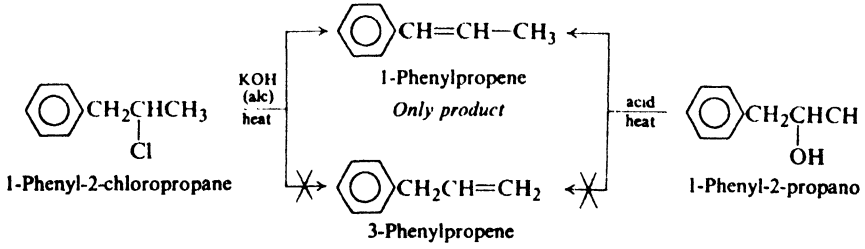


1-Phenyl-1-chloroethane Styrene

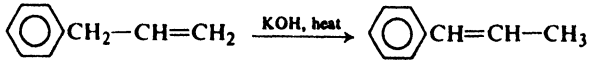


1-Phenylethanol Styrene

Dehydrohalogenation of 1-phenyl-2-chloropropane, or dehydration of 1-phenyl-2-propanol, could yield two products: 1-phenylpropene or 3-phenylpropene. Actually, only the first of these products is obtained. We saw earlier (Secs. 5.14 and 5.23) that where isomeric alkenes can be formed by elimination, the

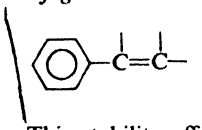


preferred product is the more stable alkene. This seems to be the case here, too. That 1-phenylpropene is much more stable than its isomer is shown by the fact that 3-phenylpropene is rapidly converted into 1-phenylpropene by treatment with hot alkali.



3-Phenylpropene (Allylbenzene) 1-Phenylpropene

A double bond that is separated from a benzene ring by one single bond is said to be *conjugated with the ring*. Such conjugation confers unusual stability on



Double bond conjugated with ring:
unusually stable system

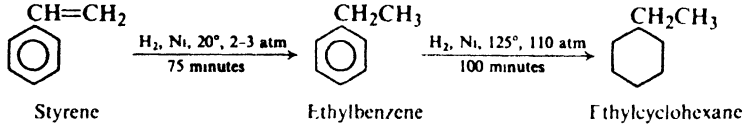
a molecule. This stability affects not only orientation of elimination, but, as we shall see (Sec. 21.6), affects the ease with which elimination takes place.

Problem 12.11 Account for the stability of alkenes like styrene on the basis of: (a) delocalization of π electrons, showing both resonance structures and orbital overlap; and (b) change in hybridization.

12.17 Reactions of alkenylbenzenes

As we might expect, alkenylbenzenes undergo two sets of reactions: **substitution in the ring**, and **addition to the double bond in the side chain**. Since both ring and double bond are good sources of electrons, there may be competition between the two sites for certain electrophilic reagents; it is not surprising that, in general, the double bond shows higher reactivity than the resonance-stabilized benzene ring. Our main interest in these reactions will be the way in which the aromatic ring affects the reactions of the double bond.

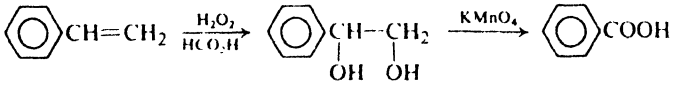
Although both the benzene ring and the carbon carbon double bond can be hydrogenated catalytically, the conditions required for the double bond are much



Styrene Ethylbenzene Ethylcyclohexane

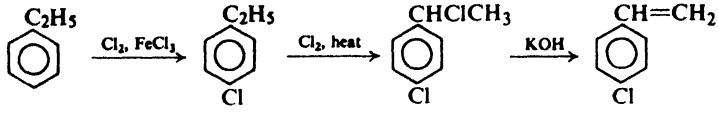
milder; by proper selection of conditions it is quite easy to hydrogenate the side chain without touching the aromatic ring.

Mild oxidation of the double bond yields a glycol; more vigorous oxidation cleaves the carbon-carbon double bond and generally gives a carboxylic acid in which the —COOH group is attached to the ring.



Styrene A glycol Benzoic acid

Both double bond and ring react with halogens by ionic mechanisms that have essentially the same first step: attack on the π cloud by positively charged halogen. Halogen is consumed by the double bond first, and only after the side chain is completely saturated does substitution on the ring occur. Ring-halogenated alkenylbenzenes must be prepared, therefore, by generation of the double bond after halogen is already present on the ring. For example:



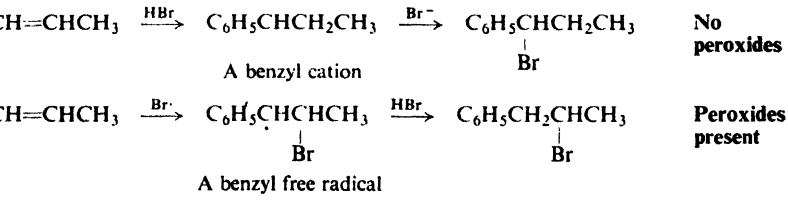
p-Chlorostyrene

In a similar way, alkenylbenzenes undergo the other addition reactions characteristic of the carbon-carbon double bond. Let us look further at the reactions of *conjugated* alkenylbenzenes, and the way in which the ring affects *orientation* and *reactivity*.

12.18 Addition to conjugated alkenylbenzenes: orientation. Stability of the benzyl cation

Addition of an unsymmetrical reagent to a double bond may in general yield two different products. In our discussion of alkenes (Secs. 6.11 and 6.17), we found that usually one of the products predominates, and that we can predict which it will be in a fairly simple way: *in either electrophilic or free-radical addition, the first step takes place in the way that yields the more stable particle*, carbonium ion in one kind of reaction, free radical in the other kind. Does this rule apply to reactions of alkenylbenzenes?

The effect of the benzene ring on orientation can be well illustrated by a single example, addition of HBr to 1-phenylpropene. In the absence of peroxides, bromine becomes attached to the carbon adjacent to the ring; in the presence of peroxides, bromine becomes attached to the carbon once removed from the ring. According to the mechanisms proposed for these two reactions, these products are formed as follows:



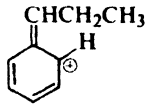
The first step of each of these reactions takes place in the way that yields the *benzyl* cation or the *benzyl* free radical rather than the alternative secondary cation or secondary free radical. Is this consistent with our rule that the more stable particle is formed faster?

Consideration of bond dissociation energies has already shown us that a benzyl free radical is an extremely stable one. We have accounted for this stability on the basis of resonance involving the benzene ring (Sec. 12.14).

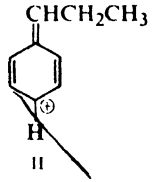
What can we say about a benzyl cation? From the ionization potential (179 kcal) of the benzyl free radical, we can calculate (Sec. 5.18) that the benzyl cation is 69 kcal more stable than the methyl cation, and just about as stable as the *tert*-butyl cation. We can now expand our sequence of Sec. 8.21 to include the benzyl cation:

Stability of carbonium ions benzyl 3° > allyl 2° > 1° > CH_3^+

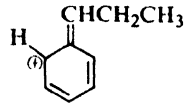
The stability of a benzyl cation—relative to the compounds from which it is made—is also accounted for by resonance involving the benzene ring. Both the carbonium ion and the compound from which it is made are hybrids of Kekulé structures. In addition, the carbonium ion can be represented by three other structures, I, II, and III, in which the positive charge is located on the *ortho* and *para* carbon atoms. Whether we consider this as resonance stabilization or simply



I



II



III

as dispersal of charge, contribution from these structures stabilizes the carbonium ion.

The orbital picture of the benzyl cation is similar to that of the benzyl free radical (Sec. 12.14) except that the *p* orbital that overlaps the π cloud is an *empty* one. The *p* orbital contributes no electrons, but permits further delocalization of the π electrons to include the carbon nucleus of the side chain.

Problem 12.12 How do you account for the following facts? (a) Triphenylchloromethane is completely ionized in certain solvents (e.g., liquid SO_2); (b) triphenylcarbinol, $(C_6H_5)_3COH$, dissolves in concentrated H_2SO_4 to give a solution that has the same intense yellow color as triphenylchloromethane solutions. (*Note:* This yellow color is different from that of solutions of triphenylmethyl.)

Problem 12.13 In light of Problem 12.12, can you suggest a possible reason, besides steric hindrance, why the reaction of CCl_4 with benzene stops at triphenylchloromethane? (See Sec. 12.6.)

12.19 Addition to conjugated alkenylbenzenes: reactivity

On the basis of the stability of the particle being formed, we might expect addition to a conjugated alkenylbenzene, which yields a stable *benzyl* cation or free radical, to occur faster than addition to a simple alkene.

On the other hand, we have seen (Sec. 12.17) that conjugated alkenylbenzenes are more stable than simple alkenes. On this basis alone, we might expect addition to conjugated alkenylbenzenes to occur more slowly than to simple alkenes.

The situation is exactly analogous to the one discussed for addition to conjugated dienes (Sec. 8.24). Both *reactant* and *transition state* are stabilized by resonance; whether reaction is faster or slower than for simple alkenes depends upon *which* is stabilized *more* (see Fig. 8.9, p. 275).

The fact is that conjugated alkenylbenzenes are much more reactive than simple alkenes toward both ionic and free-radical addition. Here again—as in *most* cases of this sort—resonance stabilization of the transition state leading to a carbonium ion or free radical is more important than resonance stabilization of the reactant. We must realize, however, that this is *not always* true.

Problem 12.14 Draw a potential energy diagram similar to Fig. 8.9 (p. 275) to summarize what has been said in this section.

Problem 12.15 Suggest one reason why tetraphenylethylene does not react with bromine in carbon tetrachloride.

12.20 Alkynylbenzenes

The preparations and properties of the alkynylbenzenes are just what we might expect from our knowledge of benzene and the alkynes.

Problem 12.16 Outline all steps in the conversion of: (a) ethylbenzene into phenylacetylene; (b) *trans*-1-phenylpropene into *cis*-1-phenylpropene.

12.21 Analysis of alkylbenzenes

Aromatic hydrocarbons with saturated side chains are distinguished from alkenes by their failure to decolorize bromine in carbon tetrachloride (without evolution of hydrogen bromide) and by their failure to decolorize cold, dilute, neutral permanganate solutions. (Oxidation of the side chains requires more vigorous conditions; see Sec. 12.10.)

They are distinguished from alkanes by the readiness with which they are sulfonated by—and thus dissolve in—cold fuming sulfuric acid (see Sec. 11.4).

They are distinguished from alcohols and other oxygen-containing compounds by their failure to dissolve immediately in cold concentrated sulfuric acid, and from primary and secondary alcohols by their failure to give a positive chromic anhydride test (Sec. 6.30).

Upon treatment with chloroform and aluminum chloride, alkylbenzenes give orange to red colors. These colors are due to triarylmethyl cations, Ar_3C^+, which are probably produced by a Friedel-Crafts reaction followed by a transfer of hydride ion (Sec. 6.16):

$$ArH \xrightarrow{CHCl_3,\ AlCl_3} ArCHCl_2 \xrightarrow{ArH,\ AlCl_3} Ar_2CHCl \xrightarrow{ArH,\ AlCl_3} Ar_3CH$$

$$Ar_2CHCl \xrightarrow{AlCl_3} Ar_2CH^+AlCl_4^- \xrightarrow{Ar_3CH} Ar_2CH_2 + Ar_3C^+\ AlCl_4^-$$

Orange to red color

This test is given by any aromatic compound that can undergo the Friedel-Crafts reaction, with the particular color produced being characteristic of the aromatic system involved: orange to red from halobenzenes, blue from *naphthalene*, purple from *phenanthrene*, green from *anthracene* (Chap. 30).

Problem 12.17 Describe simple chemical tests (if any) that would distinguish between: (a) *n*-propylbenzene and *o*-chlorotoluene; (b) benzene and toluene; (c) *m*-chlorotoluene and *m*-dichlorobenzene; (d) bromobenzene and bromocyclohexane; (e) bromobenzene and 3-bromo-1-hexene; (f) ethylbenzene and benzyl alcohol ($C_6H_5CH_2OH$). Tell exactly what you would *do* and *see*.

The number and orientation of side chains in an alkylbenzene is shown by the carboxylic acid produced on vigorous oxidation (Sec. 12.10).

Problem 12.18 On the basis of characterization tests and physical properties, an unknown compound of b.p. 182° is believed to be either *m*-diethylbenzene or *n*-butylbenzene. How could you distinguish between the two possibilities?

(Analysis of alkylbenzenes by spectroscopic methods will be discussed in Secs. 13.15–13.16.)

12.22 Analysis of alkenyl- and alkynylbenzenes

Aromatic hydrocarbons with unsaturated side chains undergo the reactions characteristic of aromatic rings and of the carbon–carbon double or triple bond. (Their analysis by spectroscopic methods is discussed in Secs. 13.15–13.16.)

Problem 12.19 Predict the response of allylbenzene to the following test reagents: (a) cold concentrated sulfuric acid; (b) Br_2 in CCl_4; (c) cold, dilute, neutral permanganate; (d) $CHCl_3$ and $AlCl_3$; (e) CrO_3 and H_2SO_4.

Problem 12.20 Describe simple chemical tests (if any) that would distinguish between: (a) styrene and ethylbenzene; (b) styrene and phenylacetylene; (c) allylbenzene and 1-nonene; (d) allylbenzene and allyl alcohol ($CH_2{=}CH{-}CH_2OH$). Tell exactly what you would *do* and *see*.

PROBLEMS

1. Draw the structure of:

(a) *m*-xylene
(b) mesitylene
(c) *o*-ethyltoluene
(d) *p*-di-*tert*-butylbenzene
(e) cyclohexylbenzene
(f) 3-phenylpentane
(g) isopropylbenzene (cumene)
(h) *trans*-stilbene
(i) 1,4-diphenyl-1,3-butadiene
(j) *p*-dibenzylbenzene
(k) *m*-bromostyrene
(l) diphenylacetylene

2. Outline all steps in the synthesis of ethylbenzene from each of the following compounds, using any needed aliphatic or inorganic reagents.

(a) benzene
(b) styrene
(c) phenylacetylene
(d) α-phenylethyl alcohol ($C_6H_5CHOHCH_3$)
(e) β-phenylethyl alcohol ($C_6H_5CH_2CH_2OH$)
(f) 1-chloro-1-phenylethane
(g) 2-chloro-1-phenylethane
(h) *p*-bromoethylbenzene
(i) acetophenone ($C_6H_5\overset{\overset{O}{\|}}{C}CH_3$)

3. Give structures and names of the principal organic products expected from reaction (if any) of *n*-propylbenzene with each of the following. Where more than one product is to be expected, indicate which will predominate.

(a) H_2, Ni, room temperature, low pressure
(b) H_2, Ni, 200°, 100 atm.
(c) cold dilute $KMnO_4$
(d) hot $KMnO_4$
(e) $K_2Cr_2O_7$, H_2SO_4, heat
(f) boiling NaOH(aq)
(g) boiling HCl(aq)
(h) HNO_3, H_2SO_4
(i) H_2SO_4, SO_3
(j) $Tl(OOCCF_3)_3$
(k) Cl_2, Fe
(l) Br_2, Fe
(m) I_2, Fe
(n) Br_2, heat, light
(o) CH_3Cl, $AlCl_3$, 0°
(p) $C_6H_5CH_2Cl$, $AlCl_3$, 0° (*Note:* A benzyl halide is *not* an aryl halide.)
(q) C_6H_5Cl, $AlCl_3$, 80°
(r) isobutylene, HF
(s) *tert*-butyl alcohol, H_2SO_4
(t) cyclohexene, HF

4. Give structures and names of the principal organic products expected from reaction (if any) of *trans*-1-phenyl-1-propene with:

(a) H_2, Ni, room temperature, low pressure
(b) H_2, Ni, 200°, 100 atm.
(c) Br_2 in CCl_4
(d) excess Br_2, Fe
(e) HCl
(f) HBr
(g) HBr (peroxides)
(h) cold conc. H_2SO_4
(i) Br_2, H_2O
(j) cold dilute $KMnO_4$
(k) hot $KMnO_4$
(l) HCO_2OH
(m) O_3, then H_2O/Zn
(n) Br_2, 300°
(o) $CHBr_3$, *t*-BuOK
(p) product (c), KOH(alc)

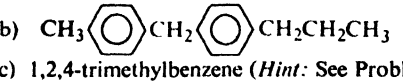
5. Give structures and names of the principal organic products expected from each of the following reactions:

(a) benzene + cyclohexene + HF
(b) phenylacetylene + alcoholic $AgNO_3$
(c) *m*-nitrobenzyl chloride + $K_2Cr_2O_7$ + H_2SO_4 + heat
(d) allylbenzene + HCl
(e) *p*-chlorotoluene + hot $KMnO_4$
(f) *eugenol* ($C_{10}H_{12}O_2$, 2-methoxy-4-allylphenol) + hot KOH $\longrightarrow$ *isoeugenol* ($C_{10}H_{12}O_2$)
(g) benzyl chloride + Mg + dry ether
(h) product of (g) + H_2O
(i) *p*-xylene + Br_2 + Fe
(j) 1-phenyl-1,3-butadiene + one mole H_2 + Ni, 2 atm., 30°
(k) *trans*-stilbene + O_3, then H_2O/Zn
(l) 1,3-diphenylpropyne + H_2, Pd $\longrightarrow$ $C_{15}H_{14}$
(m) 1,3-diphenylpropyne + Li, NH_3(liq) $\longrightarrow$ $C_{15}H_{14}$
(n) p-$CH_3OC_6H_4CH{=}CHC_6H_5$ + HBr

6. Treatment of benzyl alcohol ($C_6H_5CH_2OH$) with cold concentrated H_2SO_4 yields a high-boiling resinous material. What is a likely structure for this material, and how is it probably formed?

7. Label each set of hydrogens in each of the following compounds in order of expected ease of abstraction by bromine atoms. Use (1) for the most reactive, (2) for the next, etc.

(a) 1-phenyl-2-hexene

(b) 

(c) 1,2,4-trimethylbenzene (*Hint:* See Problem 12.8, p. 390.)
(d) What final monobromination product or products would abstraction of each kind of hydrogen in (a) lead to?

8. Give structures and names of the products expected from dehydrohalogenation of each of the following. Where more than one product can be formed, predict the major product.

(a) 1-chloro-1-phenylbutane
(b) 1-chloro-2-phenylbutane
(c) 2-chloro-2-phenylbutane
(d) 2-chloro-1-phenylbutane
(e) 3-chloro-2-phenylbutane

9. Answer Problem 8 for dehydration of the alcohol corresponding to each of the halides given. (*Hint:* Do not forget Sec. 5.22.)

10. Arrange in order of ease of dehydration: (a) the alcohols of Problem 9; (b) $C_6H_5CH_2CH_2OH$, $C_6H_5CHOHCH_3$, $(C_6H_5)_2C(OH)CH_3$.

11. Arrange the compounds of each set in order of reactivity toward the indicated reaction.

(a) addition of HCl: styrene, *p*-chlorostyrene, *p*-methylstyrene
(b) dehydration: α-phenylethyl alcohol ($C_6H_5CHOHCH_3$), α-(*p*-nitrophenyl)ethyl alcohol, α-(*p*-aminophenyl)ethyl alcohol.

12. (a) Draw structures of all possible products of addition of one mole of Br_2 to 1-phenyl-1,3-butadiene. (b) Which of these possible products are consistent with the intermediate formation of the most stable carbonium ion? (c) Actually, only 1-phenyl-3,4-dibromo-1-butene is obtained. What is the most likely explanation of this fact?

13. (a) The heats of hydrogenation of the stereoisomeric stilbenes (1,2-diphenylethenes) are: *cis*-, 26.3 kcal; *trans*-, 20.6 kcal. Which isomer is the more stable? (b) *cis*-Stilbene is converted into *trans*-stilbene (but not vice versa) either (i) by action of a very small amount of Br_2 in the presence of light, or (ii) by action of a very small amount of HBr (but not HCl) in the presence of peroxides. What is the agent that probably brings about the conversion? Can you suggest a way in which the conversion might take place? (c) Why is *trans*-stilbene not converted into *cis*-stilbene?

14. One mole of triphenylcarbinol lowers the freezing point of 1000 g of 100% sulfuric acid twice as much as one mole of methanol. How do you account for this?

15. Can you account for the order of acidity: triphenylmethane > diphenylmethane > toluene > *n*-pentane (*Hint:* See Sec. 12.19.)

16. When a mixture of toluene and $CBrCl_3$ was irradiated with ultraviolet light, there were obtained, in almost exactly equimolar amounts, benzyl bromide and $CHCl_3$. (a) Show in detail all steps in the most likely mechanism for this reaction. (b) There were also obtained, in small amounts, HBr and C_2Cl_6; the ratio of $CHCl_3$ to HBr was 20:1. How do you account for the formation of HBr? Of C_2Cl_6? What, specifically, does the 20:1 ratio tell you about the reaction? (c) When the reaction was carried out on a series of *p*-substituted toluenes, $G-C_6H_4-CH_3$, the following order of reactivity was observed

$$G = CH_3O > CH_3 > H > Br$$

How do you account for this order of reactivity?

17. When the product of the HF-catalyzed reaction of benzene with 1-dodecene, previously reported to be pure 2-phenyldodecane, was analyzed by gas chromatography, five evenly-spaced peaks of about the same size were observed, indicating the presence of five components, probably closely related in structure. What five compounds most likely make up this mixture, and how could you have anticipated their formation?

18. The bond dissociation energy for the central C–C bond of hexacyclopropylethane is only 45 kcal/mole. Besides steric interaction, what is a second factor that may contribute to the weakness of this bond? (*Hint:* See Sec. 9.9.)

19. On theoretical grounds it is believed that a primary isotope effect is greatest if bond breaking and bond making have proceeded to an equal extent in the transition state. (a) In free-radical halogenation of the side chain of toluene, k^H/k^D is about 2 in chlorination and about 5 in bromination. There are two possible interpretations of this. What are they? (b) In light of Sec. 2.23, which interpretation is the more likely?

20. The three xylenes are obtained as a mixture from the distillation of coal tar; further separation by distillation is difficult because of the closeness of their boiling points (see Table 12.1, p. 375), and so a variety of chemical methods have been used. In each case below tell which isomer you would expect to react preferentially, and why.

(a) An old method: treatment of the mixture at room temperature with 80% sulfuric acid.

(b) Another old method: sulfonation of all three xylenes, and then treatment of the sulfonic acids with dilute aqueous acid.

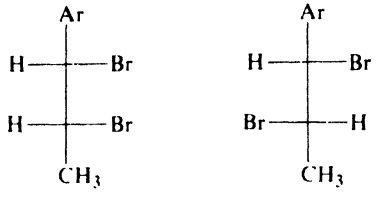
(c) A current method: extraction of one isomer into a BF_3/HF layer.

(d) A proposed method:

$$C_6H_5C(CH_3)_2{}^-Na^+ + \text{xylenes} \rightleftharpoons C_6H_5CH(CH_3)_2 + A + \text{two xylenes}$$

(*Hint* to part (d): See Secs. 8.10, 5.17, and 11.18.)

21. Upon ionic addition of bromine, *cis*-1-phenyl-1-propene gives a mixture of 17% *erythro* dibromide and 83% *threo*; *trans*-1-phenyl-1-propene gives 88% *erythro*, 12% *threo*; and *trans*-1-(*p*-methoxyphenyl)propene gives 63% *erythro*, 37% *threo*.



and enantiomer — *Erythro*

and enantiomer — *Threo*

How do these results compare with those obtained with the 2-butenes (Sec. 7.11)? Suggest a possible explanation for the difference. What is the effect of the *p*-methoxy group, and how might you account for this?

22. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene and/or toluene, using any necessary aliphatic or inorganic reagents. Follow instructions on p. 224. Assume a pure *para* isomer can be separated from an *ortho,para* mixture.

(a) ethylbenzene
(b) styrene
(c) phenylacetylene
(d) isopropylbenzene
(e) 2-phenylpropene
(f) 3-phenylpropene (allylbenzene)
(g) 1-phenylpropyne (two ways)
(h) *trans*-1-phenylpropene
(i) *cis*-1-phenylpropene
(j) *p-tert*-butyltoluene
(k) *p*-nitrostyrene
(l) *p*-bromobenzyl bromide
(m) *p*-nitrobenzal bromide
(n) *p*-bromobenzoic acid
(o) *m*-bromobenzoic acid
(p) 1,2-diphenylethane
(q) *p*-nitrodiphenylmethane (p-$O_2NC_6H_4CH_2C_6H_5$) (*Hint:* See Problem 3(p).)

23. Describe simple chemical tests that would distinguish between:

(a) benzene and cyclohexane
(b) benzene and 1-hexene
(c) toluene and *n*-heptane
(d) cyclohexylbenzene and 1-phenylcyclohexene
(e) benzyl alcohol ($C_6H_5CH_2OH$) and *n*-pentylbenzene
(f) cinnamyl alcohol ($C_6H_5CH{=}CHCH_2OH$) and 3-phenyl-1-propanol ($C_6H_5CH_2CH_2CH_2OH$)
(g) chlorobenzene and ethylbenzene
(h) nitrobenzene and *m*-dibromobenzene

24. Describe chemical methods (not necessarily simple tests) that would enable you to distinguish between the compounds of each of the following sets. (For example, make use of Table 18.1, page 580.

(a) 1-phenylpropene, 2-phenylpropene, 3-phenylpropene (allylbenzene)
(b) all alkylbenzenes of formula C_9H_{12}
(c) *m*-chlorotoluene and benzyl chloride
(d) *p*-divinylbenzene (p-$C_6H_4(CH{=}CH_2)_2$) and 1-phenyl-1,3-butadiene
(e) $C_6H_5CHClCH_3$, p-$CH_3C_6H_4CH_2Cl$, and p-$ClC_6H_4C_2H_5$

25. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, etc. Where necessary, make use of Table 18.1, page 580.

	b.p.		b.p.
bromobenzene	156°	*p*-chlorotoluene	162°
3-phenylpropene	157	*o*-ethyltoluene	162
m-ethyltoluene	158	*p*-ethyltoluene	163
n-propylbenzene	159	mesitylene	165
o-chlorotoluene	159	2-phenylpropene	165
m-chlorotoluene	162		

26. The compound *indene*, C_9H_8, found in coal tar, rapidly decolorizes Br_2/CCl_4 and dilute $KMnO_4$. Only one mole of hydrogen is absorbed readily to form *indane*, C_9H_{10}. More vigorous hydrogenation yields a compound of formula C_9H_{16}. Vigorous oxidation of indene yields phthalic acid. What is the structure of indene? Of indane? (*Hint:* See Problem 9.17, p. 313.)

27. A solution of 0.01 mole *tert*-butyl peroxide (p. 114) in excess ethylbenzene was irradiated with ultraviolet light for several hours. Gas chromatographic analysis of the product showed the presence of nearly 0.02 mole of *tert*-butyl alcohol. Evaporation of the alcohol and unreacted ethylbenzene left a solid residue which was separated by chromatography into just two products: X (1 g) and Y (1 g). X and Y each had the empirical formula C_8H_9 and m.w. 210; each was inert toward cold dilute $KMnO_4$ and toward Br_2/CCl_4.

When isopropylbenzene was substituted for ethylbenzene in the above reaction, exactly similar results were obtained, except that the single compound Z (2.2 g) was obtained instead of X and Y. Z had the empirical formula C_9H_{11}, m.w. 238, and was inert toward cold, dilute $KMnO_4$ and toward Br_2/CCl_4.

What are the most likely structures for X, Y, and Z, and what is the most likely mechanism by which they are formed?

Chapter 13 Spectroscopy and Structure

13.1 Determination of structure: spectroscopic methods

Near the beginning of our study (Sec. 3.32), we outlined the general steps an organic chemist takes when he is confronted with an unknown compound and sets out to find the answer to the question: *what is it?* We have seen, in more detail, some of the ways in which he carries out the various steps: determination of molecular weight and molecular formula; detection of the presence—or absence—of certain functional groups; degradation to simpler compounds; conversion into derivatives; synthesis by an unambiguous route.

At every stage of structure determination—from the isolation and purification of the unknown substance to its final comparison with an authentic sample—the use of instruments has, since World War II, revolutionized organic chemical practice. Instruments not only help an organic chemist to do what he does *faster* but, more important, let him do what could not be done *at all* before: to analyze complicated mixtures of closely related compounds; to describe the structure of molecules in detail never imagined before; to detect, identify, and measure the concentration of short-lived intermediates whose very existence was, not so long ago, only speculation.

By now, we are familiar with some of the features of the organic chemical landscape; so long as we do not wander too far from home, we can find our way about without becoming lost. We are ready to learn a little about how to interpret the kind of information these modern instruments give, so that they can help us to see more clearly the new things we shall meet, and to recognize them more readily when we encounter them again. The instruments most directly concerned with our primary interest, molecular structure, are the *spectrometers*—measurers of spectra. Of the various spectra, we shall actually work with only two: *infrared (ir) and nuclear magnetic resonance (nmr)*, since they are the workhorses of the organic chemical laboratory today; of these, we shall spend most of our time with nmr.

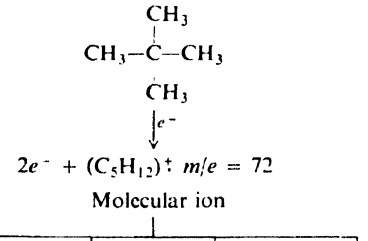
We shall look very briefly at three other kinds of spectra: *mass*, *ultraviolet* (*uv*), and *electron spin resonance* (*esr*).

In all this, we must constantly keep in mind that what we learn at this stage must be greatly simplified. There are many exceptions to the generalizations we shall learn; there are many pitfalls into which we can stumble. Our ability to apply spectroscopic methods to the determination of organic structure is limited by our understanding of organic chemistry as a whole—and in this we are, of course, only beginners. But so long as we are aware of the dangers of a little learning, and are willing to make mistakes and profit from them, it is worthwhile for us to become beginners in this area of organic chemistry, too.

Let us look first at the mass spectrum, and then at the others, which, as we shall see, are all parts—different ranges of wavelengths—of a single spectrum: that of electromagnetic radiation.

13.2 The mass spectrum

In the mass spectrometer, molecules are bombarded with a beam of energetic electrons. The molecules are ionized and broken up into many fragments, some of which are positive ions. Each kind of ion has a particular ratio of mass to charge, or *m/e value*. For most ions, the charge is 1, so that *m/e* is simply the mass of the ion. Thus, for neopentane:



	$(C_4H_9)^+$	$(C_3H_5)^+$	$(C_2H_5)^+$	$(C_2H_3)^+$	and others
m/e:	57	41	29	27	
Relative intensity:	100	41.5	38.5	15.7	
	Base peak				

The set of ions is analyzed in such a way that a signal is obtained for each value of *m/e* that is represented; the intensity of each signal reflects the relative abundance of the ion producing the signal. The largest peak is called the *base peak*; its intensity is taken as 100, and the intensities of the other peaks are expressed relative to it. A plot—or even a list—showing the relative intensities of signals at the various *m/e* values is called a *mass spectrum*, and is highly characteristic of a particular compound. Compare, for example, the spectra of two isomers shown in Fig. 13.1.

Mass spectra can be used in two general ways: (a) to prove the identity of two compounds, and (b) to help establish the structure of a new compound.

Two compounds are shown to be identical by the fact that they have identical physical properties: melting point, boiling point, density, refractive index, etc. The greater the number of physical properties measured, the stronger the evidence.

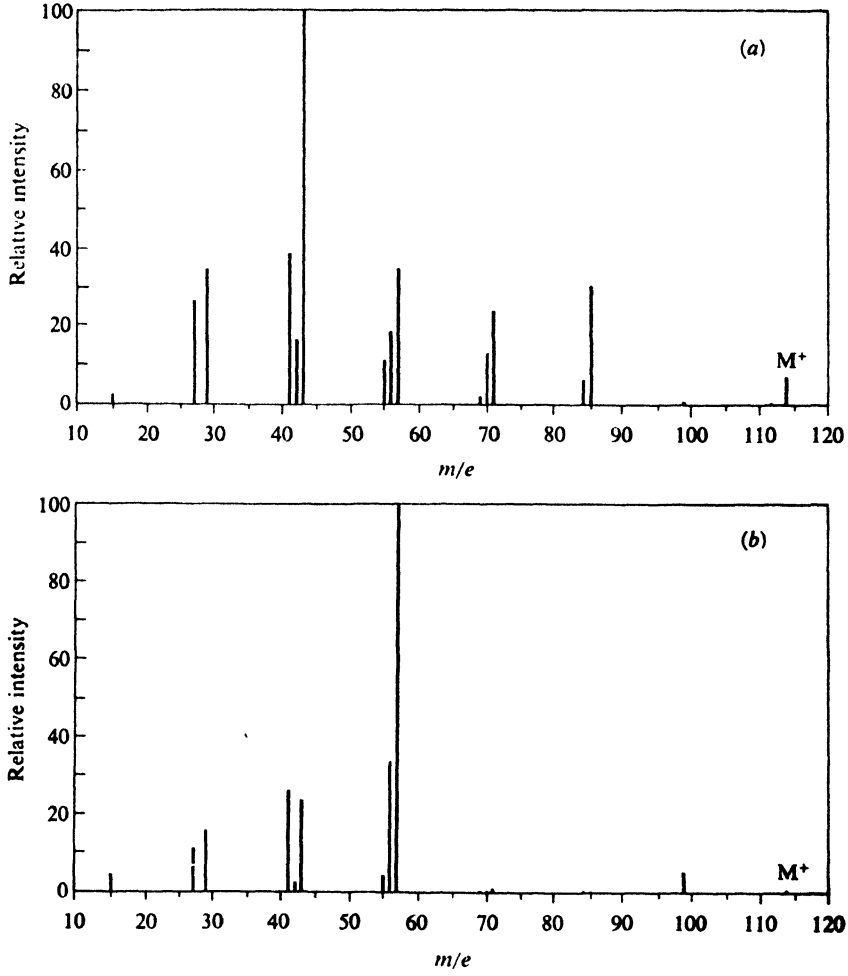


Figure 13.1. Mass spectra of two isomeric alkanes. (*a*) *n*-Octane; (*b*) 2,2,4-trimethylpentane.

Now, a single mass spectrum amounts to dozens of physical properties, since it shows the relative abundances of dozens of different fragments. If we measure the mass spectrum of an unknown compound and find it to be identical with the spectrum of a previously reported compound of known structure, then we can conclude that—almost beyond the shadow of a doubt—the two compounds are identical.

The mass spectrum helps to establish the structure of a *new* compound in several different ways: it can give an exact molecular weight; it can give a molecular formula or at least narrow the possibilities to a very few; and it can indicate the presence in a molecule of certain structural units.

If one electron is removed from the parent molecule, there is produced the *molecular ion* (or *parent ion*), whose *m/e* value is, of course, the molecular weight of

the compound. Sometimes the M^+ peak is the base peak, and is easily recognized; often, though, it is not the base peak—it may even be very small—and considerable work is required to locate it. Once identified, it gives the most accurate molecular weight obtainable.

$$M + e^- \longrightarrow \underset{\substack{\text{Molecular ion}\\ \text{(Parent ion)}\\ m/e = \text{mol. wt.}}}{M^+} + 2e^-$$

We might at first think that the M^+ peak would be the peak of highest m/e value. This is not so, however. Most elements occur naturally as several isotopes; generally the lightest one greatly predominates, and the heavier ones occur to lesser extent. Table 13.1 lists the relative abundances of several heavy isotopes.

Table 13.1 ABUNDANCE OF SOME HEAVY ISOTOPES

Heavy isotope	Abundance relative to isotope of lowest atomic weight
^2H	0.015%
^{13}C	1.11
^{15}N	0.37
^{18}O	0.20
^{33}S	0.78
^{34}S	4.4
^{37}Cl	32.5
^{81}Br	98.0

The molecular weight that one usually measures and works with is the sum of the average atomic weights of the elements, and reflects the presence of these heavy isotopes. This is not true, however, of the molecular weight obtained from the mass spectrum; here, the M^+ peak is due to molecules containing only the commonest isotope of each element.

Consider benzene, for example. The M^+ peak, m/e 78, is due only to ions of formula $C_6H_6^+$. There is a peak at m/e 79, the M + 1 peak, which is due to $C_5{}^{13}CH_6^+$ and $C_6H_5D^+$. There is an M + 2 peak at m/e 80, due to $C_4{}^{13}C_2H_6^+$, $C_5{}^{13}CH_5D^+$, and $C_6H_4D_2^+$. Now, because of the low natural abundance of most heavy isotopes, these isotopic peaks are generally much less intense than the M^+ peak; just how much less intense depends upon which elements they are due to. In the case of benzene, the M + 1 and M + 2 peaks are, respectively, 6.58% and 0.18% as intense as the M^+ peak. (Table 13.1 shows us, however, that a monochloro compound would have an M + 2 peak about one-third as intense as the M^+ peak, and a monobromo compound would have M and M + 2 peaks of about equal intensity.)

It is these isotopic peaks that make it possible for us to determine the molecular formula of the compound. Knowing the relative natural abundances of isotopes, one can calculate for any molecular formula the relative intensity to be expected for each isotopic peak: M + 1, M + 2, etc. The results of such calculations are available in tables. Consider, for example, a compound for which M^+ is 44.

The compound might be (among other less likely possibilities) N_2O, CO_2, C_2H_4O, or C_3H_8. By use of Table 13.2, we clearly could pick out the most likely formula from the mass spectral data.

Table 13.2 CALCULATED INTENSITIES OF ISOTOPIC PEAKS

	M	M + 1	M + 2
N_2O	100	0.80	0.20
CO_2	100	1.16	0.40
C_2H_4O	100	1.91	0.01
C_3H_8	100	3.37	0.04

Finally, study of compounds of known structure is beginning to reveal the factors that determine which fragments a particular structure is likely to break into. In this we can find much that is familiar to us: the preferential formation of carbonium ions that we recognize as being relatively stable ones; elimination of small, stable molecules like water, ammonia, and carbon monoxide. Under the energetic conditions, extensive rearrangement can occur, complicating the interpretation; but here, too, patterns are emerging. The *direction* of rearrangement is, as we would expect, toward more stable ions. As this knowledge accumulates, the process is reversed: from the kind of fragmentation an unknown compound gives, its structure is deduced.

Problem 13.1 (a) Referring to the neopentane fragmentation (p. 406), what is a likely structure for $C_4H_9^+$; $C_3H_5^+$; $C_2H_5^+$; $C_2H_3^+$? (b) Write a balanced equation for the formation of $C_4H_9^+$ from the molecular ion $C_5H_{12}^{+\cdot}$.

13.3 The electromagnetic spectrum

We are already familiar with various kinds of electromagnetic radiation: light—visible, ultraviolet, infrared—x-rays, radio and radar waves. These are simply different parts of a broad spectrum that stretches from gamma rays, whose wavelengths are measured in fractions of an Angstrom unit, to radio waves, whose wavelengths are measured in meters or even kilometers. All these waves have the same velocity, 3×10^{10} centimeters per second. Their frequency is related to the wavelength by the expression

$$\nu = c/\lambda$$

where ν = frequency, in Hz (*Hertz*, cycles/sec)
λ = wavelength, in cm
c = velocity, 3×10^{10} cm/sec

The shorter the wavelength, the higher the frequency.

When a beam of electromagnetic radiation is passed through a substance, the radiation can be either absorbed or transmitted, depending upon its frequency and the structure of the molecules it encounters. Electromagnetic radiation is energy, and hence when a molecule absorbs radiation, it gains energy. Just how

much energy it gains depends upon the frequency of the radiation: the higher the frequency (the shorter the wavelength), the greater the gain in energy.

$$\Delta E = h\nu$$

where ΔE = gain in energy, in ergs
h = Planck's constant, 6.5×10^{-27} erg-sec
ν = frequency, in Hz

The energy gained by the molecule in this way may bring about increased vibration or rotation of the atoms, or may raise electrons to higher energy levels. The particular frequency of radiation that a given molecule can absorb depends upon the changes in vibrations or rotations or electronic states that are permitted to a molecule of that structure. The spectrum of a compound is a plot that shows how much electromagnetic radiation is absorbed (or transmitted) at each frequency. It can be highly characteristic of the compound's structure.

13.4 The infrared spectrum

Of all the properties of an organic compound, the one that, by itself, gives the most information about the compound's structure is its infrared spectrum.

A molecule is constantly vibrating: its bonds *stretch* (and contract), and *bend* with respect to each other. Changes in vibrations of a molecule are caused by absorption of infrared light; light lying beyond (lower frequency, longer wavelength, less energy) the red end of the visible spectrum.

A particular part of the infrared spectrum is referred to either by its wavelength or—and this is considered preferable—by its frequency. Wavelength is expressed in microns, μ ($1\ \mu = 10^{-4}$ cm or 10^4 A). Frequency is expressed, not in Hertz, but in *wavenumbers*, cm^{-1}, often called *reciprocal centimeters*; the wavenumber is simply the number of waves per centimeter, and is equal to the reciprocal of the wavelength in centimeters.

Like the mass spectrum, an infrared spectrum is a highly characteristic property of an organic compound—see, for example, the spectra in Fig. 13.2, p. 411—and can be used both to establish the identity of two compounds and to reveal the structure of a new compound.

Two substances that have identical infrared spectra are, in effect, identical in thousands of different physical properties · the absorption of light at thousands of different frequencies—and must almost certainly be the same compound. (One region of the infrared spectrum is called, appropriately, the *fingerprint* region.)

The infrared spectrum helps to reveal the structure of a new compound by telling us what groups are present in—or absent from—the molecule. A particular group of atoms gives rise to *characteristic absorption bands*; that is to say, a particular group absorbs light of certain frequencies that are much the same from compound to compound. For example, the —OH group of alcohols absorbs strongly at 3200–3600 cm^{-1}; the C=O group of ketones at 1710 cm^{-1}; the —C≡N group, at 2250 cm^{-1}; the —CH_3 group at 1450 and 1375 cm^{-1}.

Interpretation of an infrared spectrum is not a simple matter. Bands may be obscured by the overlapping of other bands. Overtones (harmonics) may appear at just twice the frequency of the fundamental band. The absorption band of a

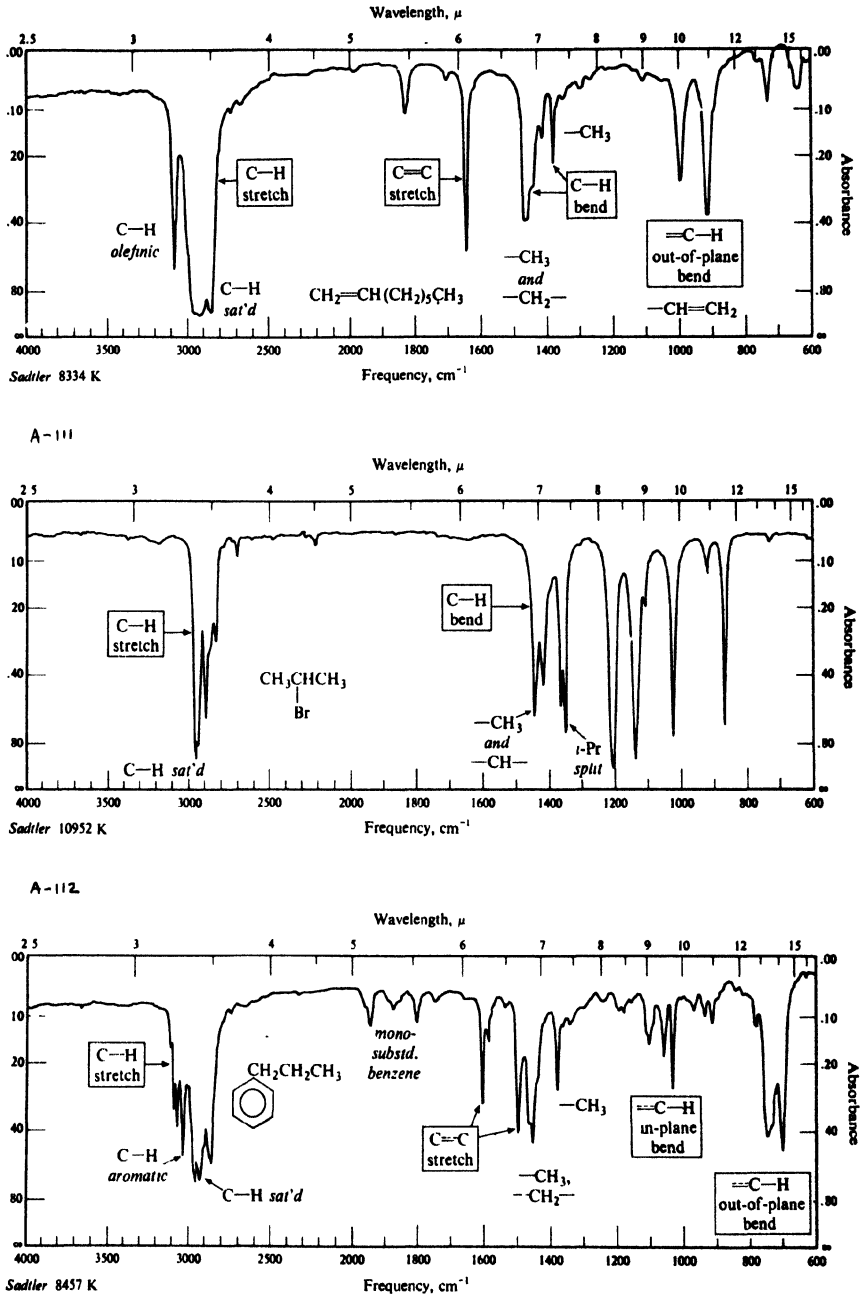


Figure 13.2. Infrared spectra. (*a*) 1-Octene; (*b*) isopropyl bromide; (*c*) *n*-butylbenzene.

particular group may be *shifted* by various structural features—conjugation, electron withdrawal by a neighboring substituent, angle strain or van der Waals strain, hydrogen bonding—and be mistaken for a band of an entirely different group. (On the other hand, recognized for what they are, such shifts *reveal* the structural features that cause them.)

In our work we shall have modest aims: to learn to recognize a few of the more striking absorption bands, and to gain a little practice in correlating infrared data with other kinds of information. We must realize that we shall be taking from an infrared spectrum only a tiny fraction of the information that is there, and which can be gotten from it by an experienced person with a broad understanding of organic structure.

Table 13.3 lists infrared absorption frequencies characteristic of various groups. We shall look more closely at the infrared spectra of hydrocarbons in Sec. 13.15 and, in following chapters, at the infrared spectra of other families of compounds.

Table 13.3 CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES[a]

Bond	Compound type	Frequency range, cm^{-1}	Reference
C—H	Alkanes	2850–2960	Sec. 13.15
		1350–1470	
C—H	Alkenes	3020–3080 (*m*)	Sec. 13.15
		675–1000	
C—H	Aromatic rings	3000–3100 (*m*)	Sec. 13.15
		675–870	
C—H	Alkynes	3300	Sec. 13.15
C=C	Alkenes	1640–1680 (*v*)	Sec. 13.15
C≡C	Alkynes	2100–2260 (*v*)	Sec. 13.15
C=C	Aromatic rings	1500, 1600 (*v*)	Sec. 13.15
C—O	Alcohols, ethers, carboxylic acids, esters	1080–1300	Sec. 16.13
			Sec. 17.17
			Sec. 18.22
			Sec. 20.25
C=O	Aldehydes, ketones, carboxylic acids, esters	1690–1760	Sec. 19.17
			Sec. 18.22
			Sec. 20.25
O—H	Monomeric alcohols, phenols	3610–3640 (*v*)	Sec. 16.13
			Sec. 24.13
	Hydrogen-bonded alcohols, phenols	3200–3600(*broad*)	Sec. 16.13
			Sec. 24.13
	Carboxylic acids	2500–3000 (*broad*)	Sec. 18.22
N—H	Amines	3300–3500 (*m*)	Sec. 23.20
C—N	Amines	1180–1360	Sec. 23.20
C≡N	Nitriles	2210–2260 (*v*)	
$—NO_2$	Nitro compounds	1515–1560	
		1345–1385	

[a] All bands strong unless marked: *m*, moderate; *w*, weak; *v*, variable.

13.5 The ultraviolet spectrum

Light of wavelength between about 4000 A and 7500 A (400–750 mμ) is visible. Just beyond the red end of the visible spectrum (λ greater than 750 mμ) lies the

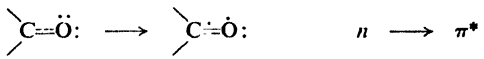
infrared region which we have just discussed. Just beyond the violet end of the visible spectrum (λ less than 400 mμ) lies the ultraviolet region.

The ultraviolet spectrometers commonly used measure absorption of light in the visible and "near" ultraviolet region, that is, in the 200–750 mμ range. This light is of higher frequency (and greater energy) than infrared light and, when it is absorbed by a molecule, the changes it produces are, naturally, ones that require greater energy: changes in electronic states.

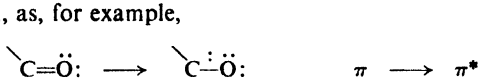
In a transition to a higher electronic level, a molecule can go *from* any of a number of sub-levels—corresponding to various vibrational and rotational states—*to* any of a number of sub-levels; as a result, ultraviolet absorption bands are broad. Where an infrared spectrum shows many sharp peaks, a typical ultraviolet spectrum shows only a few broad humps. One can conveniently describe such a spectrum in terms of the *position* of the top of the hump (λ_{max}) and the *intensity* of that absorption (ϵ_{max}, the extinction coefficient).

When we speak of a molecule as being raised to a higher electronic level, we mean that an electron has been changed from one orbital to another orbital of higher energy. This electron can be of any of the kinds we have encountered: a σ electron, a π electron, or an n electron (a non-bonding electron—that is, one of an unshared pair). A σ electron is held tightly, and a good deal of energy is required to excite it: energy corresponding to ultraviolet light of short wavelength, in a region—"far" ultraviolet—outside the range of the usual spectrometer. It is chiefly excitations of the comparatively loosely held n and π electrons that appear in the (near) ultraviolet spectrum, and, of these, only jumps to the lower—more stable—excited states.

The electronic transitions of most concern to the organic chemist are: (a) $n \rightarrow \pi^*$, in which the electron of an unshared pair goes to an unstable (*antibonding*) π orbital, as, for example,



and (b) $\pi \rightarrow \pi^*$, in which an electron goes from a stable (*bonding*) π orbital to an unstable π orbital, as, for example,



A $\pi \rightarrow \pi^*$ transition can occur for even a simple alkene, like ethylene, but absorption occurs in the far ultraviolet. Conjugation of double bonds, however, lowers the energy required for the transition, and absorption moves to longer wavelengths, where it can be more conveniently measured. If there are enough double bonds in conjugation, absorption will move into the visible region, and the compound will be colored. β-Carotene, for example, is a yellow pigment found in carrots and green leaves, and is a precursor of vitamin A; it contains eleven carbon–carbon double bonds in conjugation, and owes its color to absorption at the violet end of the visible spectrum (λ_{max} 451 mμ).

How does conjugation bring about this effect? We have seen (Sec. 8.17) that 1,3-butadiene, for example, is stabilized by contribution from structures involving formal bonds. Stabilization is not very great, however, since such structures—and additional, ionic structures—are not very stable and make only

small contribution to the hybrid. Similar structures contribute to an excited state of butadiene, too, but here, because of the instability of the molecule, they make much larger contribution. Resonance stabilizes the excited state *more* than it stabilizes the ground state, and thus reduces the difference between them.

In contrast to the infrared spectrum, the ultraviolet spectrum is not used primarily to show the presence of individual functional groups, but rather to show relationships between functional groups, chiefly conjugation: conjugation between two or more carbon–carbon double (or triple) bonds; between carbon–carbon and carbon–oxygen double bonds; between double bonds and an aromatic ring; and even the presence of an aromatic ring itself. It can, in addition, reveal the number and location of substituents attached to the carbons of the conjugated system.

Problem 13.2 In Problem 9.19, page 313, you calculated the number of rings in β-carotene. Taking into account also the molecular formula, the number of double bonds, conjugation, its natural occurrence, and its conversion into vitamin A (p. 277), what possible structure for β-carotene occurs to you?

Problem 13.3 Compounds A, B, and C have the formula C_5H_8, and on hydrogenation all yield *n*-pentane. Their ultraviolet spectra show the following values of λ_{max}: A, 176 mμ; B, 211 mμ; C, 215 mμ. (1-Pentene has λ_{max} 178 mμ.) (a) What is a likely structure for A? For B and C? (b) What kind of information might enable you to assign specific structures to B and C?

13.6 The nuclear magnetic resonance (nmr) spectrum

Like electrons, the nuclei of certain atoms are considered to *spin*. The spinning of these charged particles—the circulation of charge—generates a *magnetic moment* along the axis of spin, so that these nuclei act like tiny bar magnets. One such nucleus—and the one we shall be mostly concerned with—is the *proton*, the nucleus of ordinary hydrogen, ^1H.

Now, if a proton is placed in an external magnetic field, its magnetic moment, according to quantum mechanics, can be aligned in either of two ways: *with* or *against* the external field. Alignment with the field is the more stable, and energy must be absorbed to "flip" the tiny proton magnet over to the less stable alignment, against the field.

Just how much energy is needed to flip the proton over depends, as we might expect, on the strength of the external field: the stronger the field, the greater the tendency to remain lined up with it, and the higher the frequency (*Remember:* $\Delta E = h\nu$) of the radiation needed to do the job.

$$\nu = \frac{\gamma H_0}{2\pi}$$

where

ν = frequency, in Hz
H_0 = strength of the magnetic field, in gauss
γ = a nuclear constant, the *gyromagnetic ratio*, 26,750 for the proton

In a field of 14,092 gauss, for example, the energy required corresponds to electromagnetic radiation of frequency 60 MHz (60 megahertz or 60 million cycles per

second): radiation in the radiofrequency range, and of much lower energy (lower frequency, longer wavelength) than even infrared light.

In principle, we could place a substance in a magnetic field of constant strength, and then obtain a spectrum in the same way we obtain an infrared or an ultraviolet spectrum: pass radiation of steadily changing frequency through the substance, and observe the frequency at which radiation is absorbed. In practice, however, it has been found more convenient to keep the radiation frequency constant, and to vary the strength of the magnetic field; at some value of the field strength the energy required to flip the proton matches the energy of the radiation, absorption occurs, and a signal is observed. Such a spectrum is called a *nuclear magnetic resonance* (nmr) *spectrum* (Fig. 13.3).

Since the nucleus involved is the proton, the spectrum is sometimes called a *pmr* (proton magnetic resonance) spectrum, to differentiate it from spectra involving such nuclei as ^{13}C (called *cmr* spectra) or ^{19}F.

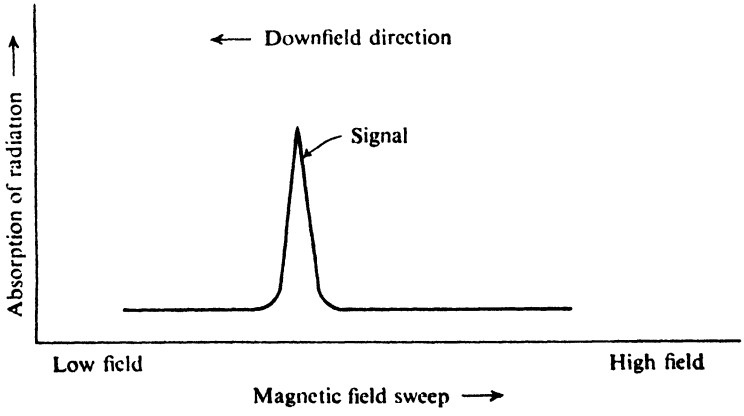


Figure 13.3. The nmr spectrum.

Now, if the situation were as simple as we have so far described it, all the protons in an organic molecule would absorb at exactly the same field strength, and the spectrum would consist of a single signal that would tell us little about the structure of the molecule. But the frequency at which a proton absorbs depends on the magnetic field which that proton *feels*, and this *effective* field strength is not exactly the same as the *applied* field strength. The effective field strength at each proton depends on the environment of that proton—on, among other things, the electron density at the proton, and the presence of other, nearby protons. Each proton—or, more precisely, each set of equivalent protons—will have a slightly different environment from every other set of protons, and hence will require a slightly *different applied* field strength to produce the *same effective* field strength: the particular field strength at which absorption takes place.

At a given radiofrequency, then, *all protons absorb at the same effective field strength, but they absorb at different applied field strengths.* It is this applied field strength that is measured, and against which the absorption is plotted.

The result is a spectrum showing many absorption peaks, whose relative positions, reflecting as they do differences in environment of protons, can give almost unbelievably detailed information about molecular structure.

In the following sections, we shall look at various aspects of the nmr spectrum:

(a) the *number of signals*, which tells us how many different "kinds" of protons there are in a molecule;

(b) the *positions of the signals*, which tell us something about the electronic environment of each kind of proton;

(c) the *intensities of the signals*, which tell us how many protons of each kind there are; and

(d) the *splitting of a signal* into several peaks, which tells us about the environment of a proton with respect to other, nearby protons.

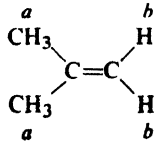
13.7 Nmr. Number of signals. Equivalent and non-equivalent protons

In a given molecule, protons with the same environment absorb at the same (applied) field strength; protons with different environments absorb at different (applied) field strengths. A set of protons with the same environment are said to be *equivalent*; the number of signals in the nmr spectrum tells us, therefore, how many sets of equivalent protons—how many "kinds" of protons—a molecule contains.

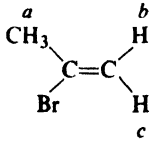
For our purposes here, equivalent protons are simply chemically equivalent protons, and we have already had considerable practice in judging what these are. Looking at each of the following structural formulas, for example, we readily pick out as equivalent the protons designated with the same letter:

CH_3—CH_2—Cl	CH_3—CHCl—CH_3	CH_3—CH_2—CH_2—Cl
a *b*	*a* *b* *a*	*a* *b* *c*
2 nmr signals	*2 nmr signals*	*3 nmr signals*
Ethyl chloride	Isopropyl chloride	*n*-Propyl chloride

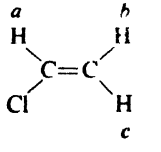
Realizing that, to be chemically equivalent. protons must also be *stereo*-chemically equivalent, we find we can readily analyze the following formulas, too:



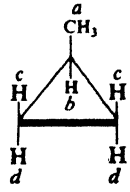
2 nmr signals
Isobutylene



3 nmr signals
2-Bromopropene



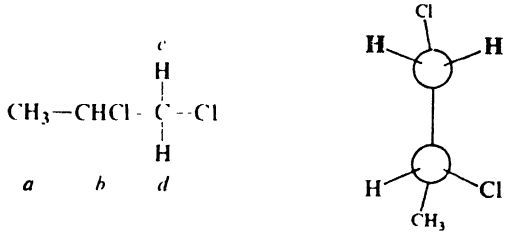
3 nmr signals
Vinyl chloride



4 nmr signals
Methylcyclopropane

1,2-Dichloropropane (optically active or optically inactive) gives four nmr

signals, and it takes only a little work with models or stereochemical formulas to see that this should indeed be so.



4 nmr signals
1,2-Dichloropropane

The environments of the two protons on C–1 are *not* the same (and no amount of rotation about single bonds will make them so); the protons are not equivalent, and will absorb at different field strengths.

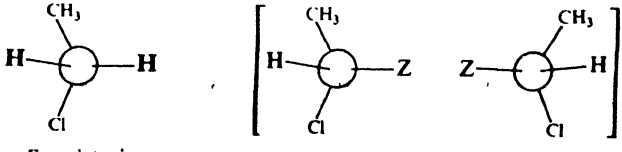
We can tell from a formula which protons are in different environments and hence should give different signals. We cannot always tell—particularly with stereochemically different protons—just *how* different these environments are; they may not be different enough for the signals to be noticeably separated, and we may see *fewer* signals than we predict.

Now, just how did we arrive at the conclusions of the last few paragraphs? Most of us—perhaps without realizing it—judge the equivalence of protons by following the approach of isomer number (Sec. 4.2). This is certainly the easiest way to do it. We imagine each proton in turn to be replaced by some other atom Z. If replacement of either of two protons by Z would yield the same product—or enantiomeric products—then the two protons are chemically equivalent. We ignore the existence of conformational isomers and, as we shall see in Sec. 13.13, this is just what we should do.

Take, for example, ethyl chloride. Replacement of a methyl proton would give $CH_2Z—CH_2Cl$; replacement of a methylene proton would give $CH_3—CHZCl$. These are, of course, different products, and we easily recognize the methyl protons as being non-equivalent to the methylene protons.

The product $CH_2Z—CH_2Cl$ is the same regardless of *which one* of the three methyl protons is replaced. The (average) environment of the three protons is identical, and hence we expect one nmr signal for all three.

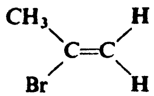
Replacement of either of the two methylene protons would give one of a pair of enantiomers:



Enantiotopic protons
Ethyl chloride

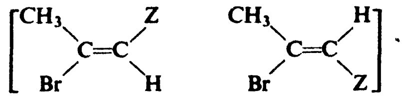
Such pairs of protons are called **enantiotopic protons**. The environments of these two protons are mirror images of each other; these protons are equivalent, and we see one nmr signal for the pair. (Like any other physical property—except rotation of polarized light—the nmr spectrum does not distinguish between mirror images.)

Turning to 2-bromopropene, we see that replacement of either of the vinylic protons gives one of a pair of diastereomers (geometric isomers, in this case):



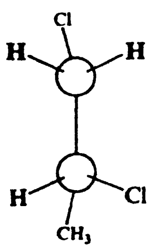
Diastereotopic protons

2-Bromopropene



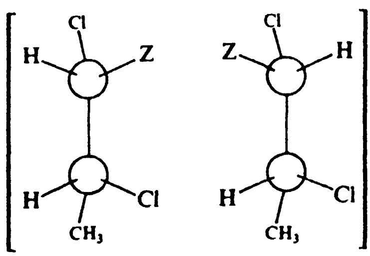
Such pairs of protons are called **diastereotopic protons**. The environments of these two protons are neither identical nor mirror images of each other; these protons are non-equivalent, and we expect an nmr signal from each one.

Similarly, in 1,2-dichloropropane the two protons on C-1 are diastereotopic, non-equivalent, and give separate nmr signals.



Diastereotopic protons

1,2-Dichloropropane



In Sec. 13.13, we shall take a closer look at equivalence. The guidelines we have laid down here, however—based on rapid rotation about single bonds—hold for most spectra taken under ordinary conditions, specifically, at room temperature.

Problem 13.4 Draw the structural formula of each of the following compounds (disregarding enantiomerism), and label all sets of equivalent protons. How many nmr signals would you expect to see from each?

(a) the two isomers of formula $C_2H_4Cl_2$
(b) the four isomers of $C_3H_6Br_2$
(c) ethylbenzene and *p*-xylene
(d) mesitylene, *p*-ethyltoluene, isopropylbenzene
(e) CH_3CH_2OH and CH_3OCH_3
(f) $CH_3CH_2OCH_2CH_3$, $CH_3OCH_2CH_2CH_3$, $CH_3OCH(CH_3)_2$, $CH_3CH_2CH_2CH_2OH$
(g) CH_2—CH_2 (ring closed by CH_2—O), CH_3—CH—CH_2 (ring closed by O) (*Hint:* Make Models.)

(h) $CH_3CH_2\overset{\overset{O}{\|}}{C}-H$, $CH_3\overset{\overset{O}{\|}}{C}CH_3$, and $CH_2{=}CHCH_2OH$

Problem 13.5 Three isomeric dimethylcyclopropanes give, respectively, 2, 3, and 4 nmr signals. Draw a stereoisomeric formula for the isomer giving rise to each number of signals.

Problem 13.6 How many nmr signals would you expect from cyclohexane? Why?

13.8 Nmr. Positions of signals. Chemical shift

Just as the number of signals in an nmr spectrum tells us how many kinds of protons a molecule contains, so the *positions of the signals* help to tell us *what kinds* of protons they are: aromatic, aliphatic, primary, secondary, tertiary; benzylic, vinylic, acetylenic; adjacent to halogen or to other atoms or groups. These different kinds of protons have different electronic environments, and it is the electronic environment that determines just where in the spectrum a proton absorbs.

When a molecule is placed in a magnetic field—as it is when one determines an nmr spectrum—its electrons are caused to circulate and, in circulating, they generate secondary magnetic fields: *induced* magnetic fields.

Circulation of electrons *about the proton itself* generates a field aligned in such a way that—at the proton—it opposes the applied field. The field felt by the proton is thus diminished, and the proton is said to be **shielded**.

Circulation of electrons—specifically, π electrons—*about nearby nuclei* generates a field that can either oppose or reinforce the applied field at the proton, depending on the proton's location (Fig. 13.4). If the induced field opposes the

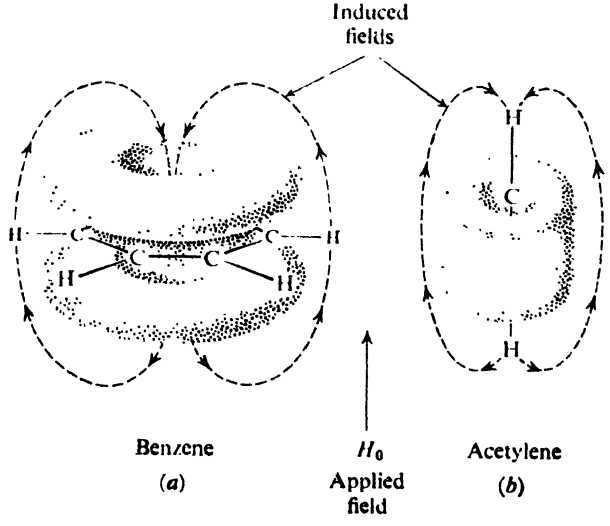


Figure 13.4. Induced field (*a*) reinforces applied field at the aromatic protons, and (*b*) opposes applied field at the acetylenic protons. Aromatic protons are deshielded; acetylenic protons are shielded.

applied field, the proton is shielded, as before. If the induced field reinforces the applied field, then the field felt by the proton is augmented, and the proton is said to be **deshielded**.

Compared with a naked proton, a shielded proton requires a higher applied field strength—and a deshielded proton requires a lower applied field strength—to provide the particular effective field strength at which absorption occurs. Shielding thus shifts the absorption upfield, and deshielding shifts the absorption downfield. Such shifts in the position of nmr absorptions, arising from shielding and deshielding by electrons, are called **chemical shifts.**

How are the direction and magnitude—the *value*—of a particular chemical shift to be measured and expressed?

The unit in which a chemical shift is most conveniently expressed is parts per million (ppm) of the total applied magnetic field. Since shielding and deshielding arise from *induced* secondary fields, the magnitude of a chemical shift is proportional to the strength of the applied field—or, what is equivalent, proportional to the radiofrequency the field must match. If, however, it is expressed as a *fraction* of the applied field—that is, if the observed shift is divided by the particular radiofrequency used—then a chemical shift has a constant value that is independent of the radiofrequency and the magnetic field that the nmr spectrometer employs.

The **reference point** from which chemical shifts are measured is, for practical reasons, not the signal from a naked proton, but the signal from an actual compound: usually tetramethylsilane, $(CH_3)_4Si$. Because of the low electronegativity of silicon, the shielding of the protons in the silane is greater than in most other organic molecules; as a result, most nmr signals appear in the same direction from the tetramethylsilane signal: *downfield.*

The most commonly used scale is the δ (*delta*) scale. The position of the tetramethylsilane signal is taken as 0.0 ppm. Most chemical shifts have δ values between 0 and 10 (minus 10, actually). A *small* δ value represents a *small* downfield shift, and a *large* δ value represents a *large* downfield shift.

One commonly encounters another scale: the τ (*tau*) scale, on which the tetramethylsilane signal is taken as 10.0 ppm. Most τ values lie between 0 and 10. The two scales are related by the expression $\tau = 10 - \delta$.

An nmr signal from a particular proton appears at a different field strength than the signal from tetramethylsilane. This difference—the chemical shift—is measured not in gauss, as we might expect, but in the equivalent frequency units (*Remember:* $\nu = \gamma H_0/2\pi$), and it is divided by the frequency of the spectrometer used. Thus, for a spectrometer operating at 60 MHz, that is, at 60×10^6 Hz:

$$\delta = \frac{\text{observed shift (Hz)} \times 10^6}{60 \times 10^6 \text{ (Hz)}}$$

The chemical shift for a proton is determined, then, by the electronic environment of the proton. In a given molecule, protons with different environments—non-equivalent protons—have different chemical shifts. Protons with the same environment—equivalent protons—have the same chemical shift; indeed, *for nmr purposes, equivalent protons are defined as those with the same chemical shift.* (We have already seen what the equivalence of protons means in terms of molecular structure.)

Table 13.4 CHARACTERISTIC PROTON CHEMICAL SHIFTS

Type of proton		Chemical shift, ppm
		δ
Cyclopropane		0.2
Primary	RCH_3	0.9
Secondary	R_2CH_2	1.3
Tertiary	R_3CH	1.5
Vinylic	C=C—H	4.6–5.9
Acetylenic	C≡C—H	2–3
Aromatic	Ar—H	6–8.5
Benzylic	Ar—C—H	2.2–3
Allylic	C=C—CH_3	1.7
Fluorides	HC—F	4–4.5
Chlorides	HC—Cl	3–4
Bromides	HC—Br	2.5–4
Iodides	HC—I	2–4
Alcohols	HC—OH	3.4–4
Ethers	HC—OR	3.3–4
Esters	RCOO—CH	3.7–4.1
Esters	HC—COOR	2–2.2
Acids	HC—COOH	2–2.6
Carbonyl compounds	HC—C=O	2–2.7
Aldehydic	RCHO	9–10
Hydroxylic	ROH	1–5.5
Phenolic	ArOH	4–12
Enolic	C=C—OH	15–17
Carboxylic	RCOOH	10.5–12
Amino	RNH_2	1–5

Furthermore, it has been found that a proton with a particular environment shows much the same chemical shift, whatever the molecule it happens to be part of. Take, for example, our familiar classes of hydrogens: primary, secondary, and tertiary. In the absence of other nearby substituents, absorption occurs at about these values:

RCH_3 δ 0.9
R_2CH_2 δ 1.3
R_3CH δ 1.5

All these protons, in turn, differ widely from aromatic protons which, because of the powerful deshielding due to the circulation of the π electrons (see Fig. 13.4, p. 419), absorb far downfield:

Ar—H δ 6-8.5

Attachment of chlorine to the carbon bearing the proton causes a downfield shift. If the chlorine is attached to the carbon once removed from the carbon bearing the proton, there is again a downward shift, but this time much weaker.

CH_3—Cl	δ 3.0	CH_3—C—Cl	δ 1.5
R—CH_2—Cl	δ 3.4	R—CH_2—C—Cl	δ 1.7
R_2CH—Cl	δ 4.0	R_2CH—C—Cl	δ 1.6

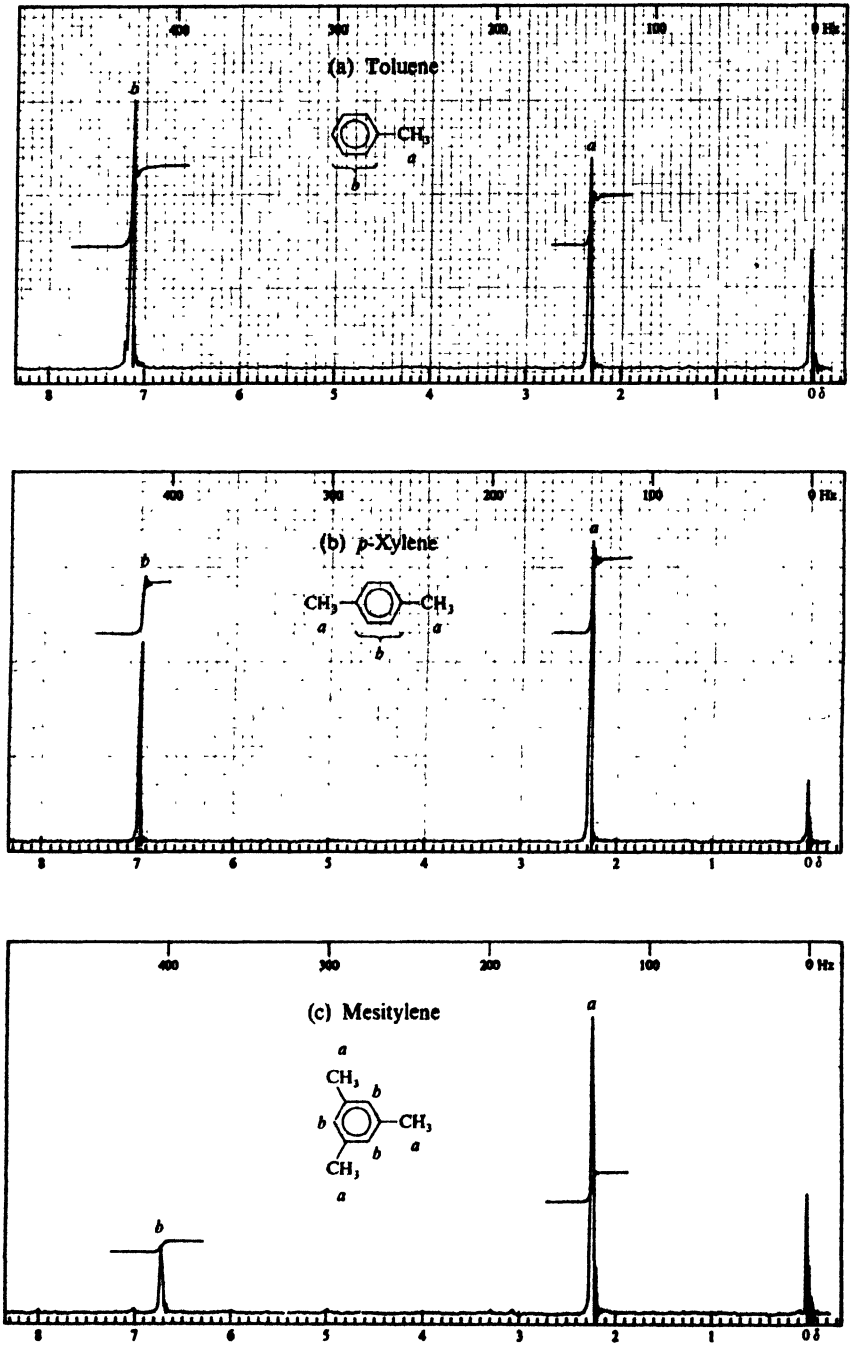


Figure 13.5. Nmr spectra: chemical shift. (a) Toluene; (b) *p*-xylene; (c) mesitylene.

Two chlorines cause a greater downfield shift. Other halogens show similar effects.

The downfield shift caused by chlorine is what we might have expected from its inductive effect: electron withdrawal lowers the electron density in the vicinity of the proton and thus causes deshielding. The effect of a substituent on the chemical shift is unquestionably the net result of many factors; yet we shall often observe chemical shifts which strongly suggest that an inductive effect is at least one of the factors at work.

Table 13.4 lists chemical shifts for protons in a variety of environments.

The nmr spectra (Fig. 13.5, p. 422) of the alkylbenzenes *toluene*, *p-xylene*, and *mesitylene* illustrate the points we have just made. In each spectrum there are two signals: one for the side-chain protons, and one for the ring protons. (Here, as in some—though not most—aromatic compounds, the *ortho*, *meta*, and *para* protons have nearly the same chemical shifts, and hence for nmr purposes are nearly equivalent.)

In each spectrum, the ring protons show the low-field absorption we have said is characteristic of aromatic protons. Absorption is not only at low field, but at nearly the *same* field strength for the three compounds: at δ 7.17, 7.05, and 6.78. (These values are not *exactly* the same, however, since the environments of the aromatic protons are not exactly the same in the three compounds.)

In each compound, side-chain protons—benzylic protons—are close enough to the ring to feel a little of the deshielding effect of the π electrons (Fig. 13.4, p. 419), and hence absorb somewhat downfield from ordinary alkyl protons: at δ 2.32, 2.30, and 2.25. In all three compounds, the environment of the side-chain protons is almost identical, and so are the chemical shifts.

The similarity in structure among these three alkylbenzenes is thus reflected in the similarity of their nmr spectra. There is, however, a major difference in their structures—a difference in *numbers* of aromatic and side-chain protons—and, as we shall see in the next section, this is reflected in a major difference in nmr spectra.

The chemical shift is fundamental to the nmr spectrum since, by separating the absorption peaks due to the various protons of a molecule, it reveals all the other features of the spectrum. The *numerical values* of chemical shifts, although significant, do not have the overriding importance that absorption frequencies have in the infrared spectrum. In our work with nmr, we shall escape much of the uncertainty that accompanies the beginner's attempts to identify precisely infrared absorption bands; at the same time, we have a greater *variety* of concepts to learn about—but these, at our present level, we may find more satisfying and intellectually more stimulating.

Problem 13.7 What is a possible explanation for the following differences in chemical shift for aromatic protons? Benzene δ 7.37; toluene δ 7.17; *p*-xylene δ 7.05; mesitylene δ 6.78.

13.9 Nmr. Peak area and proton counting

Let us look again at the nmr spectra (Fig. 13.5, p. 422) of toluene, *p*-xylene, and mesitylene, and this time focus our attention, not on the positions of the signals, but on their relative *intensities*, as indicated by the sizes of the absorption peaks.

Judging roughly from the peak heights, we see that the (high-field) peak for

side-chain protons is smaller than the (low-field) peak for aromatic protons in the case of toluene, somewhat larger in the case of *p*-xylene, and considerably larger in the case of mesitylene. More exact comparison, based on the *areas under the peaks*, shows that the peaks for side-chain and aromatic protons have sizes in the ratio 3:5 for toluene; 3:2 (or 6:4) for *p*-xylene; and 3:1 (or 9:3) for mesitylene.

This illustrates a general quality of all nmr spectra. *The area under an nmr signal is directly proportional to the number of protons giving rise to the signal.*

It is not surprising that this is so. The absorption of every quantum of energy is due to exactly the same thing: the flipping over of a proton in the same effective magnetic field. The more protons flipping, the more the energy absorbed, and the greater is the area under the absorption peak.

Areas under nmr signals are measured by an electronic integrator, and are usually given on the spectrum chart in the form of a stepped curve; heights of steps are proportional to peak areas. Nmr chart paper is cross-hatched, and we can conveniently estimate step heights by simply counting squares. We arrive at a set of numbers that are in the same ratio as the numbers of different kinds of protons. We convert this set of numbers into a set of smallest whole numbers just as we did in calculating empirical formulas (Sec. 2.27). The number of protons

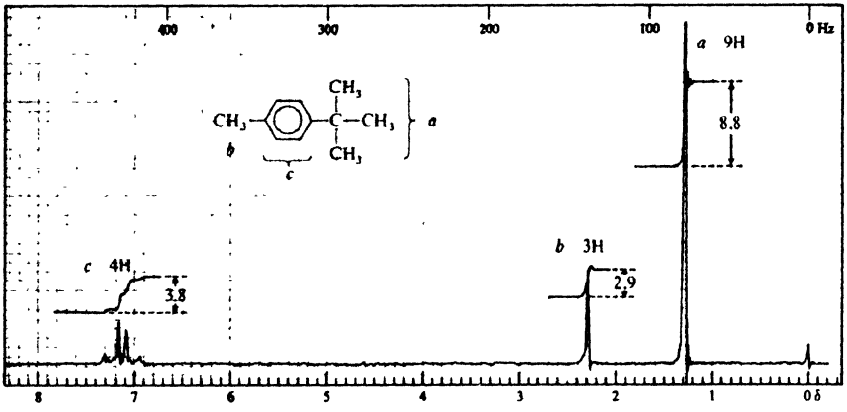


Figure 13.6. Nmr spectrum of *p-tert*-butyltoluene. Proton counting.

The ratio of step heights $a:b:c$ is

$$8.8:2.9:3.8 = 3.0:1.0:1.3 = 9.0:3.0:3.9$$

Alternatively, since the molecular formula $C_{11}H_{16}$ is known,

$$\frac{16\text{ H}}{15.5\text{ units}} = 1.03\text{ H per unit}$$

$$a = 1.03 \times 8.8 = 9.1 \qquad b = 1.03 \times 2.9 = 3.0 \qquad c = 1.03 \times 3.8 = 3.9$$

Either way, we find: *a*, 9H; *b*, 3H; *c*, 4H.

The 4H of *c* (δ 7.1) are in the aromatic range, suggesting a disubstituted benzene $-C_6H_4-$. The 3H of *b* (δ 2.28) have a shift expected for benzylic protons, giving $CH_3-C_6H_4-$. There is left C_4H_9 which, in view of the 9H of *a* (δ 1.28) must be $-C(CH_3)_3$; since these are once removed from the ring their shift is nearly normal for an alkyl group. The compound is *tert*-butyltoluene (actually, as shown by the absorption pattern of the aromatic protons, the *p*-isomer).

giving rise to each signal is equal to the whole number for that signal—or to some multiple of it. See, for example, Fig. 13.6.

We take any shortcuts we can. If we know the molecular formula and hence the total number of protons, we can calculate from the combined step heights the number of squares per proton. If we suspect a particular structural feature that gives a characteristic signal—an aldehydic (—CHO) or carboxylic (—COOH) proton, say, which gives a far-downfield peak—we can use this step height as a starting point.

Working the following problems will give us some idea of the tremendous help "proton counting" by nmr can be in assigning a structure to a compound.

Problem 13.8 Go back to Problem 13.4 (p. 418), where you predicted the number of nmr signals from several compounds. Tell, where you can, the relative positions of the signals (that is, their sequence as one moves downfield) and, roughly, the δ value expected for each. For each signal tell the number of protons giving rise to it.

Problem 13.9 Give a structure or structures consistent with each of the nmr spectra shown in Fig. 13.7 (p. 426).

13.10 Nmr. Splitting of signals. Spin–spin coupling

An nmr spectrum, we have said, shows a signal for each kind of proton in a molecule; the few spectra we have examined so far bears this out. If we look much further, however, we soon find that most spectra are—or *appear* to be—much more complicated than this. Figure 13.8 (p. 427), for example, shows the nmr spectra for three compounds,

$CH_2Br—CHBr_2$	$CH_3—CHBr_2$	$CH_3—CH_2Br$
1,1,2-Tribromoethane	1,1-Dibromoethane	Ethyl bromide

each of which contains only two kinds of protons; yet, instead of two peaks, these spectra show *five*, *six*, and *seven* peaks, respectively

What does this multiplicity of peaks mean? How does it arise, and what can it tell us about molecular structure?

The answer is that we are observing the *splitting* of nmr signals caused by spin–spin coupling. The signal we expect from each set of equivalent protons is appearing, not as a single peak, but as a *group* of peaks. Splitting reflects the environment of the absorbing protons: not with respect to electrons, but with respect to other, nearby protons. It is as though we were permitted to sit on a proton and look about in all directions: we can *see* and *count* the protons attached to the carbon atoms next to our own carbon atom and, sometimes, even see protons still farther away.

Let us take the case of adjacent carbon atoms carrying, respectively, a pair of secondary protons and a tertiary proton, and consider first the absorption by one of the secondary protons:

$$—\overset{|}{C}H—CH_2—$$

The magnetic field that a secondary proton feels at a particular instant is slightly increased or slightly decreased by the spin of the neighboring tertiary proton: *increased* if the tertiary proton happens at that instant to be aligned *with* the applied

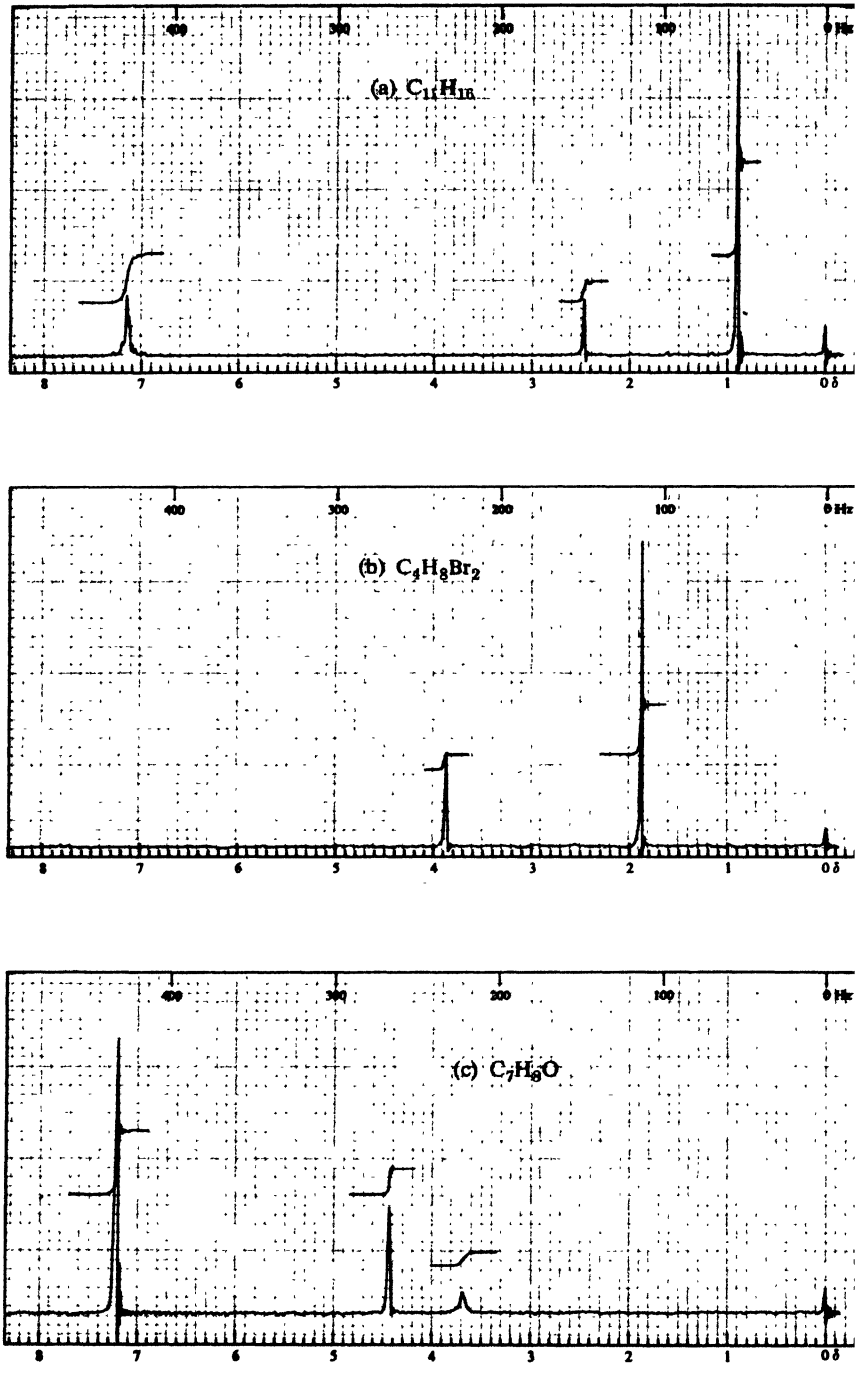


Figure 13.7. Nmr spectra for Problem 13.9, p. 425.

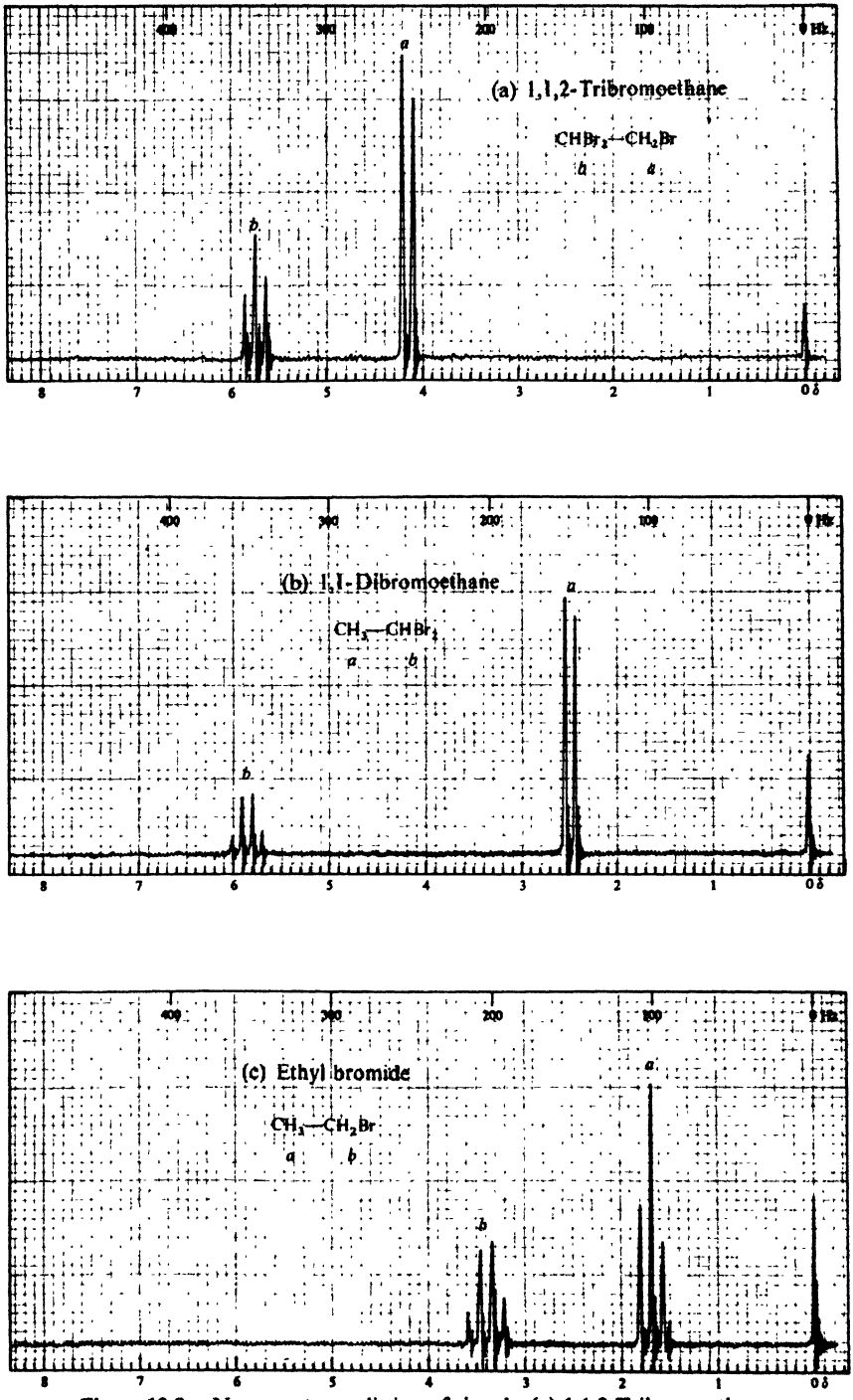


Figure 13.8. Nmr spectra: splitting of signals. (a) 1,1,2-Tribromoethane; (b) 1,1-dibromoethane; (c) ethyl bromide.

field; or *decreased* if the tertiary proton happens to be aligned *against* the applied field.

For half the molecules, then, absorption by a secondary proton is shifted slightly downfield, and for the other half of the molecules the absorption is shifted slightly upfield. The signal is split into *two* peaks: a *doublet*, with equal peak intensities (Fig. 13.9).

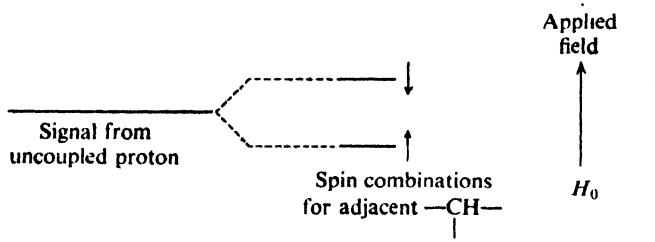


Figure 13.9. Spin–spin coupling. Coupling with one proton gives a 1:1 doublet.

Next, what can we say about the absorption by the tertiary proton?

$$-\overset{|}{\underset{|}{C}}H-CH_2-$$

It is, in its turn, affected by the spin of the neighboring secondary protons. But now there are *two* protons whose alignments in the applied field we must consider. There are four equally probable combinations of spin alignments for these two protons, of which two are equivalent. At any instant, therefore, the tertiary proton feels any one of three fields, and its signal is split into three equally spaced peaks: a *triplet*, with relative peak intensities 1:2:1, reflecting the combined (double) probability of the two equivalent combinations (Fig. 13.10).

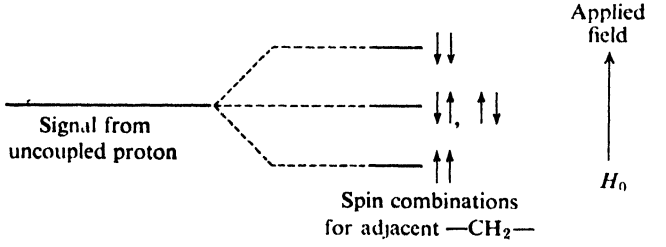


Figure 13.10. Spin–spin coupling. Coupling with two protons gives a 1:2:1 triplet.

Figure 13.11 (p. 429) shows an idealized nmr spectrum due to the grouping —CH—CH_2—. We see a 1:1 doublet (from the —CH_2—) and a 1:2:1 triplet (from the —CH—). The total area (both peaks) under the doublet is *twice* as big as the total area (all three peaks) of the triplet, since the doublet is due to absorption by twice as many protons as the triplet.

A little measuring shows us that the separation of peaks (the *coupling constant*,

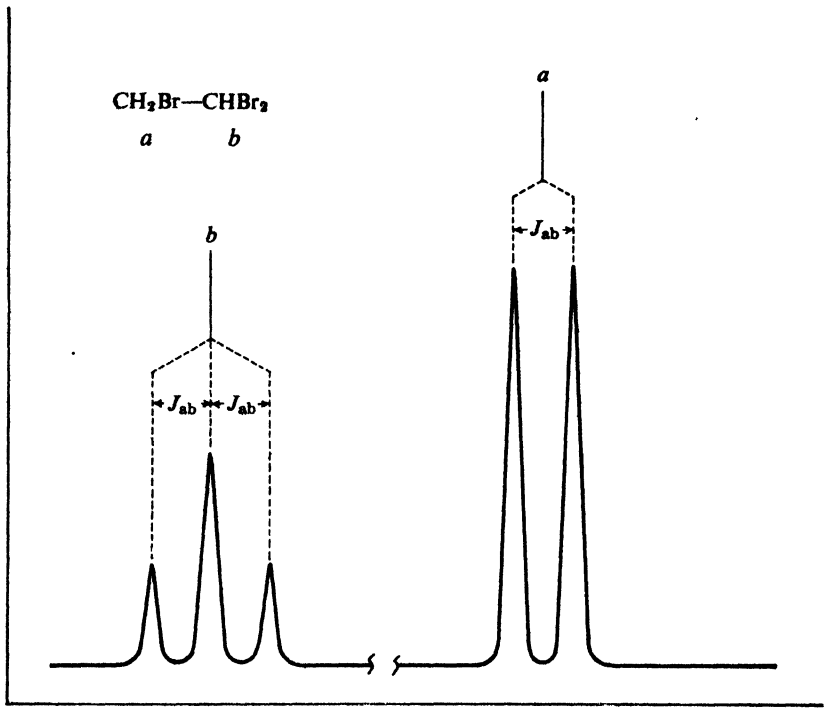


Figure 13.11. Spin–spin splitting. Signal *a* is split into a doublet by coupling with one proton; signal *b* is split into a triplet by two protons. Spacings in both sets the same (J_{ab}).

J, Sec. 13.11) in the doublet is exactly the same as the separation of peaks in the triplet. (Spin–spin coupling is a *reciprocal* affair, and the effect of the secondary protons on the tertiary proton must be identical with the effect of the tertiary proton on the secondary protons.) Even if they were to appear in a complicated spectrum of many absorption peaks, the identical peak separations would tell us that this doublet and triplet were related: that the (two) protons giving the doublet and the (one) proton giving the triplet are coupled, and hence are attached to adjacent carbon atoms.

We have seen that an nmr signal is split into a doublet by one nearby proton, and into a triplet by two (equivalent) nearby protons. What splitting can we expect more than two protons to produce? In Fig. 13.12 (p. 430), we see that three equivalent protons split a signal into four peaks—a quartet—with the intensity pattern 1:3:3:1.

It can be shown that, in general, *a set of n equivalent protons will split an nmr signal into n + 1 peaks.*

If we turn once more to Fig. 13.8 (p. 427), we no longer find these spectra so confusing. We now see not just five or six or seven peaks, but instead a doublet and a triplet, or a doublet and a quartet, or a triplet and a quartet. We recognize each of these multiplets from the even spacings within it, and from its symmetrical

intensity pattern (1:1, or 1:2:1, or 1:3:3:1). Each spectrum does show absorption by just two kinds of protons; but clearly it shows a great deal more than that.

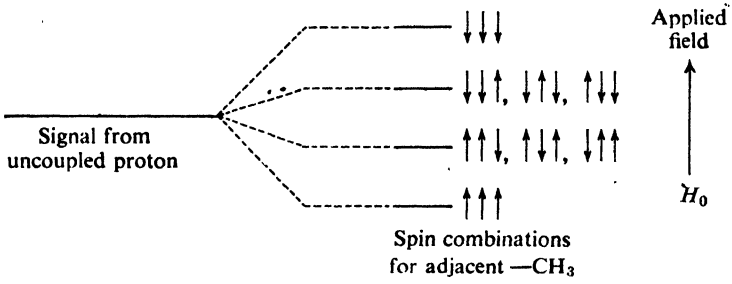


Figure 13.12. Spin–spin coupling. Coupling with three protons gives a 1:3:3:1 quartet.

If we keep in mind that the peak area reflects the number of *absorbing* protons, and the multiplicity of splittings reflects the number of *neighboring* protons, we find in each spectrum just what we would expect.

In the spectrum of $CHBr_2$—CH_2Br we see

Downfield triplet and *Upfield doublet*
Area: 1 *Area: 2*

In the spectrum of CH_3—$CHBr_2$ we see

Downfield quartet and *Upfield doublet*
Area: 1 *Area: 3*

and in the spectrum of CH_3—CH_2Br we see

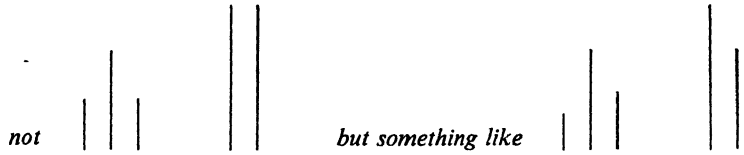
Downfield quartet and *Upfield triplet*
Area: 2 *Area: 3*

—CH_2—CH_3 —CH_2—CH_3

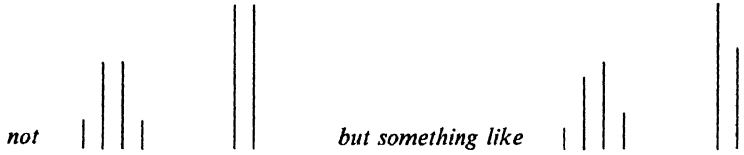
We see chemical shifts that are consistent with the deshielding effect of halogens: in each spectrum, the protons on the carbon carrying the greater number of halogens absorb farther downfield (larger δ).

In each spectrum, we see that the spacing of the peaks within one multiplet is the same as within the other, so that even in a spectrum with many other peaks, we could pick out these two multiplets as being coupled.

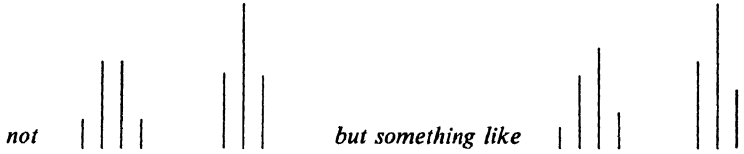
Finally, we see a feature that we have not yet discussed: the various multiplets do not show quite the symmetry we have attributed to them. In spectrum (a), we see



and in spectrum (b)



and in spectrum (c)

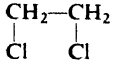


In each case, the inner peaks—the peaks nearer the other, coupled multiplets—are larger than the outer peaks.

Perfectly symmetrical multiplets are to be expected only when the separation between multiplets is very large relative to the separation within multiplets—that is, when the chemical shift is much larger than the coupling constant (Sec. 13.11). The patterns we see here are very commonly observed, and are helpful in matching up multiplets: we know in which direction—upfield or downfield—to look for the second multiplet.

We have not yet answered a very basic question: just which protons in a molecule can be coupled? *We may expect to observe spin-spin splitting only between non-equivalent neighboring protons.* By "non-equivalent" protons we mean protons with different chemical shifts, as we have already discussed (Sec. 13.8). By "neighboring" protons we mean most commonly protons on *adjacent* carbons, as in the examples we have just looked at (Fig. 13.8, p. 427); sometimes protons further removed from each other may also be coupled, particularly if π bonds intervene. (If protons on the *same* carbon are non-equivalent—as they sometimes are—they may show coupling.)

We do *not* observe splitting due to coupling between the protons making up the same $-CH_3$ group, since they are equivalent. We do *not* observe splitting due to coupling between the protons on C-1 and C-2 of 1,2-dichloroethane

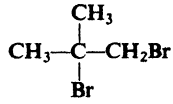


1,2-Dichloroethane

No splitting

since, although on different carbons, they, too, are equivalent.

In the spectrum of 1,2-dibromo-2-methylpropane,

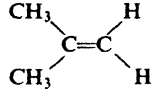


No splitting

1,2-Dibromo-2-methylpropane

we do *not* observe splitting between the six methyl protons, on the one hand, and the two $-CH_2-$ protons on the other hand. They are non-equivalent, and give rise to different nmr signals, but they are not on adjacent carbons, and their spins do not (noticeably) affect each other. The nmr spectrum contains two singlets, with a peak area ratio of 3:1 (or 6:2). For the same reason, we do *not* observe splitting due to coupling between ring and side-chain protons in alkylbenzenes (Fig. 13.5, p. 422).

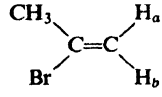
We do *not* observe splitting between the two vinyl protons of isobutylene



No splitting

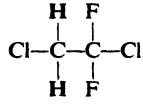
Isobutylene

since they are equivalent. On the other hand, we may observe splitting between the two vinyl protons on the same carbon if, as in 2-bromopropene, they are non-equivalent.



2-Bromopropene

The fluorine (^{19}F) nucleus has magnetic properties of the same kind as the proton. It gives rise to nmr spectra, although at a quite different frequency-field strength combination than the proton. Fluorine nuclei can be coupled not only with each other, but also with protons. *Absorption by* fluorine does not appear in the proton nmr spectrum—it is far off the scale—but the *splitting by* fluorine of proton signals can be seen. The signal for the two protons of 1,2-dichloro-1,1-difluoroethane, for example,



appears as a 1:2:1 triplet with peak spacings of 11 Hz. (What would you expect to see in the fluorine nmr spectrum?)

Figures 13.13 and 13.14, p. 433, and Fig. 13.15, p. 434, illustrate some of the kinds of splitting we are likely to encounter in nmr spectra.

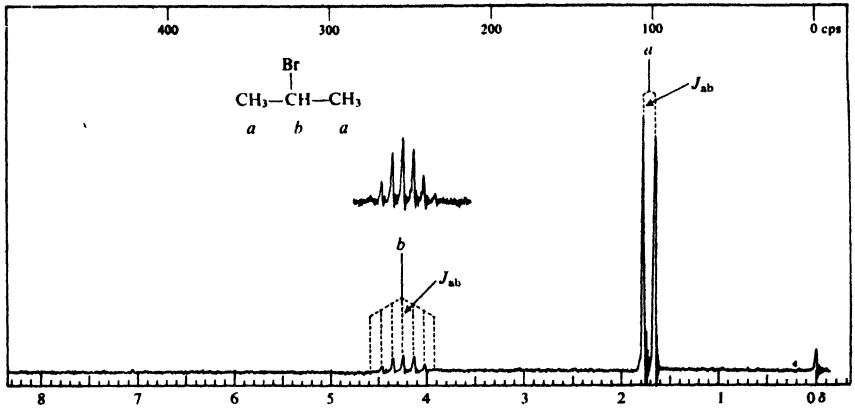


Figure 13.13. Nmr spectrum of isopropyl bromide. Absorption by the six methyl protons H_a appears upfield, split into a doublet by the single adjacent proton H_b. Absorption by the lone proton H_b appears downfield (the inductive effect of bromine) split into a septet by the six adjacent protons—with the small outside peaks typically hard to see.

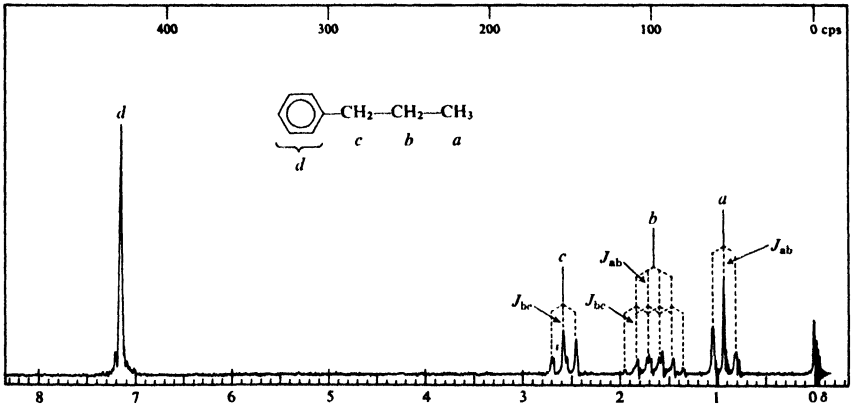


Figure 13.14. Nmr spectrum of *n*-propylbenzene. Moving downfield, we see the expected sequence of signals: *a*, primary (3H); *b*, secondary (2H); *c*, benzylic (2H); and *d*, aromatic (5H). Signals *a* and *c* are each split into a triplet by the two secondary protons H_b. The five protons adjacent to the secondary protons—three on one side and two on the other—are, of course, not equivalent; but the coupling constants, J_{ab} and J_{bc}, are nearly the same, and signal *b* appears as a sextet (5 + 1 peaks). The coupling constants are not *exactly* the same, however, as shown by the broadening of the six peaks.

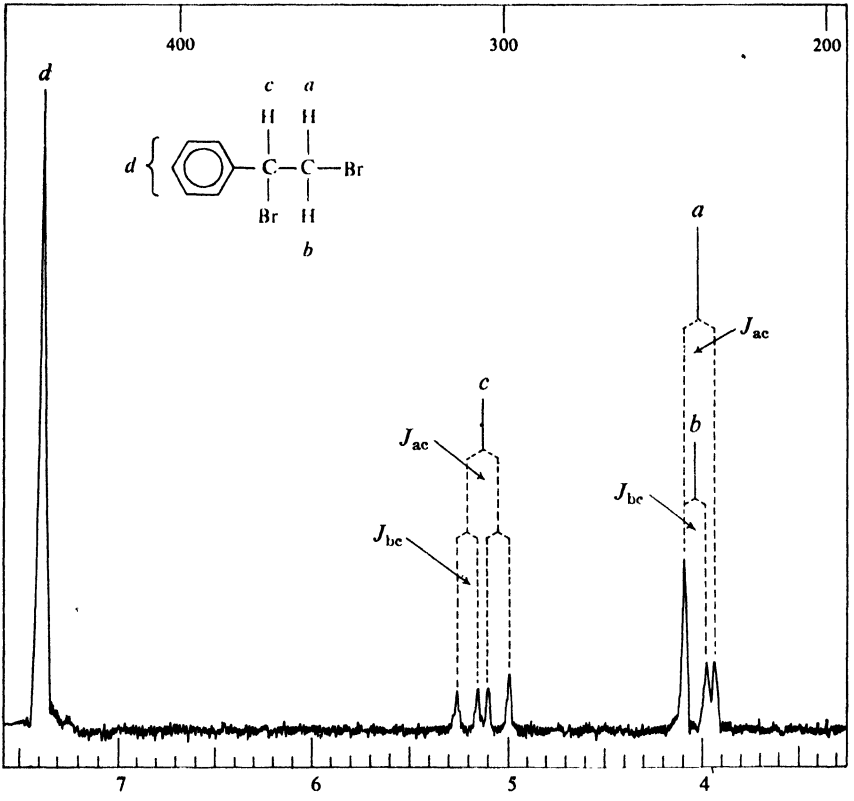


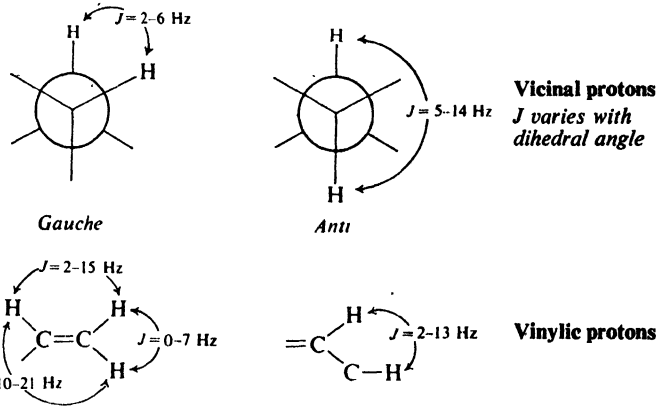
Figure 13.15. Nmr spectrum of 1,2-dibromo-1-phenylethane. The diastereotopic protons H_a and H_b give different signals, each split into a doublet by H_c; the downfield peaks of the doublets happen to coincide. (There is no discernible splitting due to coupling between H_a and H_b.)

The four-line pattern of *c* is due to successive splittings by H_a and H_b. (If J_{ac} and J_{bc} were equal—as they would have to be if, for example, H_a and H_b were equivalent—the middle peaks of *c* would merge to give the familiar 1:2:1 triplet.)

13.11 · Nmr. Coupling constants

The distance between peaks in a multiplet is a measure of the effectiveness of spin–spin coupling, and is called the **coupling constant**, J. Coupling (unlike chemical shift) is not a matter of induced magnetic fields. The value of the coupling constant —as measured, in Hz—remains the same, whatever the applied magnetic field (that is, whatever the radiofrequency used). In this respect, of course, spin–spin splitting differs from chemical shift, and, when necessary, the two can be distinguished on this basis: the spectrum is run at a second, different radiofrequency; when measured in Hz, peak separations due to splitting remain constant, whereas peak separations due to chemical shifts change. (When divided by the radiofrequency and thus converted into ppm, the numerical value of the chemical shift would, of course, remain constant.)

As we can see from the following summary, the size of a coupling constant depends markedly on the structural relationships between the coupled protons.



For example, in any substituted ethylene—or in any pair of geometric isomers—J is always larger between *trans* protons than between *cis* protons; furthermore, the size of J varies in a regular way with the electronegativity of substituents, so that one can often assign configuration without having both isomers in hand.

A coupling constant is designated as + or − to permit certain theoretical correlations; for many compounds this sign has been determined. We shall be concerned only with the absolute size of J, as reflected in the distance between peaks.

Although we shall not work very much with the *values* of coupling constants, we should realize that, to an experienced person, they can often be the most important feature of an nmr spectrum: the feature that gives exactly the kind of information about molecular structure that is being looked for.

Problem 13.10 Go back to Problem 13.8 (p. 425), and tell, where you can, the kind of splitting expected for each signal.

Problem 13.11 In Problem 13.9 (p. 425) you analyzed some nmr spectra. Does the absence of splitting in these spectra now lead you to change any of your answers?

Problem 13.12 Give a structure or structures consistent with each of the nmr spectra shown in Fig. 13.16 (p. 436).

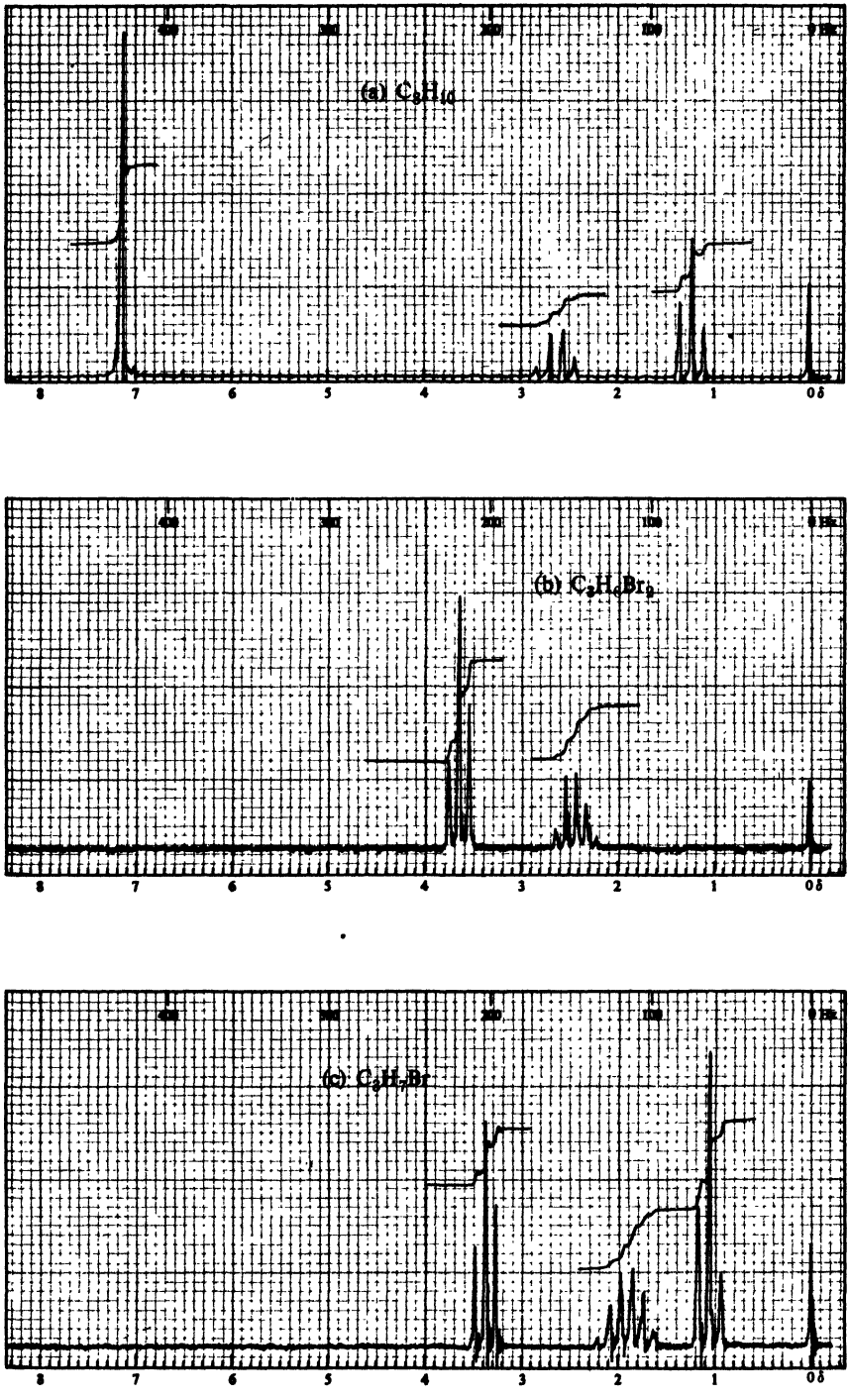


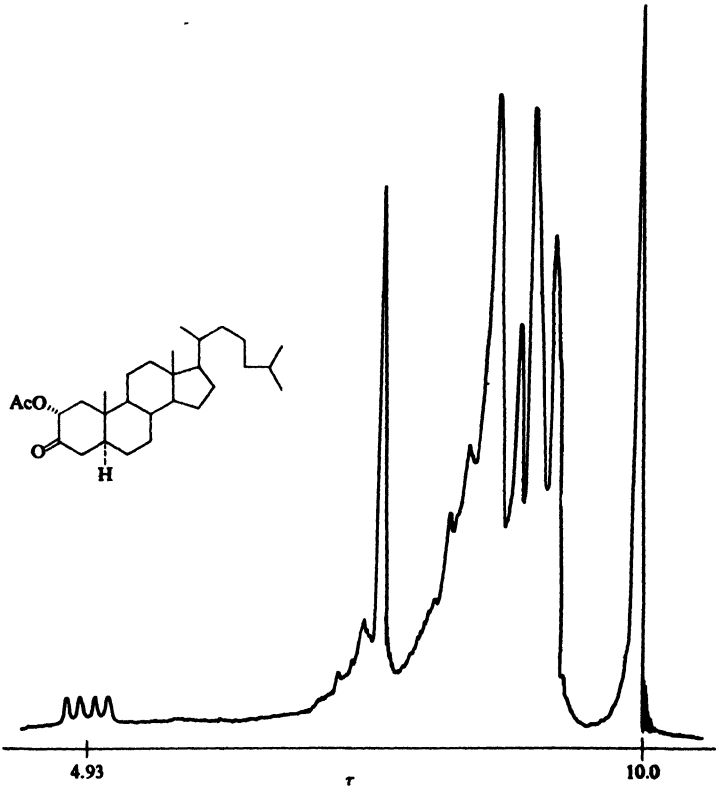
Figure 13.16. Nmr spectra for Problem 13.12, p. 435.

13.12 Nmr. Complicated spectra. Deuterium labeling

Most nmr spectra that the organic chemist is likely to encounter are considerably more complicated than the ones given in this book. How are these analyzed?

First of all, many spectra showing a large number of peaks can be completely analyzed by the same general methods we shall use here. It just takes practice.

Then again, in many cases complete analysis is not necessary for the job at hand. Evidence of other kinds may already have limited the number of possible structures, and all that is required of the nmr spectrum is that it let us choose among these. Sometimes all that we need to know is how many kinds of protons there are—or, perhaps, how many kinds and how many of each kind. Sometimes

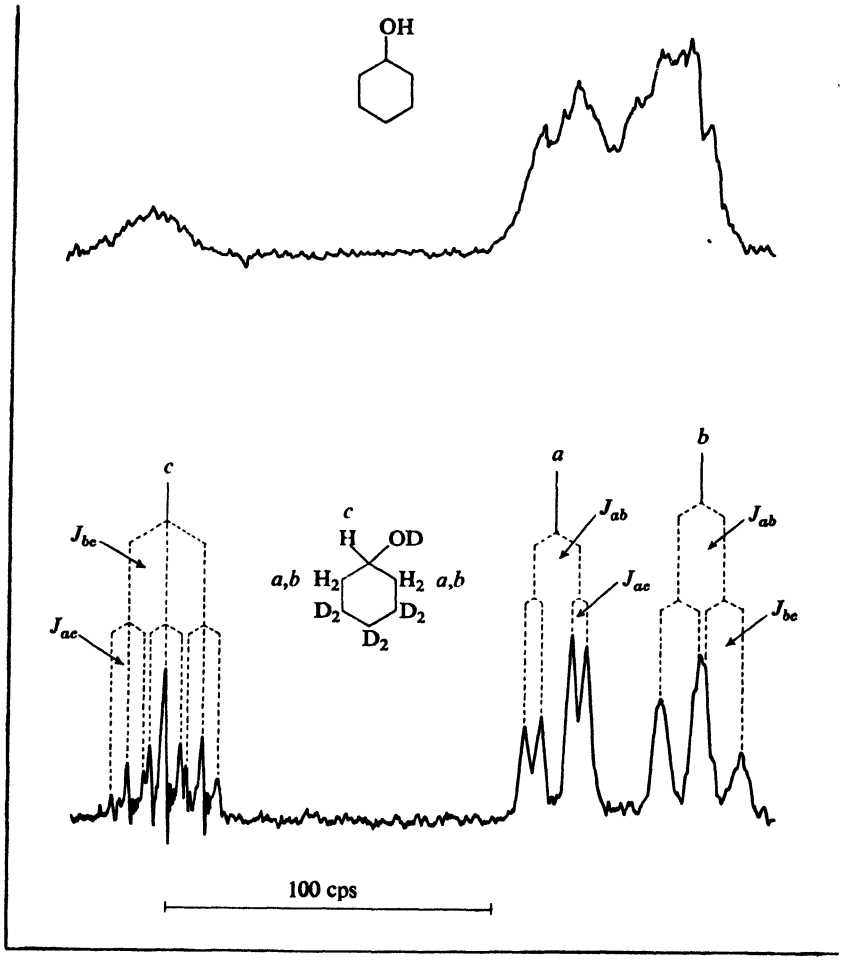


Courtesy of *The Journal of the American Chemical Society*

Figure 13.17. Nmr spectrum of 2-α-acetoxycholestane-3-one, taken by K. L. Williamson and W. S. Johnson of the University of Wisconsin and Stanford University. The four downfield peaks are due to the proton on C-2, whose signal is split successively by the axial proton and the equatorial proton on C-1.

only one structural feature is still in doubt—for example, does the molecule contain two methyl groups or one ethyl group?—and the answer is given in a set of peaks standing clear from the general confusion. (See, for example, Fig. 13.17, above.)

Instrumental techniques are available, and others are being rapidly developed,



Courtesy of *The Journal of the American Chemical Society*

Figure 13.18. Nmr spectra of (*top*) cyclohexanol and (*bottom*) 3,3,4,4,5,5-hexadeuteriocyclohexanol, taken by F. A. L. Anet of the University of Ottawa. With absorption and splitting by six protons eliminated, the pattern due to the five remaining protons can be analyzed.

The diastereotopic sets of protons, H_a and H_b, give different signals. Signal *a* is split successively into doublets by H_b (only *one* H_b splits each H_a) and by H_c. Signal *b* is split similarly by H_a and H_c. Downfield signal *c* is split successively into triplets by H_a (both protons) and H_b (both protons).

to help in the analysis of complicated spectra, and to simplify the spectra actually measured. By the method of *double resonance* (or *double irradiation*), for example, the spins of two sets of protons can be *decoupled*, and a simpler spectrum obtained.

The molecule is irradiated with two radiofrequency beams: the usual one, [illegible] and a second, much stronger beam, whose

frequency differs from that of the first in such a way that the following happens. When the field strength is reached at which the proton we are interested in absorbs and gives a signal, the splitting protons are absorbing the other, very strong radiation. These splitting protons are "stirred up" and flip over very rapidly—so rapidly that the signalling proton sees them, not in the various combinations of spin alignments (Sec. 13.10), but in a single *average* alignment. The spins are decoupled, and the signal appears as a single, unsplit peak.

A particularly elegant way to simplify an nmr spectrum—and one that is easily understood by an organic chemist—is the use of *deuterium labeling.*

Because a deuteron has a much smaller magnetic moment than a proton, it absorbs at a much higher field and so gives no signal in the proton nmr spectrum. Furthermore, its coupling with a proton is weak and it ordinarily broadens, but does not split, a proton's signal; even this effect can be eliminated by double irradiation.

As a result, then, the replacement of a proton by a deuteron removes from an nmr spectrum both the signal from that proton and the splitting by it of signals of other protons; it is as though there were no hydrogen at all at that position in the molecule. For example:

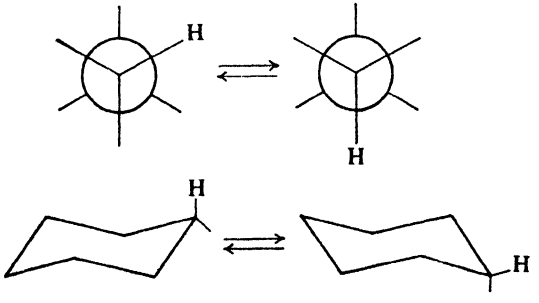
CH_3—CH_2—	CH_2D—CH_2—	CH_3—CHD—
Triplet Quartet	Triplet Triplet	Doublet Quartet
3H *2H*	*2H* *2H*	*3H* *1H*

One can use deuterium labeling to find out which signal is produced by which proton or protons: one observes the disappearance of a particular signal when a proton in a known location is replaced by deuterium. One can use deuterium labeling to simplify a complicated spectrum so that a certain set of signals can be seen more clearly: see, for example, Fig. 13.18, p. 438. (This figure also illustrates a point made at the beginning of this section: the formidable looking nine-peak multiplet is analyzed without too much difficulty.)

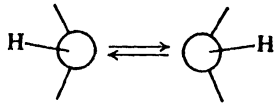
13.13 Equivalence of protons: a closer look

We have seen that equivalence—or non-equivalence—of protons is fundamental to the nmr spectrum, since it affects both the number of signals and their splitting. Let us look more closely at equivalence, and see how it is affected by the rate at which certain molecular changes occur:

(a) *rotations about single bonds*, as in the interconversion between conformations of substituted ethanes or cyclohexanes;



(b) *inversion of molecules*, that is, the turning inside out of pyramidal molecules like amines (Sec. 22.6);



(c) *proton exchange*, as, for example, of alcohols (Sec. 16.13).

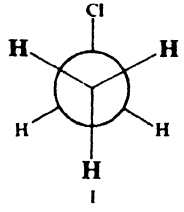
$$R^*O{-}H^* + RO{-}H \rightleftharpoons R^*O{-}H + RO{-}H^*$$

Each of these molecular changes can change the environment—both electronic and protonic—of a given proton, and hence can affect both its chemical shift and its coupling with other protons. The basic question that arises is whether or not the nmr spectrometer sees the proton in *each* environment or in an *average of all* of them. The answer is, in short, that it can often see the proton in either way, depending upon the temperature, and in this ability lies much of the usefulness of nmr spectroscopy.

In comparing it with other spectrometers, Professor John D. Roberts of the California Institute of Technology has likened the nmr spectrometer to a camera with a relatively long shutter time—that is, to a "slow" camera. Such a camera photographs the spokes of a wheel in different ways depending upon the speed with which the wheel spins: as sharp, individual spokes if spinning is slow; as blurred spokes if spinning is faster; and as a single circular smear if spinning is faster yet. In the same way, if the molecular change is relatively fast, the nmr spectrometer sees a proton in its average environment—a smeared-out picture; if the molecular process is slow, the spectrometer sees the proton in each of its environments.

In this section we shall examine the effects of rotations about single bonds on the nmr spectrum, and in later sections the effects of the other molecular changes.

Let us return to ethyl chloride (Sec. 13.7), and focus our attention on the methyl protons. If, at any instant, we could look at an individual molecule, we would almost certainly see it in conformation I. One of the methyl protons is *anti* to

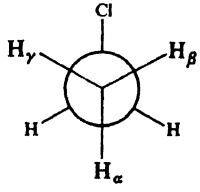


I

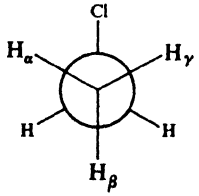
the chlorine and two protons are *gauche*; quite clearly, the *anti* proton is in a different environment from the others, and—for the moment—is not equivalent to them. Yet, we have seen, the three methyl protons of ethyl chloride give a single nmr signal (a triplet, because of the adjacent methylene group), and hence must be magnetically equivalent. How can this be? The answer is, of course, that rotation about the single bond is—compared with the nmr "shutter speed"—a fast process; the nmr "camera" takes a smeared-out picture of the three protons.

Each proton is seen in an *average* environment, which is exactly the same as the average environment of each of the other two: one-third *anti*, and two-thirds *gauche*.

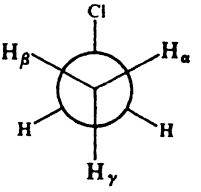
There are three conformations of ethyl chloride, II, III, and IV, identical except that a different individual proton occupies the *anti* position. Being of equal stability, the three conformations are exactly equally populated: one-third of the molecules in each. In one of these conformations a given proton is *anti* to chlorine, and in two it is *gauche*.



II

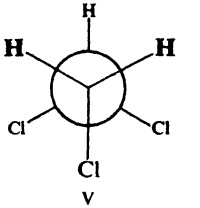


III

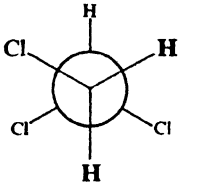


IV

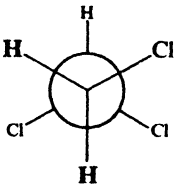
1,1,2-Trichloroethane, to take another example, presents a somewhat different conformational picture, but the net result is the same: identical average environments and hence equivalence for the two methylene protons.



V



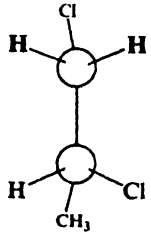
VI



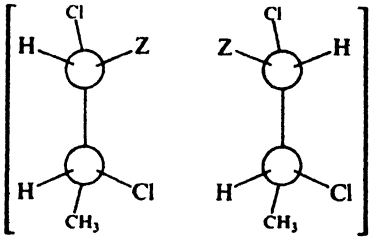
VII

The environments of the two protons are the same in V. The environments are different for the two in VI and VII, but average out the same because of the equal populations of these enantiomeric conformations. (Here, however, we cannot say just *what* the average environment is, unless we know the ratio of V to the racemic modification (VI plus VII).)

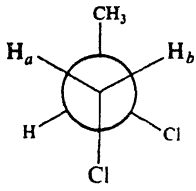
With diastereotopic protons, on the other hand, the situation is different: diastereotopic protons are non-equivalent and no rotation will change this. We decided (Sec. 13.7) that the two C–1 protons of 1,2-dichloropropane, $CH_3CHClCH_2Cl$, are diastereotopic, since replacement of either one by an atom Z would yield diastereomers:



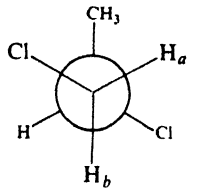
1,2-Dichloropropane



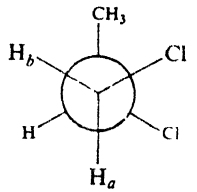
Rotation cannot interconvert the diastereomers, nor can it make the protons, H_a and H_b, equivalent. In none of the conformations (VIII, IX, or X)



VIII



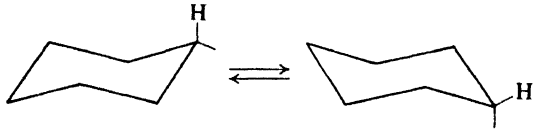
IX



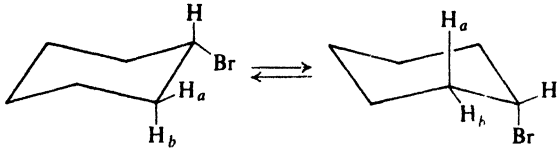
X

is the environment of the two protons the same; nor is there a pair of mirror-image conformations to balance out their environments. (This holds true whether the compound is optically active or inactive; the presence or absence of an enantiomeric molecule has no effect on the environment of a proton in any individual molecule.) These diastereotopic protons give different signals, couple with the proton on C–2 (with different coupling constants), and couple with each other.

Cyclohexane presents an exactly analogous situation, since the transformation of one chair form into another involves rotations about single bonds. In any chair conformation there are two kinds of protons: six equatorial protons and six axial protons. Yet there is a single nmr signal for all twelve, since their *average* environments are identical: half equatorial, half axial.



If, however, we replace a proton by, say, bromine, the picture changes. Now, the axial and equatorial protons on each carbon are diastereotopic protons: replacement of one would give a *cis*-diastereomer, replacement of the other a *trans*-diastereomer. Protons H_a and H_b—or any other geminal pair on the ring—have



different environments. When H_a is equatorial, so is —Br, and when H_a is axial, so is —Br; H_b always occupies a position opposite to that of —Br. Furthermore, the stabilities and hence populations of the two conformations will, in general, be different, and H_a and H_b will spend different fractions of their time in axial and equatorial positions; however, even if by coincidence the conformations are of equal stability, H_a and H_b are still not equivalent.

So far, we have discussed situations in which the speed of rotation about single bonds is so fast that the nmr spectrometer sees protons in their average environment. This is the *usual* situation. It is this situation in which our earlier

test for equivalence would work: if replacement of either of two protons by Z would give the same (or enantiomeric) products, the protons are equivalent. We ignore conformers in judging the identity of two products.

Now, if—by lowering the temperature—we could sufficiently slow down rotations about single bonds, we would expect an nmr spectrum that reflects the "instantaneous" environments of protons in each conformation. *This is exactly what happens.* As cyclohexane, for example, is cooled down, the single sharp peak observed at room temperature is seen to broaden and then, at about $-70°$, to split into two peaks, which at $-100°$ are clearly separated: one peak is due to axial protons, and the other peak is due to equatorial protons.

This does *not* mean that the molecule is frozen into a single conformation; it still flips back and forth between two (equivalent) chair conformations; a given proton is axial one moment and equatorial the next. It is just that now the time between interconversions is long enough that we "photograph" the molecule, not as a blur but sharply as one conformation or the other.

By study of the broadening of the peak, or of the coalescence of the two peaks, it is possible to estimate the E_{act} for rotation. Indeed, it was by this method that the barrier of 11 kcal/mole (Sec. 9.11) was calculated.

Problem 13.13 The fluorine nmr spectrum (Sec. 13.10) of 1,2-difluorotetrachloroethane, $CFCl_2CFCl_2$, shows a single peak at room temperature, but at $-120°$ shows two peaks (singlets) of unequal area. Interpret each spectrum, and account for the difference. What is the significance of the unequal areas of the peaks in the low-temperature spectrum? Why is there no splitting in either spectrum?

Problem 13.14 At room temperature, the fluorine nmr spectrum of CF_2BrCBr_2CN (3,3-difluoro-2,2,3-tribromopropanenitrile) shows a single sharp peak. As the temperature is lowered this peak broadens and, at $-98°$, is split into two doublets (equal spacing) and a singlet. The combined area of the doublets is considerably larger than—more than twice as large as—the area of the singlet. Interpret each spectrum, and account for the relative peak areas in the low-temperature spectrum.

13.14 The electron spin resonance (esr) spectrum

Let us consider a free radical placed in a magnetic field and subjected to electromagnetic radiation; and let us focus our attention, not on the nuclei, but on the odd, unpaired electron. This electron spins and thus generates a magnetic moment, which can be lined up with or against the external magnetic field. Energy is required to change the spin state of the electron, from alignment with the field to the less stable alignment, against the field. This energy is provided by absorption of radiation of the proper frequency. An absorption spectrum is produced, which is called an *electron spin resonance* (*esr*) *spectrum* or an *electron paramagnetic resonance* (*epr*) *spectrum*.

The esr spectrum is thus analogous to the nmr spectrum. An electron has, however, a much larger magnetic moment than the nucleus of a proton, and more energy is required to reverse the spin. In a field of 3200 gauss, for example, where nmr absorption would occur at about 14 MHz, esr absorption occurs at a much higher frequency: 9000 MHz, in the *microwave* region.

Like nmr signals, esr signals show splitting, and from exactly the same cause, coupling with the spins of certain nearby nuclei: for example, protons near carbon

atoms that carry—or help to carry—the odd electron. For this reason, esr spectroscopy can be used not only to detect the presence of free radicals and to measure their concentration, but also to give evidence about their structure: what free radicals they are, and how the odd electron is spread over the molecule.

Problem 13.15 Although all electrons spin, only molecules containing unpaired electrons—only free radicals—give esr spectra. Why is this? (*Hint:* Consider the possibility (a) that one electron of a pair has its spin reversed, or (b) that both electrons of a pair have their spins reversed.)

Problem 13.16 In each of the following cases, tell what free radical is responsible for the esr spectrum, and show how the observed splitting arises. (a) X-irradiation of methyl iodide at low temperatures: a four-line signal. (b) γ-irradiation at 77°K of propane and of *n*-butane: symmetrical signals of, respectively, 8 lines and 7 lines. (c) Triphenylmethyl chloride + zinc: a very complex signal.

13.15 Spectroscopic analysis of hydrocarbons. Infrared spectra

In this first encounter with infrared spectra, we shall see absorption bands due to vibrations of carbon–hydrogen and carbon–carbon bonds: bands that will constantly reappear in all the spectra we meet, since along with their various functional groups, compounds of all kinds contain carbon and hydrogen. We must expect to find these spectra complicated and, at first, confusing. Our aim is to learn to pick out of the confusion those bands that are most characteristic of certain structural features.

Let us look first at the various kinds of vibration, and see how the positions of the bands associated with them vary with structure.

Bands due to *carbon–carbon stretching* may appear at about 1500 and 1600 cm^{-1} for aromatic bonds, at 1650 cm^{-1} for double bonds (shifted to about 1600 cm^{-1} by conjugation), and at 2100 cm^{-1} for triple bonds. These bands, however, are often unreliable. (They may disappear entirely for fairly symmetrically substituted alkynes and alkenes, because the vibrations do not cause the change in dipole moment that is essential for infrared absorption.) More generally useful bands are due to the various carbon–hydrogen vibrations.

Absorption due to *carbon–hydrogen stretching*, which occurs at the high-frequency end of the spectrum, is characteristic of the hybridization of the carbon holding the hydrogen: at 2800–3000 cm^{-1} for tetrahedral carbon; at 3000–3100 cm^{-1} for trigonal carbon (alkenes and aromatic rings); and at 3300 cm^{-1} for digonal carbon (alkynes).

Absorption due to various kinds of *carbon–hydrogen bending*, which occurs at lower frequencies, can also be characteristic of structure. Methyl and methylene groups absorb at about 1430–1470 cm^{-1}; for methyl, there is another band, quite characteristic, at 1375 cm^{-1}. The isopropyl "split" is characteristic: a doublet, with equal intensity of the two peaks, at 1370 and 1385 cm^{-1} (confirmed by a band at 1170 cm^{-1}). *tert*-Butyl gives an unsymmetrical doublet: 1370 cm^{-1} (*strong*) and 1395 cm^{-1} (*moderate*).

Carbon–hydrogen bending in alkenes and aromatic rings is both in-plane and out-of-plane, and of these the latter kind is more useful. For **alkenes**, out-of-plane

bending gives strong bands in the 800–1000 cm^{-1} region, the exact location depending upon the nature and number of substituents, and the stereochemistry:

$RCH{=}CH_2$	910–920 cm^{-1} 990–1000	*cis*-RCH=CHR	675–730 cm^{-1} (*variable*)
$R_2C{=}CH_2$	880–900	*trans*-RCH=CHR	965–975

For **aromatic rings**, out-of-plane C—H bending gives strong absorption in the 675–870 cm^{-1} region, the exact frequency depending upon the number and location of substituents; for many compounds absorption occurs at:

monosubstituted	690–710 cm^{-1} 730–770	*m*-disubstituted	690–710 cm^{-1} 750–810
o-disubstituted	735–770	*p*-disubstituted	810–840

Now, what do we look for in the infrared spectrum of a hydrocarbon? To begin with, we can rather readily tell whether the compound is aromatic or purely aliphatic. The spectra in Fig. 13.2 (p. 411) show the contrast that is typical: aliphatic absorption is strongest at higher frequency and is essentially missing below 900 cm^{-1}; aromatic absorption is strong at lower frequencies (C—H out-of-plane bending) between 650 and 900 cm^{-1}. In addition, an aromatic ring will show C—H stretching at 3000–3100 cm^{-1}; often, there is carbon–carbon stretching at 1500 and 1600 cm^{-1} and C—H in-plane bending in the 1000–1100 cm^{-1} region.

An alkene shows C—H stretching at 3000–3100 cm^{-1} and, most characteristically, strong out-of-plane C—H bending between 800–1000 cm^{-1}, as discussed above.

A terminal alkyne, $RC{\equiv}CH$, is characterized by its C—H stretching band, a strong and sharp band at 3300 cm^{-1}, and by carbon–carbon stretching at 2100 cm^{-1}. A disubstituted alkyne, on the other hand, does not show the 3300 cm^{-1} band and, if the two groups are fairly similar, the 2100 cm^{-1} band may be missing, too.

Some of these characteristic bands are labeled in the spectra of Fig. 13.2, page 411.

Problem 13.17 What is a likely structure for a hydrocarbon of formula C_6H_{12} that shows strong absorption at 2920 and 2840 cm^{-1}, and at 1450 cm^{-1}; none above 2920 cm^{-1}; and below 1450 cm^{-1} none until about 1250 cm^{-1}?

13.16 Spectroscopic analysis of hydrocarbons. Nmr

The application of nmr spectroscopy to hydrocarbons needs no special discussion beyond that already given in Secs. 13.6–13.11. For hydrocarbons as for other kinds of compounds, we shall find that where the infrared spectrum helps to tell us what *kind* of compound we are dealing with, the nmr spectrum will help to tell us *what* compound.

About Analyzing Spectra

In problems you will be given the molecular formula of a compound and asked to deduce its structure from its spectroscopic properties: sometimes from its infrared or nmr spectrum alone, sometimes from both. The compound will generally be a simple one, and you may need to look only at a few features of the spectra to find the answer. To confirm your answer, however, and to gain experience, see how much information you can get from the spectra: try to identify as many infrared bands as you can, to assign all nmr signals to specific protons, and to analyze the various spin–spin splittings. Above all, look at as many spectra as you can find: in the laboratory, in other books, in catalogs of spectra in the library.

PROBLEMS

1. Give a structure or structures consistent with each of the following sets of nmr data.

(a) $C_3H_3Cl_5$
a triplet, δ 4.52, 1H
b doublet, δ 6.07, 2H

(b) $C_3H_5Cl_3$
a singlet, δ 2.20, 3H
b singlet, δ 4.02, 2H

(c) C_4H_9Br
a doublet, δ 1.04, 6H
b multiplet, δ 1.95, 1H
c doublet, δ 3.33, 2H

(d) $C_{10}H_{14}$
a singlet, δ 1.30, 9H
b singlet, δ 7.28, 5H

(e) $C_{10}H_{14}$
a doublet, δ 0.88, 6H
b multiplet, δ 1.86, 1H
c doublet, δ 2.45, 2H
d singlet, δ 7.12, 5H

(f) C_9H_{10}
a quintet, δ 2.04, 2H
b triplet, δ 2.91, 4H
c singlet, δ 7.17, 4H

(g) $C_{10}H_{13}Cl$
a singlet, δ 1.57, 6H
b singlet, δ 3.07, 2H
c singlet, δ 7.27, 5H

(h) $C_{10}H_{12}$
a multiplet, δ 0.65, 2H
b multiplet, δ 0.81, 2H
c singlet, δ 1.37, 3H
d singlet, δ 7.17, 5H

(i) $C_9H_{11}Br$
a quintet, δ 2.15, 2H
b triplet, δ 2.75, 2H
c triplet, δ 3.38, 2H
d singlet, δ 7.22, 5H

(j) $C_3H_5ClF_2$
a triplet, δ 1.75, 3H
b triplet, δ 3.63, 2H

2. Identify the stereoisomeric 1,3-dibromo-1,3-dimethylcyclobutanes on the basis of their nmr spectra.

Isomer X: singlet, δ 2.13, 6H
singlet, δ 3.21, 4H

Isomer Y: singlet, δ 1.88, 6H
doublet, δ 2.84, 2H
doublet, δ 3.54, 2H
doublets have equal spacing

3. When mesitylene (nmr spectrum, Fig. 13.5, p. 422) is treated with HF and SbF_5 in liquid SO_2 solution, the following peaks, all singlets, are observed in the nmr spectrum; δ 2.8, 6H; δ 2.9, 3H; δ 4.6, 2H; and δ 7.7, 2H. To what compound is the spectrum due? Assign all peaks in the spectrum.

Of what general significance to chemical theory is such an observation?

4. (a) On catalytic hydrogenation, compound A, C_5H_8, gave *cis*-1,2-dimethylcyclopropane. On this basis, three isomeric structures were considered possible for A. What were they? (b) Absence of infrared absorption at 890 cm^{-1} made one of the structures unlikely. Which one was it? (c) The nmr spectrum of A showed signals at δ 4.95 and δ 6.13 with intensity ratio 3:1. Which of the three structures in (a) is consistent with this? (d) The base peak in the mass spectrum was found at *m/e* 67. What ion was this peak probably due to, and how do you account for its abundance? (e) Compound A was synthesized in one step from open-chain compounds. How do you think this was done?

5. X-ray analysis shows that the [18]annulene (Problem 9, p. 336, $n = 9$) is planar. The nmr spectrum shows two broad bands: τ 1.1 and τ 11.8, peak area ratio 2:1. (a) Are these properties consistent with aromaticity? Explain. (b) Would you have predicted aromaticity for this compound? Explain. (*Hint:* Carefully draw a structural formula for the compound, keeping in mind bond angles and showing all hydrogen atoms.)

6. Hydrocarbon B, C_6H_6, gave an nmr spectrum with two signals: δ 6.55 and δ 3.84, peak area ratio 2:1. When warmed in pyridine for three hours, B was quantitatively converted into benzene.

Mild hydrogenation of B yielded C, whose spectra showed the following: mass spectrum, mol. wt. 82; infrared spectrum, no double bonds; nmr spectrum, one broad peak at δ 2.34.

(a) How many rings are there in C? (See Problem 9.17, p. 313.) (b) How many rings are there (probably) in B? How many double bonds in B? (c) Can you suggest a structure for B? for C?

(d) In the nmr spectrum of B, the upfield signal was a quintet, and the downfield signal was a triplet. How must you account for these splittings?

7. The five known 1,2,3,4,5,6-hexachlorocyclohexanes can be described in terms of the equatorial (e) or axial (a) disposition of successive chlorines: eeeeee, eeeeea, eeeeaa, eeaeea, eeeaaa. Their nmr spectra have been measured.

Which of these would give: (a) only one peak (two isomers); (b) two peaks, 5H:1H (one isomer); (c) two peaks, 4H:2H (two isomers)?

(d) Which one of the isomers in (a) would you expect to show no change in nmr spectrum at low temperature? Which one would show a split into two peaks? Predict the relative peak areas for the latter case.

8. (a) Although the nmr spectrum of *trans*-4-*tert*-butyl-1-bromocyclohexane is complicated, the signal from one proton stands clear (δ 3.83), downfield from the rest. Which proton is this, and why? (b) The *cis*-isomer shows a corresponding peak, but at δ 4.63. Assuming that the *tert*-butyl group exerts no direct magnetic effect, to what do you attribute the difference in chemical shifts between the two spectra? These data are typical, and are the basis of a generalization relating conformation and chemical shift. What is that generalization?

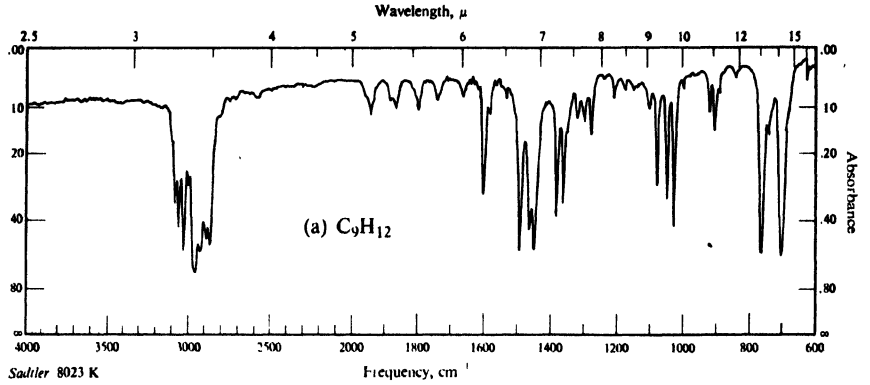
9. The nmr spectrum of bromocyclohexane shows a downfield peak (1H) at δ 4.16. This signal is a single peak at room temperature, but at $-75°$ separates into two peaks of *unequal* area (but totalling *one* proton): δ 3.97 and δ 4.64 in the ratio 4.6:1.0. How do you account for the separation of peaks? On the basis of your generalization of the previous problem, which conformation of the molecule predominates, and (at $-75°$) what percentage of molecules does it account for?

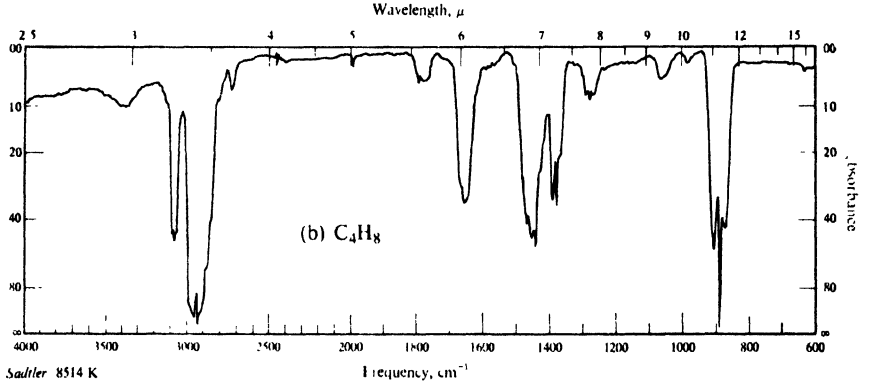
10. Give a structure or structures consistent with each of the infrared spectra in Fig. 13.19, page 448.

11. Give a structure or structures consistent with each of the nmr spectra in Fig. 13.20, page 449.

12. Give a structure or structures consistent with each of the nmr spectra in Fig. 13.21, page 450.

13. Give a structure or structures of the compound D, whose infrared and nmr spectra are shown in Fig. 13.22, p. 451.





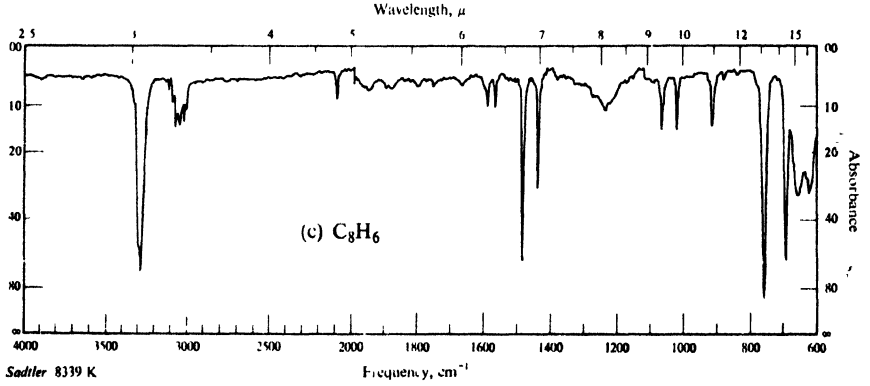


Figure 13.19. Infrared spectra for Problem 10, p. 447.

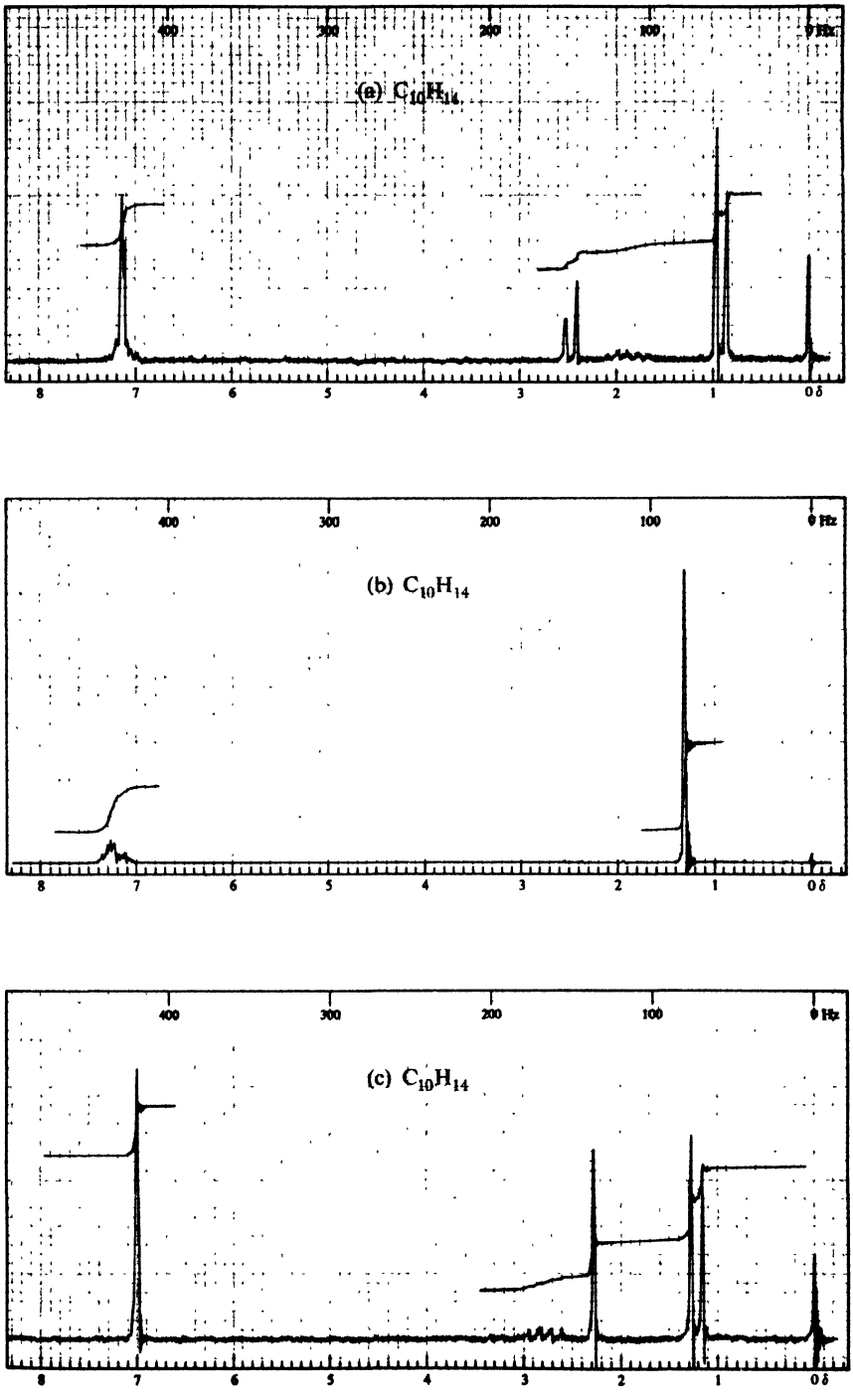


Figure 13.20. Nmr spectra for Problem 11, p. 447.

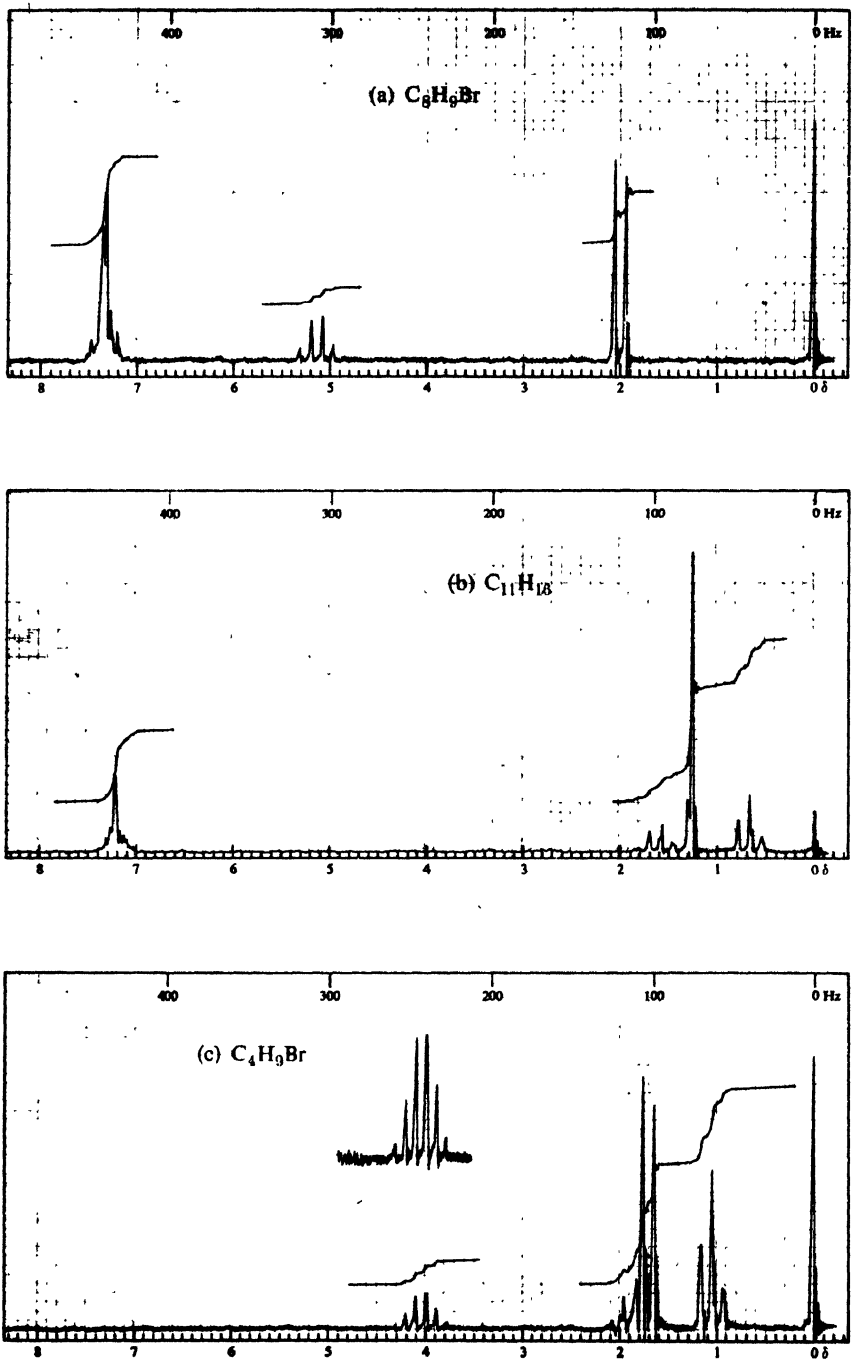
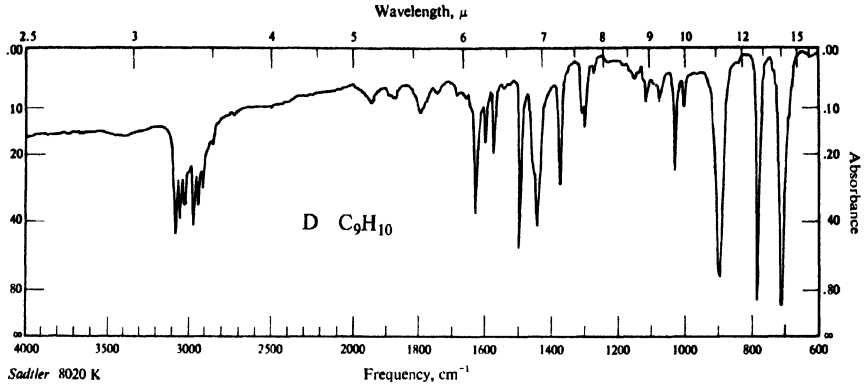


Figure 13.21. Nmr spectra for Problem 12, p. 447.



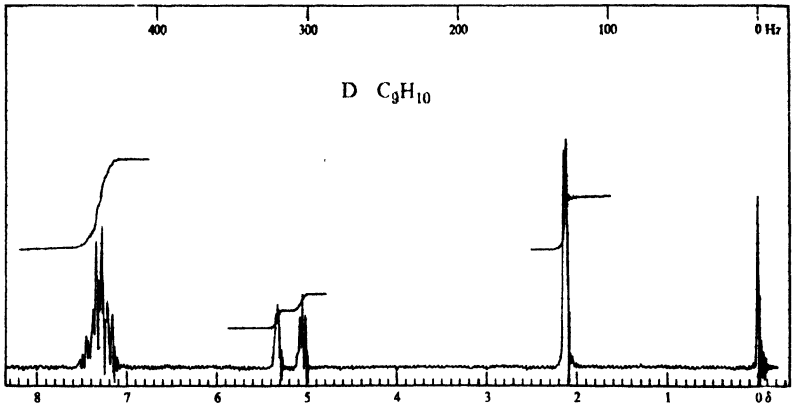


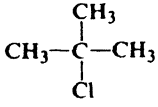
Figure 13.22. Infrared and nmr spectra for compound D, Problem 13, p. 447.

Chapter 14 Alkyl Halides

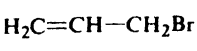
Nucleophilic Aliphatic Substitution Elimination

14.1 Structure and nomenclature

We shall consider as alkyl halides all compounds of the general formula R—X, where R is any simple alkyl or substituted alkyl group. For example:

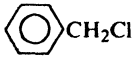


tert-Butyl chloride
2-Chloro-2-methylpropane

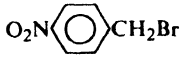


Allyl bromide
3-Bromo-1-propene

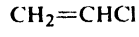
Cyclohexyl bromide



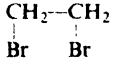
Benzyl chloride



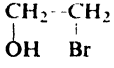
p-Nitrobenzyl bromide



Vinyl chloride



Ethylene bromide
1,2-Dibromoethane



Ethylene bromohydrin
2-Bromoethanol

Substituted alkyl halides undergo, of course, the reactions characteristic of their other functional groups—nitration of benzyl chloride, oxidation of ethylene bromohydrin, addition to allyl bromide—but as halides they react very much like ethyl or isopropyl or *tert*-butyl halides.

Compounds in which the halogen atom is attached directly to an aromatic ring (*aryl halides*, e.g., bromobenzene) differ so much from the alkyl halides in their preparations and properties that they will be taken up in a separate chapter (Chap. 25). For the present we need to know that—in the kinds of reaction typical of alkyl halides—*most aryl halides are extremely unreactive.*

As we know from our previous acquaintance with these compounds, alkyl halides are given both common names and IUPAC names.

14.2 Physical properties

Because of greater molecular weight, haloalkanes have considerably higher boiling points than alkanes of the same number of carbons. For a given alkyl group, the boiling point increases with increasing atomic weight of the halogen, so that a fluoride is the lowest boiling, an iodide the highest boiling.

Table 14.1 ALKYL HALIDES

Name	Chloride B.p., °C	Chloride Density at 20°C	Bromide B.p., °C	Bromide Density at 20°C	Iodide B.p., °C	Iodide Density at 20°C
Methyl	− 24		5		43	2.279
Ethyl	12.5		38	1.440	72	1.933
n-Propyl	47	.890	71	1.335	102	1.747
n-Butyl	78.5	.884	102	1.276	130	1.617
n-Pentyl	108	.883	130	1.223	157	1.517
n-Hexyl	134	.882	156	1.173	180	1.441
n-Heptyl	160	.880	180		204	1.401
n-Octyl	185	.879	202		225.5	
Isopropyl	36.5	.859	60	1.310	89.5	1.705
Isobutyl	69	.875	91	1.261	120	1.605
sec-Butyl	68	.871	91	1.258	119	1.595
tert-Butyl	51	.840	73	1.222	100*d*	
Cyclohexyl	142.5	1.000	165			
Vinyl (Haloethene)	− 14		16		56	
Allyl (3-Halopropene)	45	.938	71	1.398	103	
Crotyl (1-Halo-2-butene)	84				132	
Methylvinylcarbinyl (3-Halo-1-butene)	64					
Propargyl (3-Halopropyne)	65		90	1.520	115	
Benzyl	179	1.102	201		93^{10}	
α-Phenylethyl	92^{15}		85^{10}			
β-Phenylethyl	92^{20}		92^{11}		127^{19}	
Diphenylmethyl	173^{19}		184^{20}			
Triphenylmethyl	310		230^{15}			
Dihalomethane	40	1.336	99	2.49	180*d*	3.325
Trihalomethane	61	1.489	151	2.89	*subl.*	4.008
Tetrahalomethane	77	1.595	189.5	3.42	*subl.*	4.32
1,1-Dihaloethane	57	1.174	110	2.056	179	2.84
1,2-Dihaloethane	84	1.257	132	2.180	*d*	2.13
Trihaloethylene	87		164	2.708		
Tetrahaloethylene	121				*subl.*	
Benzal halide	205		140^{20}			
Benzotrihalide	221	1.38				

In spite of their polarity, alkyl halides are insoluble in water, probably because of their inability to form hydrogen bonds. They are soluble in the typical organic solvents.

Iodo, bromo, and polychloro compounds are more dense than water.

14.3 Industrial source

On an industrial scale alkyl halides—chiefly the chlorides because of the cheapness of chlorine—are most often prepared by direct halogenation of hydrocarbons at the high temperatures needed for these free-radical reactions (Secs. 3.19, 6.21, and 12.12–12.13). Even though mixtures containing isomers and compounds of different halogen content are generally obtained, these reactions are useful industrially since often a mixture can be used as such or separated into its components by distillation.

Certain important halides are prepared by methods similar to those used in the laboratory; thus, for vinyl chloride:

$$\underset{\text{Acetylene}}{HC{\equiv}CH} \xrightarrow{HCl,\ HgCl_2} \underset{\text{Vinyl chloride}}{CH_2{=}CHCl}$$

$$\underset{\text{Ethylene}}{CH_2{=}CH_2} \xrightarrow{Cl_2} \underset{\displaystyle Cl\quad Cl}{CH_2{-}CH_2} \xrightarrow{500^\circ} \underset{\text{Vinyl chloride}}{CH_2{=}CHCl}$$

Many fluorine compounds are not prepared by direct fluorination, but rather by replacement of chlorine, using inorganic fluorides:

$$CH_3Cl + Hg_2F_2 \longrightarrow \underset{\substack{\text{Methyl fluoride}\\(\text{b.p. } -79^\circ)}}{CH_3F} + Hg_2Cl_2$$

$$CCl_4 + SbF_3 \longrightarrow \underset{\substack{\text{Dichlorodifluoromethane}\\(\text{Freon-12})\\(\text{b.p. } -28^\circ)}}{CCl_2F_2}$$

The increasingly important polyfluorides known as *fluorocarbons* are prepared by replacement of hydrogen using inorganic fluorides:

$$\underset{n\text{-Heptane}}{C_7H_{16}} + 32CoF_3 \longrightarrow \underset{\substack{\text{Perfluoroheptane}\\(\textit{per} = \text{fully substituted})\\(\text{b.p. } 84^\circ)}}{C_7F_{16}} + 16HF + 32CoF_2 \qquad (2CoF_2 + F_2 \longrightarrow 2CoF_3)$$

Cobalt(III) fluoride, CoF_3, is a convenient fluorinating agent.

14.4 Preparation

In the laboratory alkyl halides are most often prepared by the methods outlined below.

PREPARATION OF ALKYL HALIDES

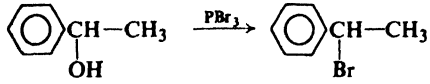
1. From alcohols. Discussed in Secs. 16.4–16.5.

$$R{-}OH \xrightarrow{HX \text{ or } PX_3} R{-}X$$

Examples:

$$CH_3CH_2CH_2OH \xrightarrow[\text{or } NaBr, H_2SO_4, \text{ heat}]{\text{conc. HBr}} CH_3CH_2CH_2Br$$

n-Propyl alcohol — *n*-Propyl bromide



1-Phenylethanol, α-Phenylethyl alcohol — 1-Bromo-1-phenylethane, α-Phenylethyl bromide

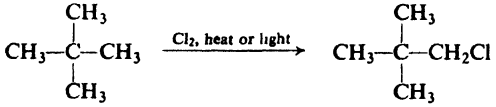
$$CH_3CH_2OH \xrightarrow{P + I_2} CH_3CH_2I$$

Ethyl alcohol — Ethyl iodide

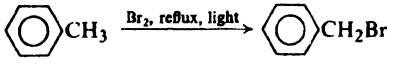
2. Halogenation of certain hydrocarbons. Discussed in Secs. 3.19, 6.21, 12.12–12.14.

$$R{-}H \xrightarrow{X_2} R{-}X + HX$$

Examples:

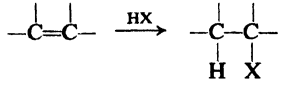


Neopentane — Neopentyl chloride

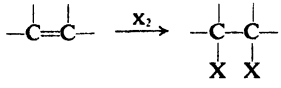


Toluene — Benzyl bromide

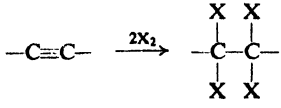
3. Addition of hydrogen halides to alkenes. Discussed in Secs. 6.6–6.7.



4. Addition of halogens to alkenes and alkynes



Discussed in Sec. 6.5.



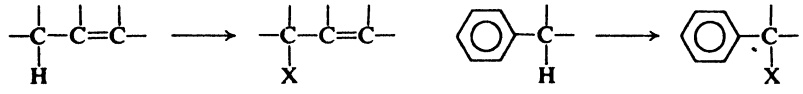
Discussed in Sec. 8.8.

5. Halide exchange. Discussed in Sec. 14.4.

$$R{-}X + I^- \xrightarrow{\text{acetone}} R{-}I + X^-$$

Alkyl halides are nearly always prepared from alcohols, which are available commercially (Sec. 15.5) or are readily synthesized (Secs. 15.7 and 16.9–16.10). Although certain alcohols tend to undergo rearrangement (Sec. 16.4) during replacement of —OH by —X, this tendency can be minimized by use of phosphorus halides.

Certain halides are best prepared by direct halogenation. The most important of these preparations involve substitution of —X for the unusually reactive allylic or benzylic hydrogens.



Allylic hydrogen — An allyl halide — Benzylic hydrogen — A benzyl halide

An alkyl iodide is often prepared from the corresponding bromide or chloride by treatment with a solution of sodium iodide in acetone; the less soluble bromide or sodium chloride precipitates from solution and can be removed by filtration.

14.5 Reactions

A halide ion is an extremely weak base. Its reluctance to share its electrons is shown by its great tendency to release a hydrogen ion, that is, by the high acidity of the hydrogen halides.

When attached to carbon, halogen can be readily displaced as halide ion by other, stronger bases. These bases possess an unshared pair of electrons and are seeking a relatively positive site, that is, are seeking a nucleus with which to share their electrons.

Basic, electron-rich reagents are called **nucleophilic reagents** (from the Greek, *nucleus-loving*). The typical reaction of alkyl halides is **nucleophilic substitution**:

$$\underset{\text{A nucleophilic reagent}}{R{:}X + {:}Z} \longrightarrow \underset{\text{Leaving group}}{R{:}Z + {:}X^-} \qquad \textbf{Nucleophilic substitution}$$

To describe the ease of displacement of the weakly basic halide ions, we refer to them as good *leaving groups*.

(Aryl and vinyl halides undergo these substitution reactions with extreme difficulty, Sec. 25.5.)

Alkyl halides react with a large number of nucleophilic reagents, both inorganic and organic, to yield a wide variety of important products. As we shall see, these reagents include not only negative ions like hydroxide, alkoxide, and cyanide, but also neutral bases like ammonia and water; their characteristic feature is an *unshared pair of electrons*.

As a synthetic tool, nucleophilic substitution involving alkyl halides is one of the three or four most useful classes of organic reactions. Much of the importance of alcohols is due to their ready conversion into alkyl halides, with their good leaving groups.

A large number of nucleophilic substitutions are listed below to give an idea of the versatility of alkyl halides; many will be left to later chapters for detailed discussion.

As we already know (Secs. 5.12 and 8.12), alkyl halides undergo not only substitution but also **elimination**, a reaction that is important in the synthesis of alkenes. Both elimination and substitution are brought about by basic reagents, and hence there must always be *competition* between the two reactions. We shall be interested to see how this competition is affected by such factors as the structure of the halide or the particular nucleophilic reagent used.

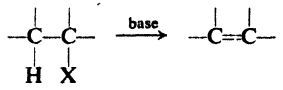
We shall look rather closely at both nucleophilic substitution and elimination reactions of the alkyl halides, for they provide a particularly good illustration of the effect of structure on reactivity, and of the methods that may be used to determine mechanisms of reactions.

REACTIONS OF ALKYL HALIDES

1. Nucleophilic substitution

$R{:}X + {:}Z$	$\longrightarrow$	$R{:}Z + {:}X^-$	
$R{:}X + {:}OH^-$	$\longrightarrow$	$R{:}OH + {:}X^-$	Alcohol
$+ H_2O$	$\longrightarrow$	$R{:}OH$	Alcohol
$+ {:}OR'^-$	$\longrightarrow$	$R{:}OR'$	Ether (Williamson synthesis, Sec. 17.5)
$+ {}^-{:}C{\equiv}CR'$	$\longrightarrow$	$R{:}C{\equiv}CR'$	Alkyne (Sec. 8.12)
$+ \overset{\delta-}{R'}\!\!-\!\!\overset{\delta+}{M}$	$\longrightarrow$	$R{:}R'$	Alkane (coupling, Sec. 3.17)
$+ {:}I^-$	$\longrightarrow$	$R{:}I$	Alkyl iodide
$+ {:}CN^-$	$\longrightarrow$	$R{:}CN$	Nitrile (Sec. 18.8)
$+ R'COO{:}^-$	$\longrightarrow$	$R'COO{:}R$	Ester
$+ {:}NH_3$	$\longrightarrow$	$R{:}NH_2$	Primary amine (Sec. 22.10)
$+ {:}NH_2R'$	$\longrightarrow$	$R{:}NHR'$	Secondary amine (Sec. 22.13)
$+ {:}NHR'R''$	$\longrightarrow$	$R{:}NR'R''$	Tertiary amine (Sec. 22.13)
$+ {:}P(C_6H_5)_3$	$\longrightarrow$	$[R{:}P(C_6H_5)_3]^+X^-$	Phosphonium salt (Sec. 21.10)
$+ {:}SH^-$	$\longrightarrow$	$R{:}SH$	Thiol (mercaptan)
$+ {:}SR'$	$\longrightarrow$	$R{:}SR'$	Thioether (sulfide)
$+ ArH + AlCl_3$	$\longrightarrow$	ArR	Alkylbenzene (Friedel-Crafts reaction, Sec. 12.6)
$+ [CH(COOC_2H_5)_2]$	$\longrightarrow$	$R{:}CH(COOC_2H_5)_2$	(Malonic ester synthesis, Sec. 26.2)
$+ [CH_3COCHCOOC_2H_5]^-$	$\longrightarrow$	$CH_3COCHCOOC_2H_5$ (R)	(Acetoacetic ester synthesis, Sec. 26.3)

2. Dehydrohalogenation: elimination. Discussed in Secs. 5.12–5.14 and 14.18–14.23.



3. Preparation of Grignard reagent. Discussed in Secs. 3.16 and 15.12.

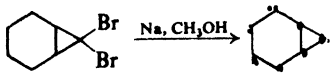
$$RX + Mg \xrightarrow{\text{dry ether}} RMgX$$

4. Reduction. Discussed in Sec. 3.15.

$$RX + M + H^+ \longrightarrow RH + M^+ + X^-$$

Examples:

$$(CH_3)_3CCl \xrightarrow{Mg} (CH_3)_3CMgCl \xrightarrow{D_2O} (CH_3)_3CD$$



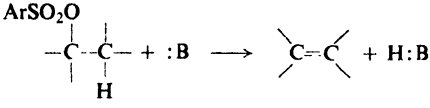
7,7-Dibromonorcarane Norcarane

14.6 Alkyl sulfonates

In following sections, we shall discuss the mechanisms of nucleophilic aliphatic substitution and of elimination using alkyl halides as our examples. But we should realize that these reactions take place in exactly the same ways with a variety of other compounds: compounds which, like alkyl halides, contain *good leaving groups.*

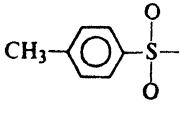
Of these other compounds, alkyl esters of sulfonic acids, $ArSO_2OR$, are most commonly used in place of alkyl halides: usually in the study of reaction mechanisms, but also in synthesis. As the anions of strong acids, sulfonate anions are weak bases and hence are good leaving groups in either nucleophilic substitution or elimination:

$$\underset{\text{Alkyl sulfonate}}{ArSO_2OR} + :Z \longrightarrow \underset{\text{Weak base: } \textit{good leaving group}}{R:Z} + ArSO_3^- \qquad \textbf{Nucleophilic substitution}$$

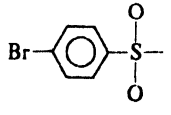


Alkyl sulfonate **Elimination**

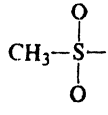
Most commonly used are esters of *p*-toluenesulfonic acid: the *p*-toluenesulfonates. The name of the *p*-toluenesulfonyl group is often shortened to *tosyl* (Ts); *p*-toluenesulfonyl chloride thus becomes *tosyl chloride* (TsCl), and *p*-toluenesulfonates become *tosylates* (TsOR).



Tosyl or *Ts*



Brosyl or *Bs*



Mesyl or *Ms*

Like alkyl halides, alkyl sulfonates are prepared from alcohols but, as we shall see in Sec. 16.7, the two syntheses differ in one very important way.

14.7 Rate of reaction: effect of concentration. Kinetics

Before we discuss nucleophilic substitution involving alkyl halides, let us return briefly to the matter of what determines the rate of a reaction.

We have seen (Sec. 2.18) that the rate of a chemical reaction can be expressed as a product of three factors:

$$\text{rate} = \begin{matrix}\text{collision}\\\text{frequency}\end{matrix} \times \begin{matrix}\text{energy}\\\text{factor}\end{matrix} \times \begin{matrix}\text{probability}\\\text{factor}\end{matrix}$$

So far, we have used this relationship to understand problems of orientation and relative reactivity; in doing this we have compared rates of *different* reactions. When the conditions that we can control (temperature, concentration) are kept the same, closely related reactions proceed at different rates chiefly because they have different energy factors, that is to say, different E_{act}'s. We have been able to account surprisingly well for many differences in E_{act}'s by using structural theory to estimate stabilities of the transition states.

It is also useful to study an *individual* reaction to see how its rate is affected by deliberate changes in experimental conditions. We can determine E_{act}, for example, if we measure the rate at different temperatures (Sec. 2.18). But perhaps the most valuable information about a reaction is obtained by studying the effect of *changes in concentration* on its rate.

How does a change in concentration of reactants affect the rate of a reaction at a constant temperature? An increase in concentration cannot alter the fraction of collisions that have sufficient energy, or the fraction of collisions that have the proper orientation; it can serve only to increase the total number of collisions. If more molecules are crowded into the same space, they will collide more often and the reaction will go faster. Collision frequency, and hence rate, depends in a very exact way upon concentration.

The field of chemistry that deals with rates of reaction, and in particular with dependence of rates on concentration, is called **kinetics**. Let us see what kinetics can tell us about nucleophilic aliphatic substitution.

14.8 Kinetics of nucleophilic aliphatic substitution. Second-order and first-order reactions

Let us take a specific example, the reaction of methyl bromide with sodium hydroxide to yield methanol:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$

This reaction would probably be carried out in aqueous ethanol, in which both reactants are soluble.

If the reaction results from collision between a hydroxide ion and a methyl bromide molecule, we would expect the rate to depend upon the concentration of both these reactants. If either OH^- concentration, $[OH^-]$, or CH_3Br concentration, $[CH_3Br]$, is doubled, the collision frequency should be doubled and the

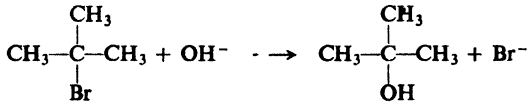
reaction rate doubled. If either concentration is cut in half, the collision frequency, and consequently the rate, should be halved.

This is found to be so. We say that the rate of reaction depends upon both $[OH^-]$ and $[CH_3Br]$, and we indicate this by the expression

$$\text{rate} = k[CH_3Br][OH^-]$$

If concentrations are expressed in, say, moles per liter, then k is the number which, multiplied by these concentrations, tells us how many moles of methanol are formed in each liter during each second. At a given temperature and for a given solvent, k always has the same value and is characteristic of this particular reaction; k is called the **rate constant**. For example, for the reaction between methyl bromide and hydroxide ion in a mixture of 80% ethanol and 20% water at 55°, the value of k is 0.0214 liters per mole per second.

What we have just seen is, of course, not surprising; we all know that an increase in concentration causes an increase in rate. But now let us look at the corresponding reaction between *tert*-butyl bromide and hydroxide ion:



As before, if we double [RBr] the rate doubles; if we cut [RBr] in half the rate is halved. But if we double $[OH^-]$, or if we cut $[OH^-]$ in half, there is no change in the rate. *The rate of reaction is independent of* $[OH^-]$.

The rate of reaction of *tert*-butyl bromide depends only upon [RBr]. This is indicated by the expression

$$\text{rate} = k[RBr]$$

For the reaction of *tert*-butyl bromide in 80% alcohol at 55°, the rate constant is 0.010 per second. This means that of every mole of *tert*-butyl bromide present, 0.010 mole reacts each second, whatever the $[OH^-]$.

The methyl bromide reaction is said to follow **second-order kinetics**, since its rate is dependent upon the concentrations of *two* substances. The *tert*-butyl bromide reaction is said to follow **first-order kinetics**; its rate depends upon the concentration of only *one* substance.

How are we to account for this difference in kinetic order? How are we to account for the puzzling fact that the rate of the *tert*-butyl bromide reaction is independent of $[OH^-]$?

To account for such differences in kinetic order, as well as for many other observations, it has been proposed that *nucleophilic substitution can proceed by two different mechanisms.* In the following sections we shall see what these two mechanisms are believed to be, the facts on which they are based, and how they account for the facts.

Recognition of the duality of mechanism for nucleophilic aliphatic substitution, formulation of the mechanisms themselves, and analysis of the factors influencing competition between them—all are largely due to Sir Christopher Ingold (of University College, London) and the people who worked with him; and this is only a fraction of their total contribution to the theory of organic chemistry.

14.9 The S_N2 reaction: mechanism and kinetics

The reaction between methyl bromide and hydroxide ion to yield methanol follows second-order kinetics; that is, the rate depends upon the concentrations of both reactants:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$

$$\text{rate} = k[CH_3Br][OH^-]$$

The simplest way to account for the kinetics is to assume that reaction requires a collision between a hydroxide ion and a methyl bromide molecule. On the basis of evidence we shall shortly discuss, it is known that in its attack the hydroxide ion stays as far away as possible from the bromine; that is to say, it attacks the molecule from the rear.

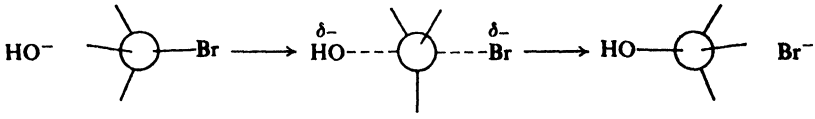


Figure 14.1. The S_N2 reaction: complete inversion of configuration. Nucleophilic reagent attacks back side.

The reaction is believed to take place as shown in Fig. 14.1. When hydroxide ion collides with a methyl bromide molecule at the face most remote from the bromine, and when such a collision has sufficient energy, a C—OH bond forms and the C—Br bond breaks, liberating the bromide ion.

The transition state can be pictured as a structure in which carbon is partially bonded to both —OH and —Br; the C—OH bond is not completely formed, the C—Br bond is not yet completely broken. Hydroxide has a diminished negative charge. since it has begun to share its electrons with carbon. Bromine has developed a partial negative charge, since it has partly removed a pair of electrons from carbon. At the same time, of course, ion–dipole bonds between hydroxide ion and solvent are being broken and ion–dipole bonds between bromide ion and solvent are being formed.

The —OH and —Br are located as far apart as possible; the three hydrogens and the carbon lie in a single plane, all bond angles being 120°. The C—H bonds are thus arranged like the spokes of a wheel, with the C—OH and the C—Br bonds lying along the axle.

This is the mechanism that is called S_N2: *substitution nucleophilic bimolecular.* The term *bi*molecular is used here since the rate-determining step involves collision of *two* particles.

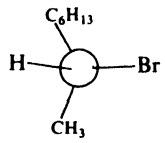
What evidence is there that alkyl halides can react in this manner? First of all, as we have just seen, the mechanism is consistent with the kinetics of a reaction like the one between methyl bromide and hydroxide ion. In general, **an S_N2 reaction follows second-order kinetics.** Let us look at some of the other evidence.

14.10 The S_N2 reaction: stereochemistry

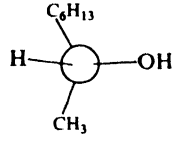
Both 2-bromooctane and 2-octanol are chiral; that is, they have molecules that are not superimposable on their mirror images. Consequently, these com-

pounds can exist as enantiomers, and can show optical activity. Optically active 2-octanol has been obtained by resolution of the racemic modification (Sec. 7.9), and from it optically active 2-bromooctane has been made.

The following configurations have been assigned (Sec. 7.5):



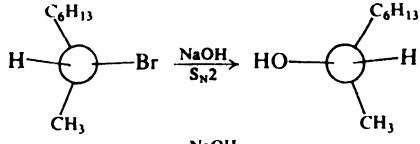
(−)-2-Bromooctane
$[\alpha] = -34.6°$



(−)-2-Octanol
$[\alpha] = -9.9°$

We notice that the (−)-bromide and the (−)-alcohol have similar configurations; that is, —OH occupies the same relative position in the (−)-alcohol as —Br does in the (−)-bromide. As we know, compounds of similar configuration do not *necessarily* rotate light in the same direction; they just happen to do so in the present case. (As we also know, compounds of similar configuration are not necessarily given the same specification of R and S (Sec. 7.5); it just happens that both are R in this case.)

When (−)-2-bromooctane is allowed to react with sodium hydroxide under conditions where second-order kinetics are followed, there is obtained (+)-2-octanol.



(−)-2-Bromooctane $\xrightarrow[S_N2]{NaOH}$ (+)-2-Octanol

$[\alpha] = -34.6°$ $[\alpha] = +9.9°$

optical purity 100% optical purity 100%

We see that the —OH group has not taken the position previously occupied by —Br; the alcohol obtained has a configuration *opposite* to that of the bromide. *A reaction that yields a product whose configuration is opposite to that of the reactant is said to proceed with* **inversion of configuration.**

(In this particular case, inversion of configuration happens to be accompanied by a change in specification, from R to S, but this is not always true. We cannot tell whether a reaction proceeds with inversion or retention of configuration simply by looking at the letters used to specify the reactant and product; we must work out and compare the absolute configurations indicated by those letters.)

Now the question arises: does a reaction like this proceed with *complete* inversion? That is to say, is the configuration of *every* molecule inverted? The answer is *yes*. **An S_N2 reaction proceeds with complete stereochemical inversion.**

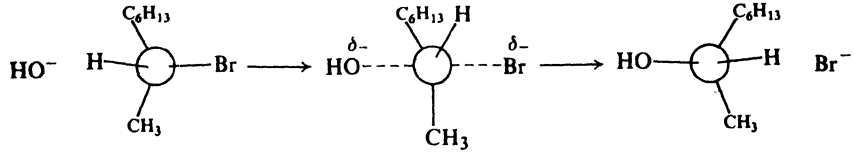
To answer a question like this, we must know the optical purity both of the reactant that we start with, and of the product that we obtain: in this case, of 2-bromooctane and 2-octanol. To know these we must, in turn, know the maximum rotation of the bromide and of the alcohol; that is, we must know the rotation of an optically pure sample of each.

Suppose, for example, that we know the rotation of optically pure 2-bromooctane to be 34.6° and that of optically pure 2-octanol to be 9.9°. If, then, a sample of optically pure bromide were found to yield optically pure alcohol, we would know that the reaction had proceeded with complete inversion. Or—and this is much more practicable—if a sample of the halide of rotation, say, −28.7° (83% optically pure) were found to yield alcohol of rotation +8.22° (83% optically pure), we would draw exactly the same conclusion.

In developing the ideas of S_N1 and S_N2 reactions, Ingold (p. 460) studied the reaction of optically active 2-bromooctane and obtained results which—when corrected for a small contribution from the S_N1 reaction, and for the effect of bromide ion generated during the reaction (see Problem 14, p. 488)—led him to conclude that the S_N2 reaction proceeds, within limits of experimental error, with complete inversion.

The particular value that Ingold used for the rotation of optically pure 2-bromooctane has been questioned, but the basic idea of complete inversion in S_N2 reactions is established beyond question: by study of systems other than alkyl halides and by elegant work involving radioactivity and optical activity (Problem 14, p. 488).

It was to account for inversion of configuration that back-side attack was first proposed for substitution of the S_N2 kind. As —OH becomes attached to carbon, three bonds are forced apart until they reach the planar "spoke" arrangement of the transition state; then, as bromide is expelled, they move on to a tetrahedral arrangement *opposite* to the original one. This process has often been likened to the turning-inside-out of an umbrella in a gale.



S_N2: *complete inversion*

The stereochemistry of the 2-bromooctane reaction indicates back-side attack in accordance with the S_N2 mechanism; studies of other optically active compounds, under conditions where the reactions follow second-order kinetics, show similar results. It is not possible to study the stereochemistry of most halides, since they are not optically active; however, there seems no reason to doubt that they, too, undergo back-side attack.

The S_N2 mechanism is supported, then, by stereochemical evidence. Indeed, the relationship between mechanism and stereochemistry is so well established that in the absence of other evidence complete inversion is taken to indicate an S_N2 reaction.

We see once more how stereochemistry can give us a kind of information about a reaction that we cannot get by any other means.

Inversion of configuration is the general rule for reactions occurring at chiral centers, being much commoner than retention of configuration. Oddly enough, it is the very prevalence of inversion that made its detection difficult. Paul Walden (at the Polytechnicum in Riga, Latvia) discovered the phenomenon of inversion in 1896 when he encountered one of the exceptional reactions in which inversion does *not* take place.

Problem 14.1 (a) What product would be formed if the reaction of *cis*-4-bromocyclohexanol with OH^- proceeded with inversion? (b) Without inversion? (c) Is it always necessary to use optically active compounds to study the stereochemistry of substitution reactions?

14.11 The S_N2 reaction: reactivity

In what way would we expect changes in structure of the alkyl group to affect reactivity in an S_N2 substitution? In contrast to the free-radical and carbonium ion reactions we have studied, this time the structure of the transition state is *not* intermediate between the structures of the reactant and product; this time we cannot simply assume that factors stabilizing the product will also stabilize the transition state.

First of all, let us compare transition state and reactants with regard to electron distribution. In the transition state, there is a partly formed bond between carbon and hydroxide ion and a partly broken bond between carbon and halide ion: hydroxide ion has brought electrons to carbon, and halide ion has taken electrons away. Unless one of the two processes, bond-making or bond-breaking, has gone much further than the other, the net charge on carbon is not greatly different from what it was at the start of the reaction. Electron withdrawal or electron release by substituents should affect stability of transition state and reactant in much the same way, and therefore should have little influence on reaction rate.

To understand how structure does influence the rate, let us compare transition state and reactants with regard to *shape*, starting with the methyl bromide reaction. The carbon in reactant and product is tetrahedral, whereas carbon in the transition state is bonded to five atoms. As indicated before, the C—H bonds are arranged like the spokes of a wheel, with the C—OH and C—Br bonds lying along the axle (Fig. 14.2).

What would be the effect of replacing the hydrogens successively by methyl

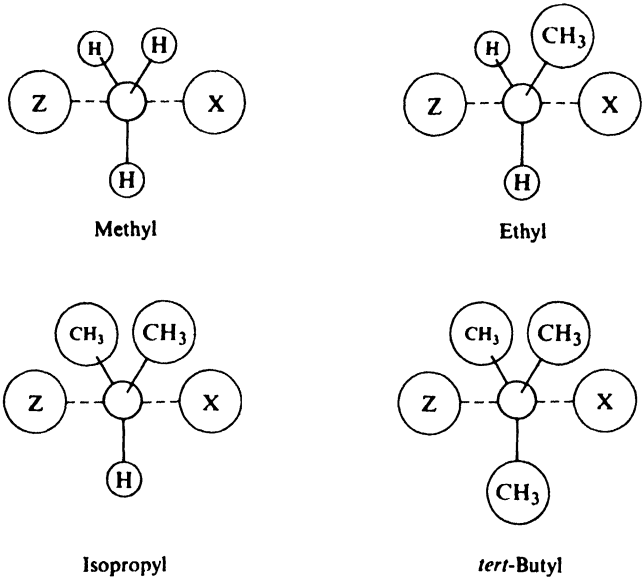
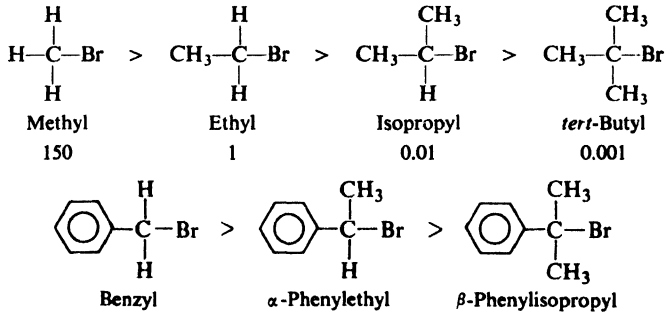


Figure 14.2. Steric factor in the S_N2 reaction. Crowding raises energy of transition state and slows down reaction.

groups? That is, how will the transition state differ as we go from methyl bromide through ethyl bromide and isopropyl bromide to *tert*-butyl bromide? As hydrogen atoms are replaced by the larger methyl groups, there is increased crowding about the carbon; this is particularly severe in the transition state, where the methyls are thrown close to both —OH and —Br (Fig. 14.2). Non-bonded interaction raises the energy of the crowded transition state more than the energy of the roomier reactant; E_{act} is higher and reaction is slower.

In agreement with this prediction, *differences in rate between two S_N2 reactions seem to be due chiefly to* **steric factors**, and not to electronic factors; that is to say, differences in rate are related to the *bulk* of the substituents and not to their ability to withdraw or release electrons. As the number of substituents attached to the carbon bearing the halogen is increased, the reactivity toward S_N2 substitution decreases. These substituents may be aliphatic, or aromatic, or both, as shown in the following two sequences:

S_N2 substitution: relative reactivity toward I^-



(To give an idea of how large these differences may be, the relative rates for a particular S_N2 reaction, substitution by iodide ion, are indicated below the formulas in the first sequence.)

In S_N2 reactions the order of reactivity of RX is $CH_3X > 1° > 2° > 3°$.

In cases where steric factors are kept constant, electronic effects on S_N2 reactions can be observed; however, these effects are found to be comparatively *small*. Some S_N2 reactions are speeded up slightly by electron release, and others are speeded up slightly by electron withdrawal, but it is not usually possible to predict which will be the case simply from the structures involved

Problem 14.2 (a) Draw the structures of ethyl, *n*-propyl, isobutyl, and neopentyl bromides. These structures can be considered methyl bromide with one of its hydrogens replaced by various alkyl groups (GCH_2Br). What is the group G in each case?

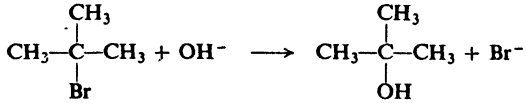
(b) The relative rates of reaction (with ethoxide ion) are roughly: methyl bromide, 100; ethyl bromide, 6; *n*-propyl bromide, 2; isobutyl bromide, 0.2; neopentyl bromide, 0.00002. What is the effect of the *size* of the group G attached to carbon bearing the halogen? How does this compare with the effect of changing the *number* of groups?

Thus we see that the S_N2 mechanism is supported by three lines of evidence: kinetics, stereochemistry, and effect of structure on reactivity.

Now let us turn to the other mechanism by which nucleophilic aliphatic substitution can take place.

14.12 The S_N1 reaction: mechanism and kinetics. Rate-determining step

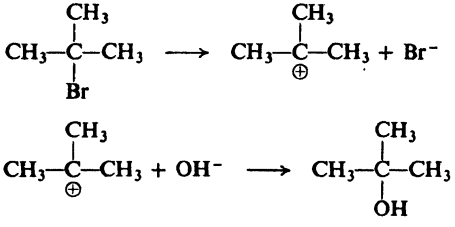
The reaction between *tert*-butyl bromide and hydroxide ion to yield *tert*-butyl alcohol follows first-order kinetics; that is, the rate depends upon the concentration of only one reactant, *tert*-butyl bromide.



$$\text{rate} = k\,[\text{RBr}]$$

How are we to interpret the fact that the rate is independent of $[OH^-]$? If the rate of reaction does not depend upon $[OH^-]$, it can only mean that the reaction *whose rate we are measuring* does not involve OH^-.

These observations are quite consistent with the following mechanism.



S_N1

tert-Butyl bromide slowly dissociates (step 1) into bromide ions and *tert*-butyl cations. The carbonium ions then combine rapidly (step 2) with hydroxide ions to yield *tert*-butyl alcohol.

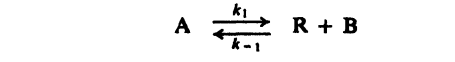
The rate of the overall reaction is determined by the slow breaking of the C—Br bond to form the carbonium ion; once formed, the carbonium ion reacts rapidly to form the product. *A single step whose rate determines the overall rate of a stepwise reaction is called a* **rate-determining step.** It is not surprising that the rate-determining step here is the one that involves the *breaking* of a bond, an energy-demanding process. The required energy is supplied by formation of many ion–dipole bonds between the two kinds of ion and the solvent. (Although each of these is weak, altogether in reactions like these they supply 110–150 kcal/mole!)

This is the mechanism that is called S_N1: *substitution nucleophilic unimolecular.* The term *uni*molecular is used here since the rate-determining step involves only *one* molecule (disregarding the many necessary solvent molecules).

What evidence is there that alkyl halides can react by this mechanism? As we have just seen, the mechanism is consistent with the first-order kinetics of a reaction like the one between *tert*-butyl bromide and hydroxide ion. In general, **an S_N1 reaction follows first-order kinetics.** The rate of the entire reaction is determined by how fast the alkyl halide ionizes, and hence depends only upon the concentration of alkyl halide.

In the following sections, we shall look at some of the other evidence.

Let us see what we mean by rate-determining step in a reaction like this,



where R is a reactive intermediate (carbonium ion, free radical) whose concentration is maintained at some low *steady state* throughout the reaction. The exact kinetics expression for the formation of the product is

$$\text{rate} = \frac{k_1[A]}{1 + \dfrac{k_{-1}[B]}{k_2[C]}} \tag{3}$$

Without going into the derivation of this equation, let us see what it means.

The term $k_1[A]$ is in the numerator and the term $k_2[C]$ is in the denominator of the denominator; the bigger they are, the faster the rate. This is reasonable, since $k_1[A]$ is the rate of step (1) and $k_2[C]$ contributes to the rate of step (2). The term $k_{-1}[B]$ is in the denominator; the bigger it is, the slower the rate. This, too, is understandable, since it contributes to the rate of the reverse of step (1).

Now if $k_2[C]$ happens to be *much larger* than $k_{-1}[B]$, the term $k_{-1}[B]/k_2[C]$ is very small—insignificant relative to 1—and drops out. Under these conditions we get our familiar rate expression for first-order kinetics:

$$\text{rate} = k_1[A]$$

But if $k_2[C]$ is much larger than $k_{-1}[B]$, it must mean that *step* (2) *is much faster than the reverse of step* (1). This is the *real* requirement for step (1) to be rate-determining If we return to Sec. 11.16, we see that the absence of an isotope effect in nitration was accounted for on just this basis.

Does this mean that, contrary to what was said before, step (1)—in the forward direction—need not be slower than step (2)? Step (1) must still be a slow step, for otherwise the reactive intermediate would be formed faster than it could be consumed, and its concentration would build up—contrary to the nature of the reactive intermediate, and a condition different from the one for which the kinetics expression (3) holds.

Problem 14.3 When iodine is added to a benzene solution of dimer I (Sec. 12.15), the color of the iodine gradually fades, at a rate that depends upon [dimer] but *is independent of* $[I_2]$. When a benzene solution of the dimer is shaken under an atmosphere of NO gas, the pressure of the gas gradually drops, at a rate that depends upon [dimer] but *is independent of* the NO pressure. The rate constants for the two reactions are *identical*. Account for these results.

14.13 The S_N1 reaction: stereochemistry

We have proposed that, under the conditions we have described, methyl bromide reacts with hydroxide ion by the S_N2 mechanism, and that *tert*-butyl bromide reacts by the S_N1 mechanism. Since *sec*-alkyl bromides are intermediate in structure between these two halides, it is not surprising to find that they can react by either or both mechanisms.

An increase in $[OH^-]$ speeds up the second-order reaction but has no effect on the first-order reaction. At high $[OH^-]$, therefore, the second-order reaction is so much the faster that *sec*-alkyl bromides react almost entirely by the S_N2 mechanism. The behavior of optically active 2-bromooctane in an S_N2 reaction has been studied (Sec. 14.10) by use of high $[OH^-]$.

In the same way, a decrease in $[OH^-]$ slows down the second-order reaction, but has no effect on the first-order reaction. The behavior of optically active 2-bromooctane in an S_N1 reaction has been studied by use of low $[OH^-]$.

Problem 14.4 In 80% ethanol at 55°, isopropyl bromide reacts with hydroxide ion according to the following kinetic equation, where the rate is expressed as moles per liter per second:

$$\text{rate} = 4.7 \times 10^{-5}[\text{RX}][\text{OH}^-] + 0.24 \times 10^{-5}[\text{RX}]$$

What percentage of the isopropyl bromide reacts by the S_N2 mechanism when $[OH^-]$ is: (a) 0.001 molar, (b) 0.01 molar, (c) 0.1 molar, (d) 1.0 molar, (e) 5.0 molar?

When (−)-2-bromooctane is converted into the alcohol under conditions (low $[OH^-]$) where first-order kinetics are followed, there is obtained (+)-2-octanol.

$$(-)\text{-}C_6H_{13}CHBrCH_3 \xrightarrow[S_N1]{OH^-,\ H_2O} (+)\text{-}C_6H_{13}CHOHCH_3$$

Lower optical purity

The product has the opposite configuration from the starting materials, as in the S_N2 reaction, but this time there is a loss in optical purity. Optically pure bromide yields alcohol that is only about two-thirds optically pure. Optically pure starting material contains only the one enantiomer, whereas the product clearly must contain both. The product is thus a mixture of the inverted compound and the racemic modification, and we say that the reaction has proceeded with **partial racemization.** How can we account for these stereochemical results?

The carbonium ion, we saw in Sec. 5.16, has a *flat* structure: carbon is bonded to three other atoms, and for this bonding uses sp^2 orbitals. Let us see how this shape affects the stereochemical course of the reaction.

In the first step the optically active 2-bromooctane ionizes to form bromide ion and the flat 2-octyl cation. The nucleophilic reagent OH^- (or very possibly H_2O) then attaches itself to the carbonium ion. But it may attach itself to either

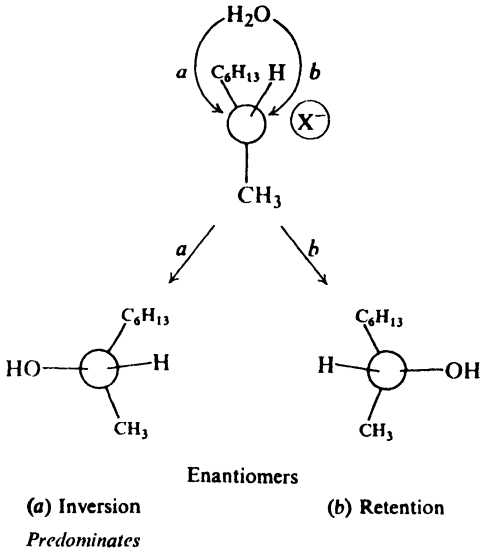


Figure 14.3. The S_N1 reaction: racemization plus inversion. Nucleophilic reagent attacks both (*a*) back side and (*b*) front side of carbonium ion. Back-side attack predominates.

face of this flat ion, and depending upon which face, yields one or the other of two products (see Fig. 14.3).

If the attack were purely random, we would expect equal amounts of the two isomers; that is to say, we would expect only the racemic modification. But the product is *not completely* racemized, for the inverted product exceeds its enantiomer. How do we account for this? The simplest explanation is that attack by the nucleophilic reagent occurs before the departing halide ion has completely left the neighborhood of the carbonium ion; to a certain extent the departing ion thus *shields* the front side of the ion from attack. As a result, back-side attack is somewhat preferred.

Racemization in an S_N1 reaction arises, then, from the *loss of configuration* in the intermediate carbonium ion. In some cases racemization may be almost complete; hydrolysis of α-phenylethyl chloride, for example, proceeds with 87% racemization and 13% inversion:

$$\underset{[\alpha] = -34^\circ}{C_6H_5CHClCH_3} \xrightarrow[S_N1]{OH^-, H_2O} \underset{[\alpha] = +1.7^\circ}{C_6H_5CHOHCH_3}$$

$$\text{Optical purity} = \frac{-34}{-109} \times 100 = 31\% \qquad \text{Optical purity} = \frac{+1.7}{+42.3} \times 100 = 4\%$$

In contrast to an S_N2 reaction, which proceeds with complete inversion, **an S_N1 reaction proceeds with racemization.**

(We shall look more closely at the stereochemistry—and, indeed, all aspects—of the S_N1 reaction in Sec. 14.17.)

Problem 14.5 Suppose that, under S_N1 conditions, 2-bromooctane of specific rotation $-21.6°$ was found to yield 2-octanol of specific rotation $+4.12°$. Using the rotations for optically pure samples given on p. 462, calculate: (a) the optical purity of reactant and of product; (b) the percentage of racemization and of inversion accompanying the reaction; (c) the percentage of front-side and of back-side attack on the carbonium ion.

14.14 The S_N1 reaction: reactivity

The rate-determining step of an S_N1 reaction is the formation of a carbonium ion. Judging from our previous experience, therefore, we expect the reactivity of an alkyl halide to depend chiefly upon *how stable a carbonium ion it can form.*

Our expectation is correct: the order of reactivity of alkyl halides in S_N1 reactions is the same as the order of stability of carbonium ions.

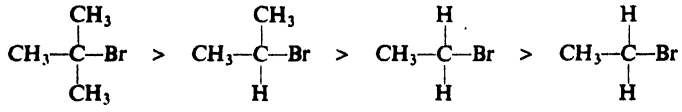
In S_N1 reactions the order of reactivity of RX is allyl, benzyl > 3° > 2° > 1° > CH_3X.

As the positive charge develops on the carbon atom in the transition state, it is dispersed by the same factors—inductive effect and resonance—that stabilize the full-fledged carbonium ion.

$$\underset{}{RX} \longrightarrow \underset{\substack{\text{Transition state} \\ \text{R } \textit{has partial} \\ \textit{positive charge}}}{\left[R\cdots X\right]^{\delta_+\ \delta_-}} \longrightarrow \underset{\substack{\text{Products} \\ \text{R } \textit{has full} \\ \textit{positive charge}}}{R^+ + X^-}$$

The following example gives some idea of how much the rate of an S_N1 reaction can be changed by changes in structure:

$$RBr + H_2O \xrightarrow{\text{formic acid}} ROH + HBr$$



	tert-Butyl	Isopropyl	Ethyl	Methyl
Relative rate:	100 million	45	1.7	1.0

(Formic acid is used here as an even better ionizing solvent than water.)

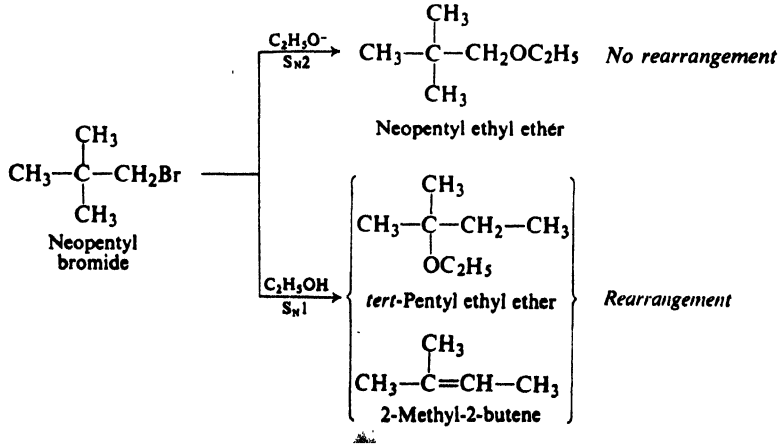
The rate of an S_N2 reaction, we saw, is affected largely by steric factors, that is, by the bulk of the substituents. In contrast, the rate of an S_N1 reaction is affected largely by **electronic factors**, that is, by the tendency of substituents to release or withdraw electrons.

Problem 14.6 Neopentyl halides are notoriously slow in nucleophilic substitution, whatever the experimental conditions. How can you account for this?

14.15 The S_N1 reaction: rearrangement

If the S_N1 reaction involves intermediate carbonium ions, we might expect it to show one of the characteristic features of carbonium ion reactions: *rearrangement*. In an S_N2 reaction, on the other hand, the halide ion does not leave until the nucleophilic reagent has become attached; there is no free intermediate particle and hence we would expect no rearrangement. These expectations are correct.

The following example illustrates this point. We shall see (Sec. 16.5) that the neopentyl cation is particularly prone to rearrange to the more stable *tert*-pentyl cation. Neopentyl bromide reacts (slowly) with ethoxide ion by an S_N2 mechanism to yield neopentyl ethyl ether; it reacts (slowly) with ethyl alcohol by an S_N1 reaction to yield almost entirely rearranged products.



Because of the strong correlation between rearrangement and formation of carbonium ions, in the absence of other information rearrangement is often taken as an indication of an S_N1 mechanism.

We notice that the S_N1 reaction is accompanied by much elimination; expulsion of a proton to yield an alkene is, of course, typical behavior of a carbonium ion.

14.16 S_N2 *vs.* S_N1

The strength of the evidence for the two mechanisms, S_N1 and S_N2, lies in its consistency. Nucleophilic substitutions that follow first-order kinetics also show racemization and rearrangement, and the reactivity sequence $3° > 2° > 1° > CH_3X$. Reactions that follow second-order kinetics show complete stereochemical inversion and no rearrangement, and follow the reactivity sequence $CH_3X > 1° > 2° > 3°$. (The few exceptions to these generalizations are understandable exceptions; see Problem 16.5, p. 525.)

$$RX = \underset{S_N1 \text{ increases}}{\overset{S_N2 \text{ increases}}{CH_3X \quad 1° \quad 2° \quad 3°}}$$

S_N2 *vs.* S_N1

Because there are two opposing reactivity sequences, we seldom encounter *either* of them in a pure form, but find instead a sequence that is a combination of the two. Most typically for halides, as we go along the series CH_3, 1°, 2°, 3°, reactivity passes through a *minimum*, usually at 2°:

$$\underset{S_N2}{CH_3X} > \underset{S_N2}{1°} > \underset{\text{Mixed}}{2°} < \underset{S_N1}{3°}$$

Reactivity by the S_N2 mechanism decreases from CH_3 to 1°, and at 2° is so low that the S_N1 reaction begins to contribute significantly; reactivity, now by S_N1, rises sharply to 3°. The change in mechanism at 2° is confirmed by kinetics and other evidence.

The occurrence of a minimum or maximum in a property—reactivity, acidity, antibacterial activity, etc.—as one proceeds along a logical series always suggests the working of opposing factors. (See, for example, the effect of acidity on certain carbonyl reactions, Sec. 19.14.) In the case of nucleophilic aliphatic substitution, a minimum of the kind we have just encountered is highly characteristic of a change in molecularity of reaction.

Problem 14.7 In 80% ethanol at 55°, the second-order rate constant for the reaction of ethyl bromide with hydroxide ion is 0.0017 liters/mole/sec. Making use of this rate constant and those in Sec. 14.8 and Problem 14.4, calculate the relative rates of hydrolysis in 0.1N hydroxide for methyl, ethyl, isopropyl, and *tert*-butyl bromides.

Despite the predisposition of a particular class of halide toward a particular reaction mechanism, we can to a certain extent control the reaction by our choice of experimental conditions. (This was done, for example, to obtain the nearly pure S_N2 sequence in Sec. 14.11 and the nearly pure S_N1 sequence in Sec. 14.14.)

The very way in which changes in experimental conditions affect the relative importance of the two mechanisms provides additional evidence for the mechanisms.

We have already seen an example of this: high **concentration of the nucleophilic reagent** favors the S_N2 reaction; low concentration favors the S_N1 reaction.

The **nature of the nucleophilic reagent** also plays an important role: for example, neopentyl bromide reacts with ethoxide ion by the S_N2 mechanism and with ethyl alcohol by the S_N1 mechanism. The strongly nucleophilic (strongly basic) ethoxide ion pushes halogen from the molecule, whereas the weakly nucleophilic ethanol waits to be invited in.

Finally, the **polarity of the solvent** can often determine the mechanism by which reaction occurs. Ionization of an alkyl halide is possible only because most of the energy needed to reach the transition state is supplied by formation of dipole-dipole bonds between the solvent and the polar transition state. The more polar the solvent, the stronger the solvation forces and the faster the ionization.

$$\underset{\text{Reactant}}{R{-}X} \longrightarrow \underset{\substack{\text{Transition state}\\ \textit{More polar than reactant:}\\ \textit{stabilized more}\\ \textit{by solvation}}}{\left[R^{\delta+}\cdots X^{\delta-}\right]} \longrightarrow \underset{\text{Products}}{R^+ + X^-}$$

Changing the solvent, say, from 80% ethanol to the much more polar water should speed up ionization and hence the rate of the S_N1 reaction. What effect will this have on the S_N2 reaction? Here we do not have a transition state that is more polar than the reactants; in fact, since the negative charge is dispersed over —OH and —X, this transition state is *less* strongly solvated than the reactants.

$$\underset{\substack{\text{Reactants}\\ \textit{Concentrated charge:}\\ \textit{stabilized more than}\\ \textit{transition state by}\\ \textit{solvation}}}{HO^- + R{-}X} \longrightarrow \underset{\substack{\text{Transition state}\\ \textit{Dispersed charge}}}{\left[HO^{\delta-}\cdots R\cdots X^{\delta-}\right]} \longrightarrow \underset{\text{Products}}{HO{-}R + X^-}$$

Increasing the polarity of the solvent slows down the S_N2 reaction slightly. Other things being equal, the more polar the solvent, the more likely it is that an alkyl halide will react by the S_N1 mechanism. (For a closer look at this matter, see Sec. 18.11.)

These mechanisms give us some idea of the kind of behavior to expect from a halide of a particular structure: its reactivity under a given set of conditions, the likelihood of racemization or of rearrangement, the extent of elimination. They tell us how to change the experimental conditions—concentration, solvent, the nucleophilic reagent—to achieve the results we want: to speed up reaction, to avoid racemization or rearrangement, to minimize elimination.

Problem 14.8 Benzyl bromide reacts with H_2O in formic acid solution to yield benzyl alcohol; the rate is independent of $[H_2O]$. Under the same conditions *p*-methylbenzyl bromide reacts 58 times as fast.

Benzyl bromide reacts with ethoxide ion in dry alcohol to yield benzyl ethyl ether ($C_6H_5CH_2OC_2H_5$); the rate depends upon both [RBr] and $[OC_2H_5^-]$. Under the same conditions *p*-methylbenzyl bromide reacts 1.5 times as fast.

Interpret these results. What do they illustrate concerning the effect of: (a) polarity

of solvent, (b) nucleophilic power of the reagent, and (c) electron release by substituents?

Problem 14.9 The rate of reaction of 3-chloro-1-butene with ethoxide ion in ethyl alcohol depends upon both [RCl] and [$OC_2H_5^-$]; the product is 3-ethoxy-1-butene, $CH_3CH(OC_2H_5)CH{=}CH_2$. The reaction of 3-chloro-1-butene with ethyl alcohol alone, on the other hand, yields not only 3-ethoxy-1-butene but also 1-ethoxy-2-butene, $CH_3CH{-}CHCH_2OC_2H_5$. How do you account for these results? (*Hint:* See Sec. 8.21.)

Problem 14.10 Predict the effect of increasing solvent polarity on the rate of: (a) the S_N2 attack by ammonia on an alkyl halide:

$$RX + NH_3 \longrightarrow RNH_3^+ + X^-$$

(b) the S_N1 reaction of an alkyldimethylsulfonium ion with the solvent:

$$RS(CH_3)_2^+ \longrightarrow (CH_3)_2S + R^+ \xrightarrow{H_2O,\ C_2H_5OH} ROH + ROC_2H_5$$

14.17 Solvolysis

Let us turn briefly to the special case of nucleophilic aliphatic substitution in which the solvent is the nucleophile: *solvolysis*. In its various aspects, solvolysis is—and has been for many years—the most intensively studied reaction in organic chemistry. Yet it is the reaction about which there is probably the most intense disagreement.

$$\underset{\text{solvent}}{R{:}X + {:}S} \longrightarrow R{:}S + X{:}^-$$

There is no added strong nucleophile and so, for many compounds, solvolysis falls into the category we have called S_N1: that is, reaction proceeds by two—or more—steps, with the intermediate formation of a carbonium ion. It is this intermediate that lies at the center of the problem: its nature, how it is formed, and how it reacts. In studying solvolysis one is studying all S_N1 reactions and, in many ways, all reactions involving intermediate carbonium ions.

Perhaps the biggest question to be answered is: just what is the role played by the solvent? Does it, at one extreme, simply cluster about the carbonium ion and the anion—and the transition state leading to their formation—aiding in heterolysis through formation of ion-dipole bonds? Or, at the other extreme, does a single solvent molecule act as a nucleophile and help push the leaving group out of the molecule? Kinetics cannot be used to give a direct answer to this question since the concentration of the solvent does not change during the course of reaction. (We can, of course, study the kinetics of hydrolysis of alkyl halides in, say, formic acid solution—but this is certainly not the same reaction as hydrolysis in water.)

It seems clear that the solvent can give *nucleophilic assistance* to solvolysis. How strong this assistance is depends upon the nucleophilic power of the solvent, and upon how badly the assistance is needed. Water and alcohols, for example, are strongly nucleophilic solvents, acetic acid is weaker, formic acid is weaker yet, and trifluoroacetic acid is very weak. Formation of tertiary cations is relatively easy and needs little nucleophilic assistance; in any case, crowding would dis-

courage such assistance. Reactivity of tertiary substrates depends little on nucleophilic power of the solvent and chiefly on its polarity. Formation of secondary cations needs much nucleophilic assistance; reactivity depends on both nucleophilic power and polarity of the solvent. With most primary substrates, reaction is probably straight-forward S_N2: a single step with solvent acting as nucleophile.

Let us concentrate, then, on secondary alkyl substrates. Just what is meant by the term *nucleophilic assistance*? First of all, it differs from the S_N2 kind of attack in this way: it leads to the formation, not of product, but of the intermediate carbonium ion. Next, it differs from general "solvation" in this way: a single solvent molecule is involved, not a cluster. This solvent molecule attacks the substrate at the back side and, acting as a nucleophile, helps to push the leaving group out the front side. There is formed a carbonium ion—or at least something with a great deal of cation character. Clinging to its back side is the solvent molecule and to the front side, the leaving group. Each may be bonded to carbon through overlap of a lobe of the empty *p* orbital. The geometry is similar to that in the S_N2 transition state, but this is an *intermediate*, and corresponds to an energy minimum in a progress-of-reaction plot. If the leaving group is an anion, and if the solvent is of only moderate polarity, bonding between cation and anion may be chiefly electrostatic, and one speaks of an *ion pair*.

This cationoid intermediate—this "carbonium ion"—now reacts. Ultimately it reacts with a solvent molecule—with formation of a full-fledged bond—to yield product. If, at the time of reaction, the leaving group is still bonded to the front side—or is still lurking there—reaction with solvent occurs at the back side. If, on the other hand, the carbonium ion has lasted long enough for the leaving group to be exchanged for a second solvent molecule—thus forming a symmetrical intermediate—reaction with solvent is equally likely at front or back side. Solvolysis can occur with complete inversion or with inversion plus varying amounts of racemization.

Elegant work by Saul Winstein (of the University of California, Los Angeles) has revealed the detailed behavior of ion pairs that are intermediates in certain cases of solvolysis: *tight* (or *intimate*) ion pairs, the cation of which is free enough to pivot about and lose configuration, and yet is held tightly enough that recombination to the covalently bonded compound is the favored process; *loose* (or *solvent-separated*) ion pairs, the cation of which is susceptible to attack by outside nucleophiles.

It has been suggested that there is a continuous spectrum of mechanisms for nucleophilic substitution ranging from the idealized S_N1 reaction (called **Lim**, for limiting) at one end, to the idealized S_N2 reaction (called **N**) at the other. On progress-of-reaction plots, the energy minimum for the carbonium ion becomes shallower and shallower as we move away from the S_N1 end; at the S_N2 end the minimum has disappeared, and we have a single maximum.

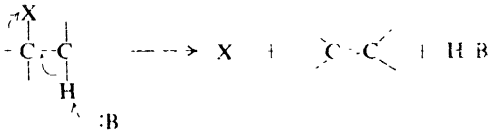
This viewpoint may well be correct. But the differences in stability between the various classes of carbonium ions are great enough that, by and large, reactions fall into three separated groups: (a) for primary substrates, S_N2; (b) for tertiary substrates, S_N1, with an intermediate that approximates our idea of a simple (solvated) carbonium ion; and (c) for secondary substrates, a two-step reaction that is S_N1 to the extent that there is a cationoid intermediate, but one formed with nucleophilic assistance and still encumbered with nucleophile (solvent) and leaving group.

14.18 Elimination: E2 and E1

We encountered dehydrohalogenation in Sec. 5.12 as one of the best methods of preparing alkenes. At that time we said that the mechanism involves a single step: base pulls a hydrogen ion away from carbon, and simultaneously a halide ion separates – aided, of course, by solvation.

E2

Bimolecular elimination

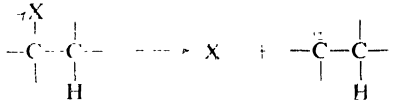


But we have just learned that alkyl halides, particularly tertiary ones, can dissociate into halide ions and carbonium ions, and we already know (Sec. 5.20) that a carbonium ion can lose a hydrogen ion to a base to form an alkene.

E1

Unimolecular elimination

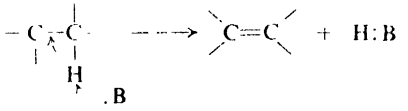
(1)



Slow

A carbonium ion

(2)



Fast

Are there, then, *two* mechanisms for dehydrohalogenation of alkyl halides? The answer is: *yes*, and they bear the same relationship to each other as do the S_N2 and S_N1 mechanisms for substitution. They are the **E2** mechanism (*elimination, bimolecular*), which involves two molecules in the rate-determining step, and the **E1** mechanism (*elimination, unimolecular*), which involves one molecule in the rate-determining step.

The order of reactivity of alkyl halides toward E2 or E1 elimination is the same:

Reactivity toward E2 or E1 elimination $3° > 2° > 1°$

This sequence reflects, for the E2 reaction, the relative stabilities of the alkenes being formed (Sec. 5.14), and for the E1 reaction, the stabilities of the carbonium ions being formed in the first (slow) step.

But, as we might expect, reactions following the two mechanisms differ in kinetics: second-order for E2, and first-order for E1. At the base concentrations ordinarily used for dehydrohalogenation, the E2 mechanism—whose rate depends

upon base concentration—is the principal reaction path. The E1 mechanism is generally encountered only with tertiary halides and in solutions of low base concentration. Using the difference in kinetics as our point of departure, let us look at the evidence for each of the mechanisms.

14.19 Evidence for the E1 mechanism

What is the evidence for the **E1 mechanism**? The elimination reactions that

(a) *follow first-order kinetics*

also:

(b) show *the same effect of structure on reactivity* as in S_N1 reactions; and
(c) where the structure permits, *are accompanied by rearrangement.*

The fact that the rate is independent of the base concentration is interpreted as it was in Sec. 14.12 for the S_N1 reaction; indeed, we see that the rate-determining step in E1 and S_N1 reactions is *exactly the same.* It follows that the order of reactivity of halides should be the same as in S_N1 reactions—and it is.

Finally, first-order elimination is accompanied by the same kind of rearrangement that we expect for a reaction proceeding by way of carbonium ions. The 2-methyl-2-butene formed from neopentyl bromide (Sec. 14.15) is clearly the product of E1 elimination. Indeed, the reaction in which we first encountered rearrangement, dehydration of alcohols, is simply E1 elimination involving the protonated alcohol (Sec. 5.22).

14.20 Evidence for the E2 mechanism

What is the evidence for the **E2 mechanism**? The elimination reactions that

(a) *follow second-order kinetics*

also:

(b) *are not accompanied by rearrangements*;
(c) show *a large deuterium isotope effect*;
(d) *do not undergo hydrogen–deuterium exchange*; and
(e) show *a large element effect.*

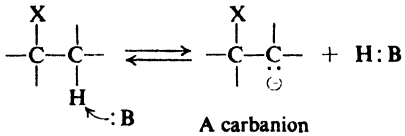
Under conditions where reactions follow second-order kinetics, dehydrobromination of ordinary isopropyl bromide by sodium ethoxide takes place *seven times as fast* as that of the labeled compound, $(CD_3)_2CHBr$. An isotope effect of this size, we have seen (Sec. 11.15), reveals the breaking of a carbon–hydrogen bond in the transition state of the rate-determining step.

Facts (a), (b), and (c) are, of course, exactly what we would expect for the E2 mechanism. The rate-determining step (the *only* step) involves reaction between a molecule of alkyl halide and a molecule of base, in which a carbon–hydrogen bond is broken, and in which there is no opportunity for rearrangement. In particular, these three facts rule out a carbonium ion (E1) mechanism for second-order elimination.

There is, however, another reasonable mechanism that we must consider: *the carbanion mechanism*, which has as its first step the abstraction of a hydrogen

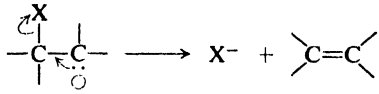
ion to form a negatively charged particle called a *carbanion*. This mechanism, like the E2, is consistent with facts (a), (b), and (c).

(1)

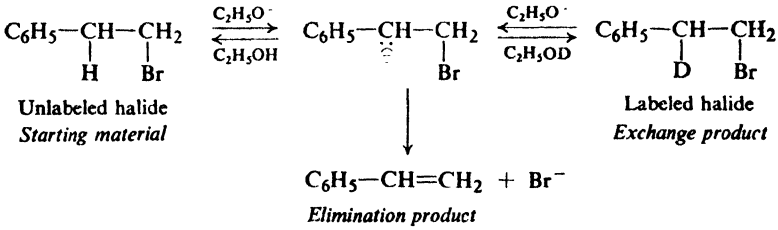


Elimination via carbanion
Seldom observed

(2)



In an attempt to distinguish between these two possibilities, dehydrohalogenation of β-phenylethyl bromide, $C_6H_5CH_2CH_2Br$, was carried out in labeled ethanol, C_2H_5OD, with ethoxide ion as base. If carbanions were formed, *some* of them might be expected to recombine with a hydrogen ion to regenerate the starting material:



But in this recombination the carbanion would be almost certain to regain a *deuteron*, not a proton, since nearly all the molecules of alcohol are C_2H_5OD, not C_2H_5OH.

When this reaction was interrupted, and unconsumed β-phenylethyl bromide recovered, it was found by mass spectrometric analysis to contain *no deuterium*. Similar experiments with other systems have given similar results: in typical second-order elimination reactions there is *no hydrogen–deuterium exchange*.

Fact (d) shows, then, that if carbanions are involved in these elimination reactions they lose halide ion much more rapidly than they combine with hydrogen ions. (That is, k_2 would have to be much larger than k_{-1}.) But if this were so, the first step (1) would be rate-determining—just as in an S_N1 reaction, or in aromatic nitration—and the rate of the second step (2) would have no effect on the overall rate of reaction.

Now, is this true? How can we tell whether or not the rate at which halide ion is lost affects the rate of elimination? We might consider looking for an isotope effect, as was done in aromatic nitration. But here that would be a very difficult job. We are not dealing with loss of hydrogen, whose isotopes differ two- or three-fold in mass; we are dealing with loss of elements like chlorine, whose isotopes differ by only a few percent, with correspondingly small differences in the ease with which bonds are broken.

It has been pointed out by Joseph Bunnett (of the University of California, Santa Cruz) that evidence against the carbanion mechanism is available in the *element effect*.

In S_N1 and S_N2 displacements the reactivity of alkyl halides follows the sequence

$$R{-}I > R{-}Br > R{-}Cl > R{-}F$$

with the ease of breaking the carbon–halogen bond depending upon its strength (see Table 1.2, p. 21). The differences in rate here are quite large: alkyl bromides, for example, react 25 to 50 times as fast as alkyl chlorides. These element effects are, in fact, much larger than the isotope effects observed for the breaking of bonds to protium and deuterium—as, indeed, they *should* be, considering the much greater differences in bond strength.

Now, in these elimination reactions, the reactivity of alkyl halides follows the same sequence as for substitution—and with element effects of just about the same size. Clearly, the rate of breaking the carbon–halogen bond *does* affect the overall rate of reaction. On this evidence, if carbanions were formed, they would find step (2) difficult and would revert to starting material many times before finally losing halide ion. But such reversible carbanion formation has been ruled out by the absence of isotopic exchange.

Thus, only the E2 mechanism fits all the facts.

14.21 Orientation of elimination. The variable E2 transition state

Where elimination can produce a mixture of isomers, which one predominates? We saw earlier (Sec. 5.14) that in dehydrohalogenation the more stable alkene is formed faster: *sec*-butyl bromide, for example, yields more 2-butene than 1-butene. We attributed this orientation to the *alkene character* of the transition

$$\underset{\substack{\text{Br}\\ \textit{sec}\text{-Butyl bromide}}}{CH_3CH_2CHCH_3} \xrightarrow{\text{alc. KOH}} \underset{\substack{\text{2-Butene}\\ 81\%}}{CH_3CH{=}CHCH_3} + \underset{\substack{\text{1-Butene}\\ 19\%}}{CH_3CH_2CH{=}CH_2}$$

state: the double bond is partly formed in the transition state, and factors that stabilize an alkene stabilize this incipient alkene.

Predominant formation of the more stable isomer is called **Saytzeff orientation** after the Russian chemist Alexander Saytzeff (University of Kazan), who in 1875 first formulated a "rule" for orientation in dehydrohalogenation.

Problem 14.11 Like Markovnikov, Saytzeff stated his rule in terms, not of product stability, but of numbers of hydrogens on carbon atoms. (a) Suggest a wording for this original Saytzeff rule. (b) Predict the major product of dehydrohalogenation of 2-bromo-1-phenylbutane on the basis of the original rule. (c) On the basis of the modern rule.

But orientation in E2 elimination is not always Saytzeff, particularly when compounds other than alkyl halides are involved. To see the various factors at work here, let us take, as a simple example, elimination from the 2-hexyl halides brought about by the strong base sodium methoxide. The iodide, bromide, and

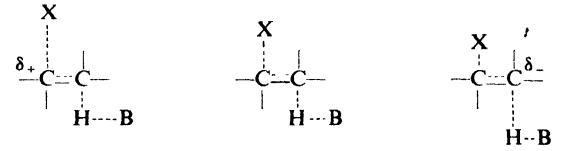
chloride do react with Saytzeff orientation, but the fluoride gives predominantly the less substituted alkene, 1-hexene. Such orientation is called **Hofmann orientation**, since it was first observed by Hofmann (in elimination from quaternary ammonium salts, Sec. 23.5). Furthermore, we can see that there is a steady increase in the fraction of 1-hexene along the series I, Br, Cl, F.

$$CH_3CH_2CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}HCH_3 \xrightarrow[E2]{CH_3ONa/CH_3OH} \text{2-hexene and 1-hexene}$$

X = I	81%	19%
Br	72	28
Cl	67	33
F	30	70

Such observations are best understood in terms of what Bunnett (p. 478) has called the *variable transition state* theory of E2 elimination. We are speaking, remember, of a one-step elimination; both the C--H and C--X bonds are being broken in the same transition state. But there is a whole spectrum of E2 transition states which differ in the relative *extent* to which the two bonds are broken.

Variable E2 Transition State



Carbonium-like Central Carbanion-like

Much alkene character

At the center of the spectrum is the transition state we have described before for elimination from alkyl halides: both C--H and C--X bonds are broken to a considerable extent, the transition state has considerable alkene character, and orientation is Saytzeff.

But, if breaking of the C--H bond greatly exceeds breaking of the C—X bond, there is little alkene character to the transition state, but instead the development of negative charge on the carbon losing the proton. In this case, the transition state has *carbanion character*, and its stability is controlled as we might expect, by dispersal or intensification of the negative charge: electron-withdrawing groups stabilize, and electron-releasing groups destabilize. At one end of the spectrum, then, we have the carbanion-like transition state.

At the other end of the spectrum is the transition state in which C—X bond-breaking greatly exceeds C—H bond-breaking. Positive charge develops on the carbon losing the leaving group, giving carbonium ion character to the transition state. Alkene character is diminished, and we might expect orientation to be less strongly Saytzeff.

Consider elimination from the 2-hexyl halides. With the iodide, there is considerable breaking of both bonds in the transition state, much alkene character, and preferred formation of the more stable alkene: Saytzeff orientation. As we go along the series I, Br, Cl, F, the C—X bond becomes stronger, and the extent to which it is broken in the transition state decreases. At the same time, the electron-withdrawing effect of X increases, favoring the development of negative charge.

With the fluoride, we have predominant C—H bond-breaking, with little alkene character but considerable carbanion character to the transition state. A primary hydrogen is preferentially abstracted by base, since that permits the negative charge to develop on a primary carbon, to which there is attached only one electron-releasing alkyl group. Orientation is Hofmann.

Bunnett believes that C—F bond-breaking lags behind C—H bond-breaking chiefly because of the strength of the C—F bond. Ingold (p. 460), who was the first to suggest carbanion character as the underlying cause of Hofmann orientation, believed that electron withdrawal by fluorine is the major factor.

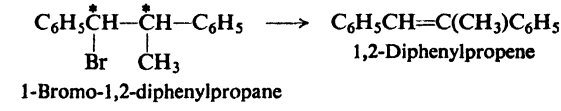
In E2 elimination with bases like KOH and CH_3ONa, most alkyl halides give Saytzeff orientation. Certain other compounds (quaternary ammonium salts, Sec. 23.5, for example) give Hofmann orientation. Alkyl sulfonates fall in between. With each kind of compound, orientation is affected—sometimes drastically—by the choice of base and solvent, and by stereochemistry. (The percentage of 1-hexene from 2-hexyl chloride, for example, jumps from 33% in CH_3ONa/CH_3OH to 91% in *t*-BuOK/*t*-BuOH, evidently for steric reasons.) In all this, we should remember that orientation is a matter of relative stabilities of competing transition states; these stabilities are determined by electronic factors—alkene character and carbanion character—with superimposed conformational factors.

So far, we have spoken only of E2 elimination. In E1 elimination, orientation is determined in the second step: conversion of carbonium ion to alkene. As we might expect, orientation is essentially the same regardless of what leaving group has departed earlier in the formation of the carbonium ion. Orientation is strongly Saytzeff, reflecting much alkene character in the transition state.

Problem 14.12 2-Phenylethyl bromide undergoes E2 elimination about 10 times as fast as 1-phenylethyl bromide, even though they both yield the same alkene. Suggest a possible explanation for this.

14.22 Stereochemistry of elimination

Dehydrohalogenation of 1-bromo-1,2-diphenylpropane gives, as we would expect, 1,2-diphenylpropene. But the halide contains two chiral centers, and we

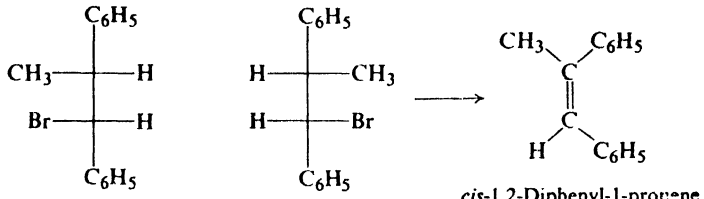


1-Bromo-1,2-diphenylpropane

1,2-Diphenylpropene

can easily show that it can exist as two pairs of enantiomers; each pair is diastereomeric with the other pair. On E2 elimination, one pair of enantiomers yields *only* the *cis*-alkene, and the other pair yields *only* the *trans*-alkene. The reaction is completely *stereospecific* (Sec. 7.11).

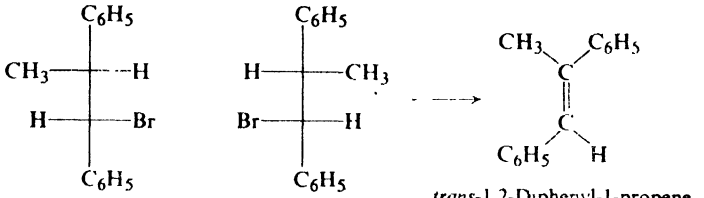
As this example and many others show, the bimolecular reaction of alkyl halides involves *anti*-elimination: in the transition state the hydrogen and the leaving group are located as far apart as possible, in the *anti* relationship (Sec. 3.3) as opposed to *gauche* or *eclipsed* (see Fig. 14.4, p. 482).



I (1R,2R) 1-Bromo-1,2-diphenylpropane

II (1S,2S) 1-Bromo-1,2-diphenylpropane

cis-1,2-Diphenyl-1-propene

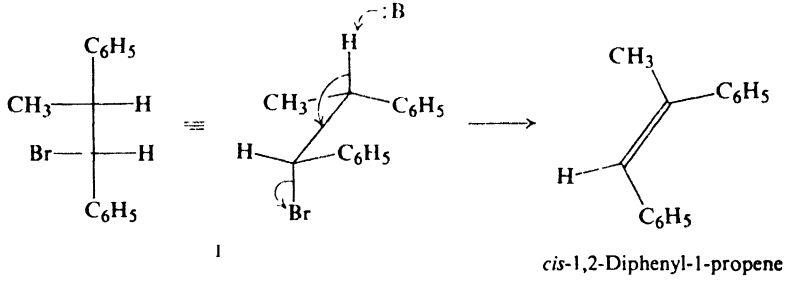


III (1S,2R) 1-Bromo-1,2-diphenylpropane

IV (1R,2S) 1-Bromo-1,2-diphenylpropane

trans-1,2-Diphenyl-1-propene

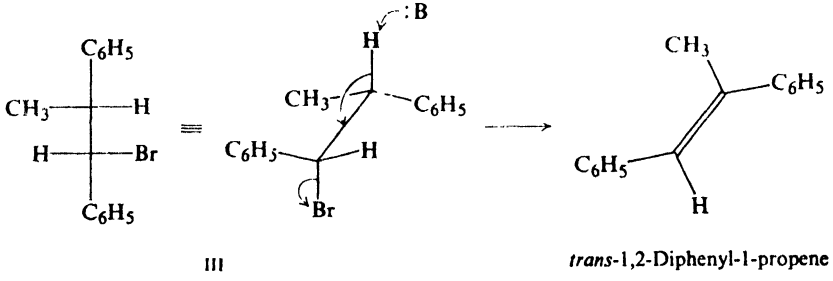
Thus, diastereomer I or its enantiomer, II, gives the *cis*-alkene:



I

cis-1,2-Diphenyl-1-propene

and diastereomer III (or its enantiomer, IV) gives the *trans*-alkene:



III

trans-1,2-Diphenyl-1-propene

The preference for *anti*-elimination from halides can be very strong. To see this is so, we must turn from open-chain compounds to cyclic compounds. In

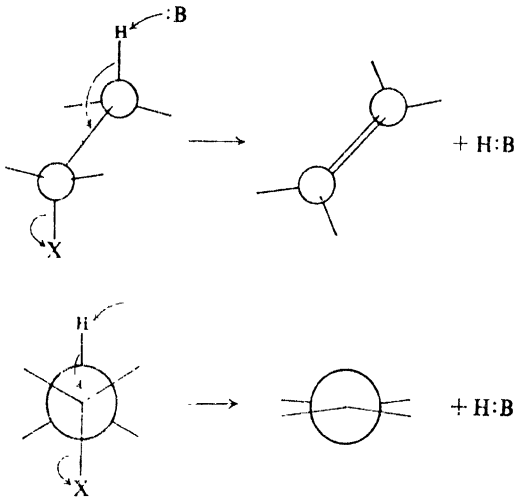
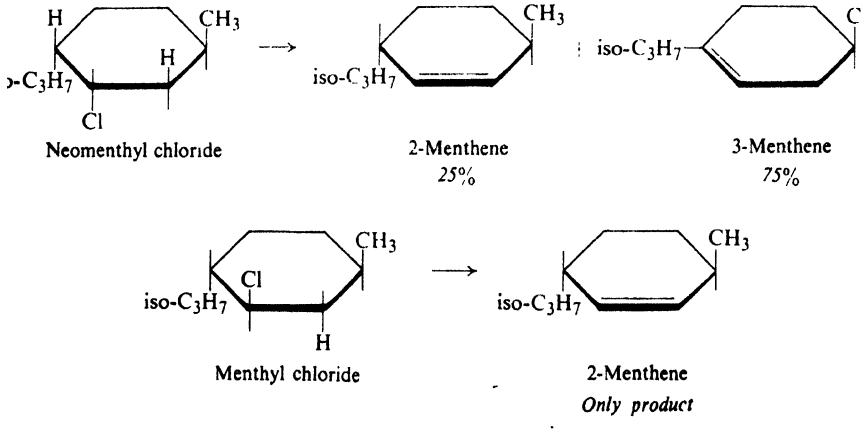


Figure 14.4. The E2 reaction of alkyl halides: *anti*-elimination. Hydrogen and the leaving group, X, are as far apart as possible, in the *anti* relationship.

cyclohexane rings, 1,2-substituents can take up the *anti* conformation only by occupying axial positions; this, in turn, is possible only if they are *trans* to each other (see Fig. 14.5, p. 483).

To take a specific example: E2 elimination converts *neomenthyl chloride* into a mixture of 75% 3-menthene and 25% 2-menthene. This is about what we might expect, the more stable because more highly substituted—3-menthene being the preferred product. But, in marked contrast, E2 elimination converts the diastereomeric *menthyl chloride* exclusively into the less stable 2-menthene.



How are we to account for these differences in behavior? In neomenthyl chloride there is a hydrogen on either side of the chlorine which is *trans* to the

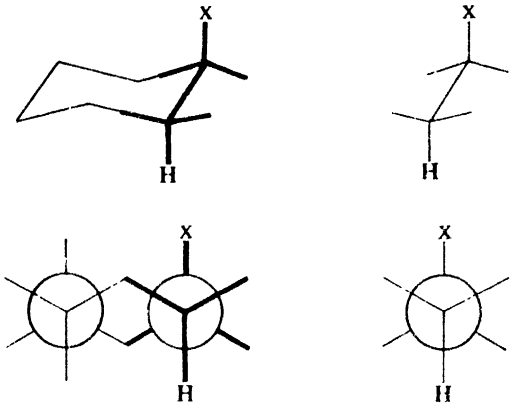
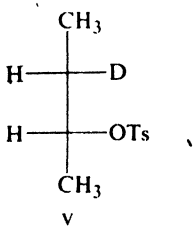


Figure 14.5. Only *trans*-1,2-substituents can assume the *anti* relationship.

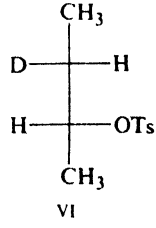
chlorine, and which can take up a conformation *anti* to it. Either hydrogen *can* be eliminated, and the ratio of products is determined in the usual way, by the relative stabilities of the alkenes being formed. In menthyl chloride, on the other hand, only one hydrogen is *trans* to the chlorine, and it is the only one that is eliminated, despite the fact that this yields the less stable alkene.

In recent years it has become clear that E2 reactions can also proceed by *syn*-elimination: in the transition state the hydrogen and leaving group are in the *eclipsed* (or *gauche*) relationship. Although uncommon for alkyl halides, *syn*-elimination is often observed for quaternary ammonium salts and sometimes for alkyl sulfonates. On electronic grounds, the most stable transition states seem to be those in which the hydrogen and leaving group are *periplanar* (in the same plane) to permit overlap of incipient *p* orbitals in the partially-formed double bond. Of the two periplanar eliminations, the *anti* is probably easier than the *syn*—other things being equal. But various factors may throw the stereochemistry one way or the other. Conformational effects enter in, and the degree of carbanion character; the stereochemistry is affected by the strength of the base and by its bulk and by the bulk of the leaving group. Ring systems present special situations: it is difficult for *cis*-1,2-substituents to become *syn*-periplanar in cyclohexanes, but easy in cyclopentanes.

Problem 14.13 When treated with *t*-BuOK in DMSO, diastereomer V (and its



V



VI

enantiomer) gave *cis*-2-butene without loss of deuterium and *trans*-2-butene with loss of deuterium; diastereomer VI (and its enantiomer) gave *trans*-2-butene without loss of deuterium. How do you account for these findings? What is the stereochemistry of elimination here?

Problem 14.14 Of the various isomeric 1,2,3,4,5,6-hexachlorocyclohexanes, one isomer undergoes dehydrohalogenation by base much more slowly than the others. Which isomer is probably the unreactive one, and why is it unreactive?

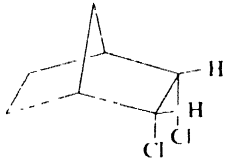
Problem 14.15 Suggest an explanation for the fact that dehydrohalogenation of *sec*-butyl chloride yields both *cis*- and *trans*-2-butene, but mostly (6:1) the *trans*-isomer. (Assume only *anti* elimination.)

Problem 14.16 How do you account for the fact that when heated in ethanol, in the absence of added base, menthyl chloride yields both 3-menthene (68%) and 2-menthene (32%)?

Problem 14.17 Using models suggest explanations for the following.

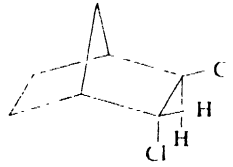
(a) On E2 elimination with *t*-BuOK/*t*-BuOH, both *cis*- and *trans*-2-phenylcyclopentyl tosylates give 1-phenylcyclopentene as the only alkene; the *cis* isomer reacts 14 times as fast as the *trans*

(b) On E2 elimination with *n*-$C_5H_{11}ONa$/*n*-$C_5H_{11}OH$ to give 2-chloronorbornene, VIII reacts about 100 times as fast as its diastereomer, VII.



VII

endo-cis-2,3-Dichloronorbornane

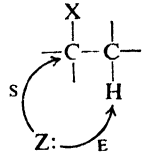


VIII

trans-2,3-Dichloronorbornane

14.23 Elimination *vs.* substitution

Let us return to a problem we encountered before, in the reaction between acetylides and alkyl halides (Sec. 8.12): competition between substitution and elimination. Both reactions result from attack by the same nucleophilic reagent: attack at carbon causes substitution, attack at hydrogen causes elimination.



E2 *vs.* S_N2

We can see more clearly now why reaction with acetylides to form alkynes is limited in practice to *primary* halides. Under the conditions of the reaction—a solvent of low polarity (liquid ammonia or ether) and a powerful nucleophilic reagent (acetylide ion)—we would expect substitution, that is, alkyne formation, to take place by an S_N2 mechanism. Primary halides should therefore form alkynes fastest tertiary halides the slowest.

On the other hand, the speed with which an alkyl halide undergoes elimination

depends chiefly (Sec. 5.14) upon the stability of the alkene formed; tertiary halides, which necessarily yield highly branched (more stable) alkenes, undergo elimination fastest.

Primary halides, then, undergo substitution fastest and elimination slowest; tertiary halides undergo substitution slowest and elimination fastest. It is not surprising that the yields of alkynes are good for primary halides and very bad for tertiary halides.

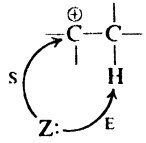
The same considerations hold for the reactions of alkyl halides with other nucleophiles. *Where substitution and elimination are competing reactions, the proportion of elimination increases as the structure of an alkyl halide is changed from primary to secondary to tertiary.* Many tertiary halides yield exclusively alkenes under these conditions.

$$\text{RX} = \underset{\text{Substitution increases}}{\overset{\text{Elimination increases}}{\overset{\longrightarrow}{\underset{\longleftarrow}{1^\circ \qquad 2^\circ \qquad 3^\circ}}}}$$

Elimination (E2)
vs.
Substitution (S_N2)

Like acetylide ion, hydroxide ion is a *strong* base; that is, it has a strong affinity for hydrogen ion. The preparation of alcohols from alkyl halides gives good yields with primary halides, somewhat poorer yields with secondary halides; it is essentially worthless for the preparation of tertiary alcohols.

Tertiary alcohols are best prepared under conditions that favor the S_N1 reaction: solvent of high polarity, and reagent of low nucleophilic power. This is accomplished by simply boiling with water, which serves both as solvent and nucleophilic reagent. Yet even here the yields of alcohol are not high; considerable elimination occurs since the intermediate is a *tertiary* carbonium ion, which can easily expel a hydrogen ion to yield a relatively stable alkene.



E1 *vs.* S_N1

When we want the product of a substitution reaction, elimination is a nuisance to be avoided. But when we want an alkene from an alkyl halide, elimination is what we are trying to bring about. To do this, we use a solvent of low polarity, and a high concentration of a strong base: concentrated alcoholic potassium hydroxide.

Problem 14.18 Which compound of each of the following sets would you expect to give the higher yield of substitution product under conditions for bimolecular reaction?

(a) ethyl bromide or β-phenylethyl bromide;
(b) α-phenylethyl bromide or β-phenylethyl bromide;
(c) isobutyl bromide or *n*-butyl bromide;
(d) isobutyl bromide or *tert*-butyl bromide.

Problem 14.19 Suggest an explanation for each of the following facts.

(a) Dehydrohalogenation of isopropyl bromide, which requires several hours of refluxing in alcoholic KOH, is brought about in less than a minute at room temperature by *t*-BuO^-K^+ in DMSO. (*Hint:* See Sec. 1.21.)

(b) The reaction of *tert*-butyl chloride in water to yield (chiefly) *tert*-butyl alcohol is not appreciably affected by dissolved sodium fluoride; in DMSO, however, sodium fluoride brings about rapid formation of isobutylene.

14.24 Analysis of alkyl halides

Simple alkyl halides respond to the common characterization tests in the same manner as alkanes: they are insoluble in cold concentrated sulfuric acid; they are inert to bromine in carbon tetrachloride, to aqueous permanganate, and to chromic anhydride. They are readily distinguished from alkanes, however, by qualitative analysis (Sec. 2.25), which shows the presence of halogen.

In many cases, the presence of halogen can be detected without a sodium fusion or Schöniger oxidation. An unknown is warmed for a few minutes with alcoholic silver nitrate (the alcohol dissolves both the ionic reagent and the organic compound); halogen is indicated by formation of a precipitate that is insoluble in dilute nitric acid.

As in almost all reactions of organic halides, reactivity toward alcoholic silver nitrate follows the sequence RI > RBr > RCl. For a given halogen atom, reactivity decreases in the order 3° > 2° > 1°, the sequence typical of carbonium ion formation; allyl and benzyl halides are highly reactive. Other evidence (stereochemistry, rearrangements) suggests that this reaction is of the S_N1 type. Silver ion is believed to dispose reaction toward this mechanism (rather than the S_N2) by *pulling* halide away from the alkyl group.

$$R{:}X + Ag^+ \longrightarrow R^+ + Ag^+X^-$$

(Vinyl and aryl halides do not react, Sec. 25.5.)

As mentioned earlier (Sec. 14.1), substituted alkyl halides also undergo the reactions characteristic of their other functional groups.

Problem 14.20 Describe simple chemical tests (if any) that would distinguish between: (a) ethylene bromohydrin and ethylene bromide; (b) 4-chloro-1-butene and *n*-butyl chloride; (c) bromocyclohexane and bromobenzene; (d) 1-chloro-2-methyl-2-propanol and 1,2-dichloro-2-methylpropane. Tell exactly what you would *do* and *see*.

14.25 Spectroscopic analysis of alkyl halides

For the spectroscopic analysis of alkyl halides, see the general discussion in Chapter 13, in which many alkyl halides were used as examples.

PROBLEMS

1. Outline the synthesis of ethyl bromide from: (a) ethane, (b) ethylene, (c) ethanol. Which method would one most probably use in the laboratory?

2. Which methods of Problem 1 would be used to prepare pure samples of:

(a) ethyl chloride
(b) ethyl fluoride
(c) ethyl iodide
(d) *n*-propyl bromide
(e) isopropyl bromide
(f) benzyl chloride
(g) α-phenylethyl chloride
(h) cyclohexyl bromide

3. Outline the synthesis of the following compounds from isopropyl alcohol:

(a) isopropyl bromide
(b) allyl chloride
(c) 1-chloro-2-propanol
(d) 1,2-dibromopropane
(e) 2,2-dibromopropane
(f) 2-bromopropene
(g) 1-bromopropene
(h) 1,3-dichloro-2-propanol
(i) 2,3-dibromo-1-propanol
(j) 2,2-dichloro-1-methylcyclopropane

4. Outline all steps in a possible laboratory synthesis of each of the following from cyclohexanol and any necessary aliphatic, aromatic, or inorganic reagents.

(a) bromocyclohexane
(b) iodocyclohexane
(c) *trans*-1,2-dibromocyclohexane
(d) 3-bromocyclohexene
(e) *trans*-2-chlorocyclohexanol
(f) norcarane (see p. 458)

5. Outline all steps in a possible laboratory synthesis of each of the following, using benzene, toluene, and any needed aliphatic or inorganic reagents.

(a) *p*-bromobenzyl chloride
(b) triphenylchloromethane
(c) allyl iodide
(d) benzal bromide
(e) *m*-nitrobenzotrichloride
(f) 1,2-dichloro-1-phenylethane
(g) phenylacetylene
(h) phenylcyclopropane

6. Give the structures and names of the chief organic products expected from the reaction (if any) of *n*-butyl bromide with:

(a) NaOH(aq)
(b) KOH(alc)
(c) cold conc. H_2SO_4
(d) Zn, H^+
(e) Li, then CuI, ethyl bromide
(f) Mg, ether
(g) product (f) + D_2O
(h) H_2, Pt
(i) dilute neutral $KMnO_4$
(j) NaI in acetone
(k) benzene, $AlCl_3$
(l) $CH_3C{\equiv}C^-Na^+$
(m) HgF_2
(n) Br_2/CCl_4

7. Referring when necessary to the list on page 457, give structures of the chief organic products expected from the reaction of *n*-butyl bromide with:

(a) NH_3
(b) $C_6H_5NH_2$
(c) NaCN
(d) $NaOC_2H_5$
(e) CH_3COOAg
(f) $NaSCH_3$

8. Write equations for the most likely side reactions in the conversion of *n*-butyl bromide into:

(a) 1-butanol by aqueous NaOH
(b) methyl *n*-butyl ether by CH_3ONa
(c) 1-butene by alcoholic KOH
(d) 1-hexyne by sodium acetylide

Will each of these side reactions be more or less important if *tert*-butyl bromide is used instead of *n*-butyl bromide?

9. Arrange the compounds of each set in order of reactivity toward S_N2 displacement:

(a) 2-bromo-2-methylbutane, 1-bromopentane, 2-bromopentane
(b) 1-bromo-3-methylbutane, 2-bromo-2-methylbutane, 3-bromo-2-methylbutane
(c) 1-bromobutane, 1-bromo-2,2-dimethylpropane, 1-bromo-2-methylbutane, 1-bromo-3-methylbutane

10. Arrange the compounds of each set in order of reactivity toward S_N1 displacement:

(a) the compounds of Problem 9(a)
(b) the compounds of Problem 9(b)
(c) benzyl chloride, *p*-chlorobenzyl chloride, *p*-methoxybenzyl chloride, *p*-methylbenzyl chloride, *p*-nitrobenzyl chloride
(d) benzyl bromide, α-phenylethyl bromide, β-phenylethyl bromide

11. Arrange the compounds in each set in order of ease of dehydrohalogenation by concentrated alcoholic KOH:

(a) compounds of Problem 9(a)
(b) compounds of Problem 9(b)
(c) 2-bromo-1-phenylpropane and 3-bromo-1-phenylpropane
(d) 5-bromo-1,3-cyclohexadiene, bromocyclohexane, 3-bromocyclohexene
(e) *cis*- and *trans*-2-bromomethylcyclohexane

12. Consider, as an example, the reaction between an alkyl halide and NaOH in a mixture of water and ethanol. In a table, with one column for S_N2 and another for S_N1, compare the two mechanisms with regard to:

(a) stereochemistry
(b) kinetic order
(c) occurrence of rearrangements
(d) relative rates of CH_3X, C_2H_5X, iso-C_3H_7X, *tert*-C_4H_9X
(e) relative rates of RCl, RBr, and RI
(f) effect on rate of a rise in temperature
(g) effect on rate of doubling [RX]
(h) effect on rate of doubling $[OH^-]$
(i) effect on rate of increasing the water content of the solvent
(j) effect on rate of increasing the alcohol content of the solvent

13. Optically active *sec*-butyl alcohol retains its activity indefinitely in contact with aqueous base, but is rapidly converted into optically inactive (racemic) *sec*-butyl alcohol by dilute sulfuric acid. How do you account for these facts? Suggest a detailed mechanism or mechanisms for the racemization by dilute acid.

14. When optically active 2-iodooctane was allowed to stand in acetone solution containing $Na^{131}I$ (radioactive iodide), the alkyl halide was observed to lose optical activity and to exchange its ordinary iodine for radioactive iodine. The rate of each of these reactions depended on both [RI] and $[I^-]$, but racemization was exactly *twice* as fast as isotopic exchange. This experiment, reported in 1935 by E. D. Hughes (of University College, London), is considered to have established the stereochemistry of the S_N2 reaction: that each molecule undergoing substitution suffers inversion of configuration. Show exactly how this conclusion is justified. (*Hint:* Take one molecule of alkyl halide at a time, and consider what happens when it undergoes substitution.)

15. When neomenthyl chloride undergoes E2 elimination, 2-menthane makes up one-fourth of the reaction product (Sec. 14.22). Since menthyl chloride can yield *only* 2-menthene, we might expect it to react at one-fourth of the rate of neomenthyl chloride. Actually, however, it reacts only 1/200 as fast as neomenthyl chloride: that is, only 1/50 as fast as we would have expected. How do you account for this unusually slow elimination from menthyl chloride? (*Hint:* Use models.)

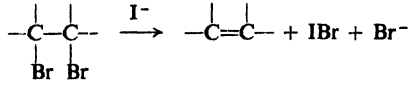
16. When either *cis*- or *trans*-1-phenylpropene was treated with chlorine in CCl_4, and the reaction product was separated by preparative-scale gas chromatography, two fractions, A and B, of formula $C_9H_{10}Cl_2$, were obtained. On treatment with potassium *tert*-butoxide in *tert*-butyl alcohol, each fraction gave 1-chloro-1-phenyl-1-propene. Nmr showed that —Cl and $-CH_3$ were *trans* in A, and *cis* in B.

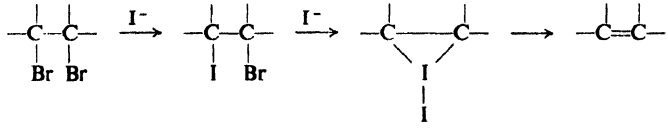
(a) Give structural formulas for A and B. (b) In this particular system, is addition of halogen stereospecific? Discuss.

17. *cis*-4-*tert*-Butylcyclohexyl tosylate reacts rapidly with NaOEt in EtOH to yield 4-*tert*-butylcyclohexene; the rate of reaction is proportional to the concentration of both tosylate and ethoxide ion. Under the same conditions, *trans*-4-*tert*-butylcyclohexyl tosylate reacts slowly to yield the alkene (plus 4-*tert*-butylcyclohexyl ethyl ether); the rate of reaction depends only on the concentration of the tosylate.

How do you account for these observations?

18. (a) It has been proposed that the conversion of vicinal dihalides into alkenes by the action of iodide ion can proceed by either a one-step mechanism (i) or a three-step mechanism (ii).

(i) 

(ii) 

Show the details, particularly the expected stereochemistry, of each step of each mechanism.

(b) The following stereochemical observations have been made:

meso-1,2-dibromo-1,2-dideuterioethane (CHDBrCHDBr) + I^- ⟶ *only cis*-CHD=CHD

meso-2,3-dibromobutane + I^- ⟶ *only trans*-2-butene

racemic 2,3-dibromobutane + I^- ⟶ *only cis*-2-butene

On the basis of the observed stereochemistry, which mechanism is most probably followed by each halide? Explain in detail. How do you account for the difference in behavior between the halides?

(c) When 1-bromocyclohexene (ordinary bromine) is allowed to react with radioactive Br_2, and the resulting tribromide is treated with iodide ion, there is obtained 1-bromocyclohexene that contains less than 0.3% of radioactive bromine.

19. On treatment with the aromatic base pyridine (Sec. 31.8), racemic 1,2-dibromo-1,2-diphenylethane loses HBr to yield *trans*-1-bromo-1,2-diphenylethene; in contrast, the *meso* dibromide loses Br_2 to yield *trans*-1,2-diphenylethene. (a) Suggest a mechanism for the reaction of each stereoisomer. (b) How do you account for the difference in their behavior?

20. Treatment of neopentyl chloride with the strong base sodamide ($NaNH_2$) yields a hydrocarbon of formula C_5H_{10}, which rapidly decolorizes bromine in carbon tetrachloride, but is not oxidized by cold, dilute, neutral permanganate. Its nmr spectrum shows absorption at δ 0.20 and δ 1.05 with peak area ratio 2:3. When the same reaction is carried out using the labeled alkyl halide, $(CH_3)_3CCD_2Cl$, the product obtained has its M^+ peak at *m/e* 71. What is a likely structure for the hydrocarbon, and how is it probably formed? Is the result of the labeling experiment consistent with your mechanism? (*Hint:* See Sec. 9.16.)

21. (a) In the liquid form, *tert*-butyl fluoride and isopropyl fluoride gave the following nmr spectra.

tert-butyl fluoride: doublet, δ 1.30, J = 20 Hz

isopropyl fluoride: two doublets, δ 1.23, 6H, J = 23 Hz and 4 Hz
two multiplets, δ 4.64, 1H, J = 48 Hz and 4 Hz

How do you account for each of these spectra? (*Hint:* See Sec. 13.10.)

(b) When the alkyl fluorides were dissolved in liquid SbF_5, the following nmr spectra were obtained.

from *tert*-butyl fluoride: singlet, δ 4.35

from isopropyl fluoride: doublet, δ 5.06, 6H, J = 4 Hz
multiplet, δ 13.5, 1H, J = 4 Hz

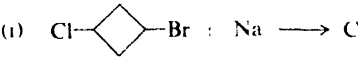
To what molecule is each of these spectra due? (*Hint:* What does the disappearance of just half the peaks observed in part (a) suggest?) Is the very large downfield shift what you might have expected for molecules like these? Of what fundamental significance to organic theory are these observations?

22. When methallyl chloride, $CH_2{=}C(CH_3)CH_2Cl$, was treated with sodamide in tetrahydrofuran solution, there was obtained a hydrocarbon, C_4H_6, which gave the following nmr spectrum:

a doublet, δ 0.83, 2H, J = 2 Hz
b doublet, δ 2.13, 3H, J = 1 Hz
c multiplet, δ 6.40, 1H

(a) What is a likely structure for this hydrocarbon, and by what mechanism was it probably formed? (b) What product would you expect to obtain by the same reaction from allyl chloride?

23. Hydrocarbon C has been prepared in two different ways:

(i)  → C

1-Chloro-3-bromocyclobutane

(ii) $CH_2{=}CH{-}CH_2{-}CHN_2 \xrightarrow{\text{light}}$ C
Allyldiazomethane

Mass spectrometry shows a molecular weight of 54 for C. (What is its molecular formula?) On gas chromatography, C was found to have a different retention time from cyclobutene, butadiene, or methylenecyclopropane. C was stable at 180° (unlike cyclobutene), but was converted into butadiene at 225°. The nmr spectrum of C showed: *a*, singlet δ 0.45, 2H; *b*, multiplet, δ 1.34, 2H; *c*, multiplet, δ 1.44, 2H.

(a) What single structure for C is consistent with all these facts? (*Hint:* In analyzing the nmr spectrum, take stereochemistry into consideration.) (b) By what familiar reaction is C formed in (i)? in (ii)?

24. Describe simple chemical tests that would serve to distinguish between:

(a) allyl chloride and *n*-propyl chloride
(b) allyl chloride and benzyl chloride
(c) ethylene chlorohydrin, ethylene chloride, and ethylene glycol
(d) cyclohexanol, cyclohexyl bromide, and cyclohexene
(e) *tert*-butyl alcohol, *tert*-butyl chloride, and 1-octene
(f) benzyl chloride and *p*-chlorotoluene.

Tell exactly what you would *do* and *see*.

25. A liquid of boiling point 39–41° was insoluble in water, dilute acids or bases, or concentrated H_2SO_4. It did not react with Br_2/CCl_4 or dilute $KMnO_4$. It was subjected to sodium fusion, and the resulting solution was filtered, acidified with nitric acid, and boiled. Addition of $AgNO_3$ gave a precipitate.

(a) On the basis of Table 14.1, what compound or compounds might this have been? (b) Several milliliters of CCl_4 were added to a portion of the acidified solution from the fusion, and the mixture was shaken with chlorine water. A violet color appeared in the CCl_4 layer. Which compound or compounds of (a) are still possible? (c) How would each of the other possibilities have responded in (b)?

26. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, etc. Where necessary, make use of Table 18.1, p. 580.

(a)	b.p., °C		b.p., °C
n-decane	174	*p*-cymene (*p*-isopropyltoluene)	177
4-methylcyclohexanol	174	limonene (see Problem 17, page 317)	178
1,3-dichloro-2-propanol	176	*n*-heptyl bromide	180

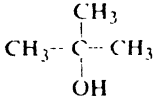
(b)

(c)

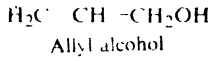
Chapter 15 Alcohols I. Preparation and Physical Properties

15.1 Structure

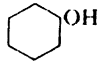
Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group. The group may be primary, secondary, or tertiary; it may be open-chain or cyclic; it may contain a double bond, a halogen atom, or an aromatic ring. For example:



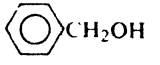
tert-Butyl alcohol



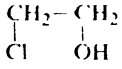
Allyl alcohol



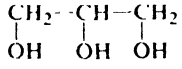
Cyclohexanol



Benzyl alcohol



Ethylene chlorohydrin
(β-Chloroethyl alcohol)



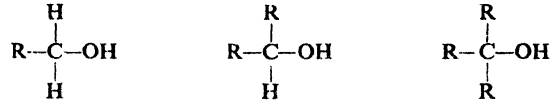
Glycerol

All alcohols contain the hydroxyl (—OH) group, which, as the functional group, determines the properties characteristic of this family. Variations in structure of the R group may affect the rate at which the alcohol undergoes certain reactions, and even, in a few cases, may affect the kind of reaction.

Compounds in which the hydroxyl group is attached directly to an aromatic ring are not alcohols; they are *phenols*, and differ so markedly from the alcohols that we shall consider them in a separate chapter.

15.2 Classification

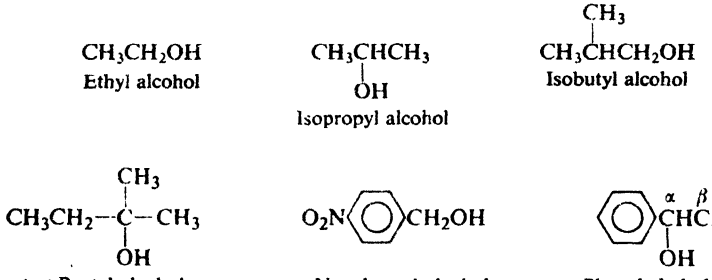
We classify a carbon atom as *primary*, *secondary*, or *tertiary* according to the number of other carbon atoms attached to it (Sec. 3.11). An alcohol is classified according to the kind of carbon that bears the —OH group:



One reaction, oxidation, which directly involves the hydrogen atoms attached to the carbon bearing the —OH group, takes an entirely different course for each class of alcohol. Usually, however, alcohols of different classes differ only in *rate* or *mechanism* of reaction, and in a way consistent with their structures. Certain substituents may affect reactivity in such a way as to make an alcohol of one class resemble the members of a different class; benzyl alcohol, for example, though formally a primary alcohol, often acts like a tertiary alcohol. We shall find that these variations, too, are consistent with the structures involved.

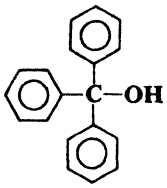
15.3 Nomenclature

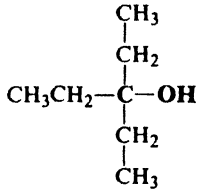
Alcohols are named by three different systems. For the simpler alcohols the **common names**, which we have already encountered (Sec. 5.19), are most often used. These consist simply of the name of the alkyl group followed by the word *alcohol*. For example:

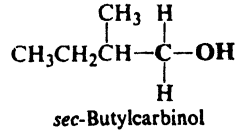


We should notice that similar names do not always mean the same classification; for example, isopropyl alcohol is a secondary alcohol, whereas isobutyl alcohol is a primary alcohol.

It is sometimes convenient to name alcohols by the **carbinol** system. According to this system, alcohols are considered to be derived from *methyl alcohol*, CH_3OH, by the replacement of one or more hydrogen atoms by other groups. We simply name the groups attached to the carbon bearing the —OH and then add the suffix *-carbinol* to include the C—OH portion:


Triphenylcarbinol


Triethylcarbinol

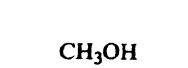

sec-Butylcarbinol

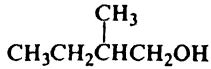
Finally, there is the most versatile system, the **IUPAC**. The rules are:

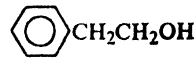
(1) Select as the parent structure the longest continuous carbon chain *that contains the —OH group*; then consider the compound to have been derived from this structure by replacement of hydrogen by various groups. The parent structure is known as *ethanol, propanol, butanol,* etc., depending upon the number of carbon atoms; each name is derived by replacing the terminal *-e* of the corresponding alkane name by **-ol**.

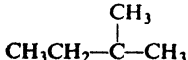
(2) Indicate by a number the position of the —OH group in the parent chain, generally using the lowest possible number for this purpose.

(3) Indicate by numbers the positions of other groups attached to the parent chain.

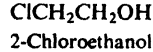

Methanol

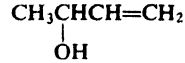

2-Methyl-1-butanol


2-Phenylethanol

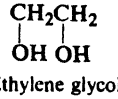

2-Methyl-2-butanol

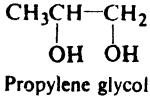

3-Methyl-2-butanol

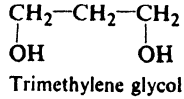

2-Chloroethanol

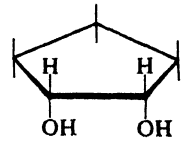

3-Buten-2-ol

Alcohols containing two hydroxyl groups are called *glycols*. They have both common names and IUPAC names.


Ethylene glycol
1,2-Ethanediol


Propylene glycol
1,2-Propanediol


Trimethylene glycol
1,3-Propanediol


cis-1,2-Cyclopentanediol

15.4 Physical properties

The compounds we have studied so far, the various hydrocarbons, are non-polar or nearly so, and have the physical properties that we might expect of such compounds: the relatively low melting points and boiling points that are characteristic of molecules with weak intermolecular forces; solubility in non-polar solvents and insolubility in polar solvents like water.

Alcohols, in contrast, contain the very polar —OH group. In particular, this group contains hydrogen attached to the very electronegative element, oxygen, and therefore permits hydrogen bonding (Sec. 1.19). The physical properties (Table 15.1) show the effects of this hydrogen bonding.

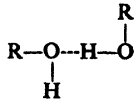


Table 15.1 ALCOHOLS

Name	Formula	M.p., °C	B.p., °C	Density at 20°C	Solub., g/100 g H_2O
Methyl	CH_3OH	− 97	64.5	0.793	∞
Ethyl	CH_3CH_2OH	−115	78.3	.789	∞
n-Propyl	$CH_3CH_2CH_2OH$	−126	97	.804	∞
n-Butyl	$CH_3(CH_2)_2CH_2OH$	− 90	118	.810	7.9
n-Pentyl	$CH_3(CH_2)_3CH_2OH$	− 78.5	138	.817	2.3
n-Hexyl	$CH_3(CH_2)_4CH_2OH$	− 52	156.5	.819	0.6
n-Heptyl	$CH_3(CH_2)_5CH_2OH$	− 34	176	.822	0.2
n-Octyl	$CH_3(CH_2)_6CH_2OH$	− 15	195	.825	0.05
n-Decyl	$CH_3(CH_2)_8CH_2OH$	6	228	.829	
n-Dodecyl	$CH_3(CH_2)_{10}CH_2OH$	24			
n-Tetradecyl	$CH_3(CH_2)_{12}CH_2OH$	38			
n-Hexadecyl	$CH_3(CH_2)_{14}CH_2OH$	49			
n-Octadecyl	$CH_3(CH_2)_{16}CH_2OH$	58.5			
Isopropyl	$CH_3CHOHCH_3$	− 86	82.5	.789	∞
Isobutyl	$(CH_3)_2CHCH_2OH$	−108	108	.802	10.0
sec-Butyl	$CH_3CH_2CHOHCH_3$	−114	99.5	.806	12.5
tert-Butyl	$(CH_3)_3COH$	25.5	83	.789	∞
Isopentyl	$(CH_3)_2CHCH_2CH_2OH$	−117	132	.813	2
active-Amyl	(−)-$CH_3CH_2CH(CH_3)CH_2OH$		128	.816	3.6
tert-Pentyl	$CH_3CH_2C(OH)(CH_3)_2$	− 12	102	.809	12.5
Cyclopentanol	*cyclo*-C_5H_9OH		140	.949	
Cyclohexanol	*cyclo*-$C_6H_{11}OH$	24	161.5	.962	
Allyl	$CH_2{=}CHCH_2OH$	−129	97	.855	∞
Crotyl	$CH_3CH{=}CHCH_2OH$		118	.853	16.6
Methylvinyl-carbinol	$CH_2{=}CHCHOHCH_3$		97		
Benzyl	$C_6H_5CH_2OH$	− 15	205	1.046	4
α-Phenylethyl	$C_6H_5CHOHCH_3$		205	1.013	
β-Phenylethyl	$C_6H_5CH_2CH_2OH$	− 27	221	1.02	1.6
Diphenylcarbinol (Benzhydrol)	$(C_6H_5)_2CHOH$	69	298		0.05
Triphenylcarbinol	$(C_6H_5)_3COH$	162.5			
Cinnamyl	$C_6H_5CH{=}CHCH_2OH$	33	257.5		
Ethylene glycol	CH_2OHCH_2OH	− 16	197	1.113	
Propylene glycol	$CH_3CHOHCH_2OH$		187	1.040	
1,3-Propanediol	$HOCH_2CH_2CH_2OH$		215	1.060	
Glycerol	$HOCH_2CHOHCH_2OH$	18	290	1.261	
Pentaerythritol	$C(CH_2OH)_4$	260			6

Let us look first at **boiling points**. Among hydrocarbons the factors that determine boiling point seem to be chiefly molecular weight and shape; this is to be expected of molecules that are held together chiefly by van der Waals forces. Alcohols, too, show increase in boiling point with increasing carbon number, and decrease in boiling point with branching. But the unusual thing about alcohols is that they boil so *high*: as Table 15.2 shows, much higher than hydrocarbons of the same molecular weight, and higher, even, than many other compounds of considerable polarity. How are we to account for this?

Table 15.2 STRUCTURE AND BOILING POINT

Name	Structure	Mol. Wt.	Dipole Moment, D	B.p., °C
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	72	0	36
Ethyl ether	$CH_3CH_2—O—CH_2CH_3$	74	1.18	35
n-Propyl chloride	$CH_3CH_2CH_2Cl$	79	2.10	47
n-Butyraldehyde	$CH_3CH_2CH_2CHO$	72	2.72	76
n-Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	74	1.63	118

The answer is, of course, that alcohols, like water, are *associated liquids*: their abnormally high boiling points are due to the greater energy needed to break the hydrogen bonds that hold the molecules together. Although ethers and aldehydes contain oxygen, they contain hydrogen that is bonded only to carbon; these hydrogens are not positive enough to bond appreciably with oxygen.

Infrared spectroscopy (Sec. 13.4) has played a key role in the study of hydrogen bonding. In dilute solution in a non-polar solvent like carbon tetrachloride (or in the gas phase), where association between molecules is minimal, ethanol, for example, shows an O—H stretching band at 3640 cm^{-1}. As the concentration of ethanol is increased, this band is gradually replaced by a broader band at 3350 cm^{-1}. The bonding of hydrogen to the second oxygen weakens the O—H bond, and lowers the energy and hence the frequency of vibration.

Problem 15.1 The infrared spectrum of *cis*-1,2-cyclopentanediol has an O—H stretching band at a lower frequency than for a free —OH group, and this band does not disappear even at high dilution. *trans*-1,2-Cyclopentanediol shows no such band. Can you suggest a possible explanation?

Problem 15.2 It has been suggested that there is weak hydrogen bonding: (a) between chloroform molecules; (b) between HCN molecules. How would you account for this? (*Hint:* See Sec. 8.10.)

The solubility behavior of alcohols also reflects their ability to form hydrogen bonds. In sharp contrast to hydrocarbons, the lower alcohols are miscible with water. Since alcohol molecules are held together by the same sort of intermolecular forces as water molecules, there can be mixing of the two kinds of molecules: the energy required to break a hydrogen bond between two water molecules or two alcohol molecules is provided by formation of a hydrogen bond between a water molecule and an alcohol molecule.

This is true, however, only for the lower alcohols, where the —OH group constitutes a large portion of the molecule. A long aliphatic chain with a small

—OH group at one end is mostly alkane, and its physical properties show this. The change in solubility with carbon number is a gradual one: the first three primary alcohols are miscible with water; *n*-butyl alcohol is soluble to the extent of 8 g per 100 g water; *n*-pentyl, 2 g; *n*-hexyl, 1 g; and the higher alcohols still less. For practical purposes we consider that the borderline between solubility and insolubility in water occurs at about four to five carbon atoms for normal primary alcohols.

Polyhydroxy alcohols provide more than one site per molecule for hydrogen bonding, and their properties reflect this. The simplest glycol, ethylene glycol, boils at 197°. The lower glycols are miscible with water, and those containing as many as seven carbon atoms show appreciable solubility in water. (Ethylene glycol owes its use as an antifreeze—e.g. Prestone—to its high boiling point, low freezing point, and high solubility in water.)

Problem 15.3 The disaccharide *sucrose*, $C_{12}H_{22}O_{11}$, is a big molecule and yet (it is ordinary table sugar) is extremely soluble in water. What might you guess about its structure? (Check your answer on p. 1119.)

Problem 15.4 How do you account for the fact that, although ethyl ether has a much lower boiling point than *n*-butyl alcohol, it has the same solubility (8 g per 100 g) in water?

15.5 Industrial source

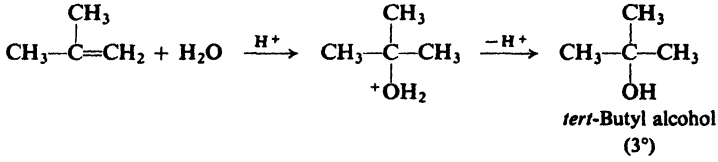
If an organic chemist were allowed to choose ten aliphatic compounds with which to be stranded on a desert island, he would almost certainly pick alcohols. From them he could make nearly every other kind of aliphatic compound: alkenes, alkyl halides, ethers, aldehydes, ketones, acids, esters, and a host of others. From the alkyl halides, he could make Grignard reagents, and from the reaction between these and the aldehydes and ketones obtain more complicated alcohols and so on. Our stranded chemist would use his alcohols not only as raw materials but frequently as the solvents in which reactions are carried out and from which products are recrystallized.

For alcohols to be such important starting materials in aliphatic chemistry, they must be not only versatile in their reactions but also available in large amounts and at low prices. There are two principal ways to get the simple alcohols that are the backbone of aliphatic organic synthesis: by **hydration of alkenes** obtained from the cracking of petroleum, and by **fermentation of carbohydrates**. In addition to these two chief methods, there are some others that have more limited application. (See Fig. 15.1.)

(a) Hydration of alkenes. We have already seen (Sec. 3.31) that alkenes containing up to four or five carbon atoms can be separated from the mixture obtained from the cracking of petroleum. We have also seen (Secs. 6.8 and 6.9) that alkenes are readily converted into alcohols either by direct addition of water, or by addition of sulfuric acid followed by hydrolysis. By this process there can

$$CH_3{-}CH{=}CH_2 + H_2SO_4 \longrightarrow CH_3{-}\underset{\displaystyle OSO_3H}{\underset{|}{CH}}{-}CH_3 \xrightarrow{H_2O} CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3$$

Isopropyl alcohol (2°)



be obtained only those alcohols whose formation is consistent with the application of Markovnikov's rule: for example, isopropyl but not *n*-propyl, *sec*-butyl but not *n*-butyl, *tert*-butyl but not isobutyl. Thus the *only* primary alcohol obtainable in this way is ethyl alcohol.

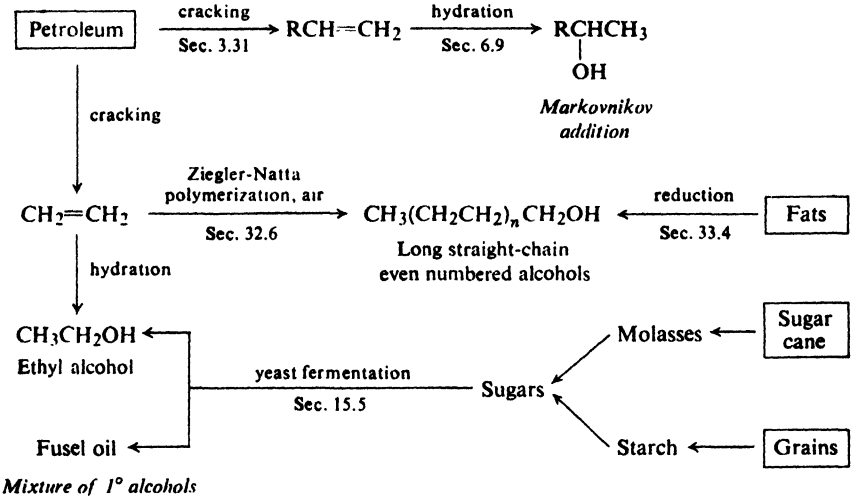


Figure 15.1. Industrial sources of alcohols.

(b) Fermentation of carbohydrates. Fermentation of sugars by yeast, the oldest synthetic chemical process used by man, is still of enormous importance for the preparation of **ethyl alcohol** and certain other alcohols. The sugars come from a variety of sources, mostly molasses from sugar cane, or starch obtained from various grains; the name "grain alcohol" has been given to ethyl alcohol for this reason.

When starch is the starting material, there is obtained, in addition to ethyl alcohol, a smaller amount of *fusel oil* (German: *Fusel*, inferior liquor), a mixture of primary alcohols: mostly isopentyl alcohol with smaller amounts of *n*-propyl alcohol, isobutyl alcohol, and 2-methyl-1-butanol, known as *active amyl alcohol* (*amyl* = *pentyl*).

Problem 15.5 The isopentyl and active amyl alcohols are formed by enzymatic transformation of the amino acids *leucine* and *isoleucine*, which come from hydrolysis of protein material in the starch.

(a) Which amino acid gives which alcohol? (b) Although both amino acids are optically active, and the transformation processes are analogous, only one gives an alcohol that is optically active. Why is this?

15.6 Ethyl alcohol

Ethyl alcohol is not only the oldest synthetic organic chemical used by man, but it is also one of the most important.

In industry ethyl alcohol is widely used as a solvent for lacquers, varnishes, perfumes, and flavorings; as a medium for chemical reactions; and in recrystallizations. In addition, it is an important raw material for synthesis; after we have learned more about the reactions of alcohols (Chap. 16), we can better appreciate the role played by the leading member of the family. For these industrial purposes ethyl alcohol is prepared both by hydration of ethylene and by fermentation of sugar from molasses (or sometimes starch); thus its ultimate source is petroleum, sugar cane, and various grains.

Ethyl alcohol is the alcohol of "alcoholic" beverages. For this purpose it is prepared by fermentation of sugar from a truly amazing variety of vegetable sources. The particular beverage obtained depends upon what is fermented (rye or corn, grapes or elderberries, cactus pulp or dandelions), how it is fermented (whether carbon dioxide is allowed to escape or is bottled up, for example), and what is done after fermentation (whether or not it is distilled). The special flavor of a beverage is not due to the ethyl alcohol but to other substances either characteristic of the particular source, or deliberately added.

Medically, ethyl alcohol is classified as a *hypnotic* (sleep producer); it is less toxic than other alcohols. (Methanol, for example, is quite *poisonous*: drinking it, breathing it for prolonged periods, or allowing it to remain long on the skin can lead to blindness or death.)

Because of its unique position as both a highly taxed beverage and an important industrial chemical, ethyl alcohol poses a special problem: it must be made available to the chemical industry in a form that is unfit to drink. This problem is solved by addition of a *denaturant*, a substance that makes it unpalatable or even poisonous. Two of the eighty-odd legal denaturants, for example, are methanol and high-test gasoline. When necessary, pure undenatured ethyl alcohol is available for chemical purposes, but its use is strictly controlled by the Federal Government.

Except for alcoholic beverages, nearly all the ethyl alcohol used is a mixture of 95% alcohol and 5% water, known simply as *95% alcohol.* What is so special about the concentration of 95%? Whatever the method of preparation, ethyl alcohol is obtained first mixed with water; this mixture is then concentrated by fractional distillation. But it happens that the component of lowest boiling point is not ethyl alcohol (b.p. 78.3°) but a *binary azeotrope* containing 95% alcohol and 5% water (b.p. 78.15°). As an azeotrope, it of course gives a vapor of the same composition, and hence cannot be further concentrated by distillation no matter how efficient the fractionating column used.

Pure ethyl alcohol is known as *absolute alcohol.* Although more expensive than 95% alcohol, it is available for use when specifically required. It is obtained by taking advantage of the existence of another azeotrope, this time a *ternary* one of b.p. 64.9°: 7.5% water, 18.5% ethyl alcohol, and 74% benzene.

Problem 15.6 Describe exactly what will happen if one distills a mixture of 150 g of 95% alcohol and 74 g of benzene.

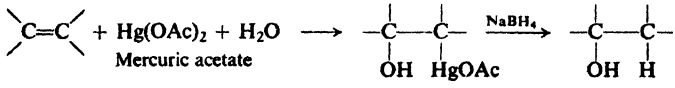
For certain special purposes (Secs. 26.2 and 26.3) even the slight trace of water found in commercial absolute alcohol must be removed. This can be accomplished by treatment of the alcohol with metallic magnesium; water is converted into insoluble $Mg(OH)_2$, from which the alcohol is then distilled.

15.7 Preparation of alcohols

Most of the simple alcohols and a few of the complicated ones are available from the industrial sources described in Sec. 15.5. Other alcohols must be prepared by one of the methods outlined below.

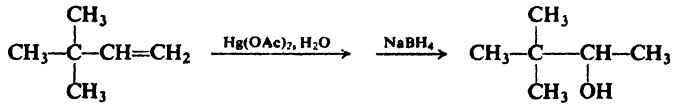
PREPARATION OF ALCOHOLS

1. Oxymercuration-demercuration. Discussed in Sec. 15.8.



Markovnikov addition

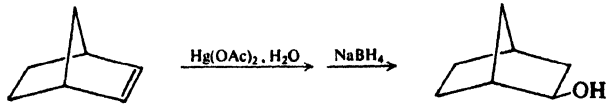
Examples:



3,3-Dimethyl-1-butene

3,3-Dimethyl-2-butanol

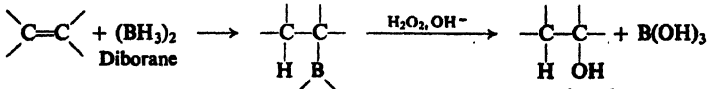
No rearrangement



Norbornene

exo-Norborneol

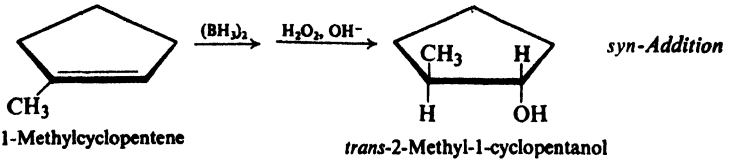
2. Hydroboration-oxidation. Discussed in Secs. 15.9–15.11.



Alkylborane

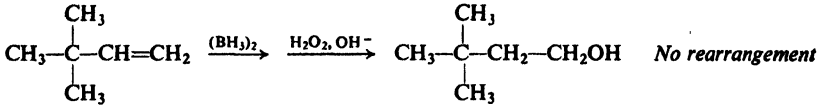
Anti-Markovnikov orientation

Examples:



1-Methylcyclopentene

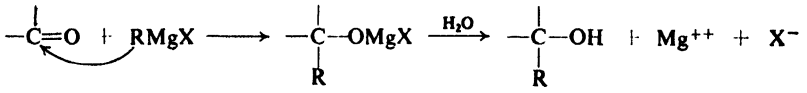
trans-2-Methyl-1-cyclopentanol

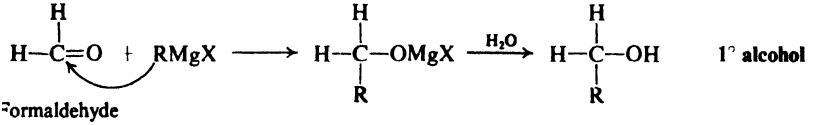


3,3-Dimethyl-1-butene

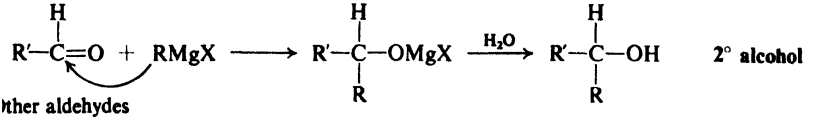
3,3-Dimethyl-1-butanol

3. Grignard synthesis. Discussed in Secs. 15.12–15.15.

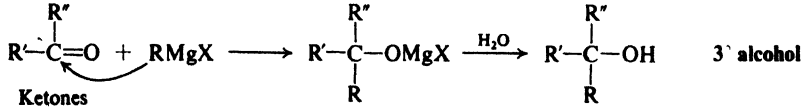




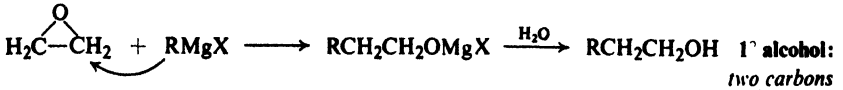
Formaldehyde



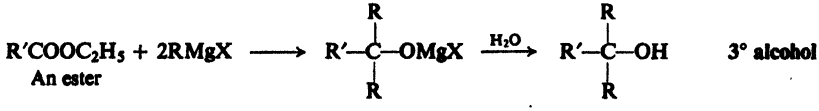
Other aldehydes



Ketones



Ethylene oxide

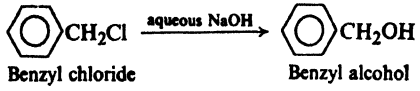


Discussed in Sec. 20.21.

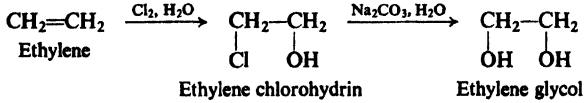
4. **Hydrolysis of alkyl halides.** Discussed in Sec. 15.7.

$$R{-}X + OH^- \text{ (or } H_2O) \longrightarrow R{-}OH + X^- \text{ (or HX)}$$

Examples:



Benzyl chloride — Benzyl alcohol



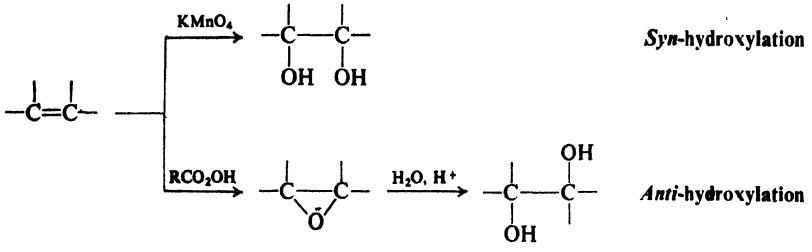
Ethylene — Ethylene chlorohydrin — Ethylene glycol

5. **Aldol condensation.** Discussed in Sec. 21.7.

6. **Reduction of carbonyl compounds.** Discussed in Sec. 19.10.

7. **Reduction of acids and esters.** Discussed in Secs. 18.18 and 20.22.

8. **Hydroxylation of alkenes.** Discussed in Secs. 6.20 and 17.12.

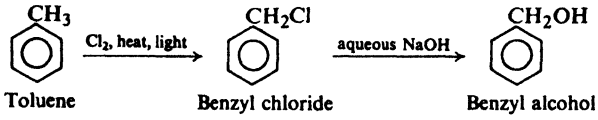


We can follow either of two approaches to the synthesis of alcohols—or, for that matter, of most other kinds of compounds. (a) We can retain the original carbon skeleton, and simply convert one functional group into another until we arrive at an alcohol; or (b) we can generate a new, bigger carbon skeleton and at the same time produce an alcohol.

By far the most important method of preparing alcohols is the **Grignard synthesis.** This is an example of the second approach, since it leads to the formation of carbon–carbon bonds. In the laboratory a chemist is chiefly concerned with preparing the more complicated alcohols that he cannot buy; these are prepared by the Grignard synthesis from rather simple starting materials. The alkyl halides from which the Grignard reagents are made, as well as the aldehydes and ketones themselves, are most conveniently prepared from alcohols; thus the method ultimately involves the synthesis of alcohols from less complicated alcohols.

Alcohols can be conveniently made from compounds containing carbon–carbon double bonds in two ways; by **oxymercuration-demercuration** and by **hydroboration-oxidation.** Both amount to addition of water to the double bond, but with *opposite orientation*—Markovnikov and anti-Markovnikov—and hence the two methods neatly complement each other.

Hydrolysis of alkyl halides is severely limited as a method of synthesizing alcohols, since alcohols are usually more available than the corresponding halides; indeed, the best general preparation of halides is from alcohols. The synthesis of benzyl alcohol from toluene, however, is an example of a useful application of this method.



For those halides that can undergo elimination, the formation of alkene must always be considered a possible side reaction.

Problem 15.7 Give structures of compounds A through D in the following industrially important synthesis.

$$CH_3CH{=}CH_2 + Cl_2 \xrightarrow{600^\circ} A\ (C_3H_5Cl)$$

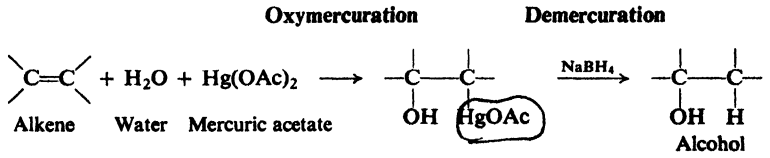
$$A + H_2O,\ OH^- \longrightarrow B\ (C_3H_6O)$$

$$B + Cl_2,\ H_2O \longrightarrow C\ (C_3H_7O_2Cl)$$

$$C + H_2O,\ OH^- \longrightarrow D\ (C_3H_8O_3)$$

15.8 Oxymercuration-demercuration

Alkenes react with mercuric acetate in the presence of water to give hydroxymercurial compounds which on reduction yield alcohols.

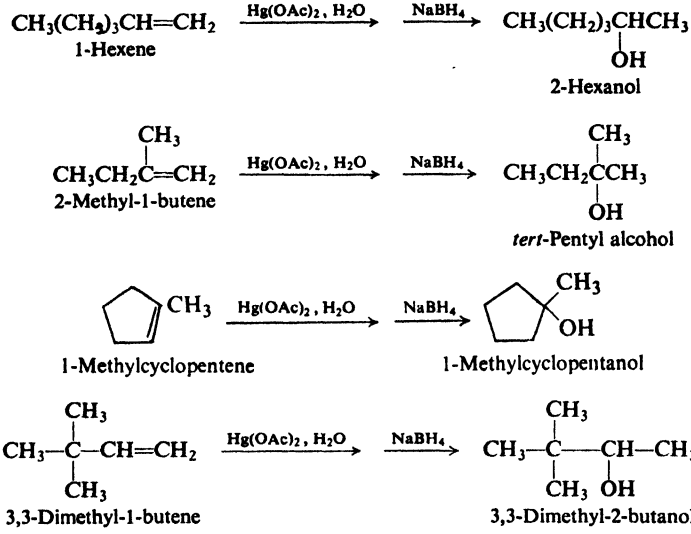


—OAc = CH_3COO—

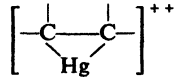
The first stage, *oxymercuration*, involves addition to the carbon–carbon double bond of —OH and —HgOAc. Then, in *demercuration*, the —HgOAc is replaced by —H. The reaction sequence amounts to hydration of the alkene, but is much more widely applicable than direct hydration.

The two-stage process of oxymercuration-demercuration is fast and convenient, takes place under mild conditions, and gives excellent yields—often over 90%. The alkene is added at room temperature to an aqueous solution of mercuric acetate diluted with the solvent tetrahydrofuran. Reaction is generally complete within minutes. The organomercurial compound is not isolated but is simply reduced *in situ* by sodium borohydride, $NaBH_4$. (The mercury is recovered as a ball of elemental mercury.)

Oxymercuration-demercuration is highly regiospecific, and gives alcohols corresponding to *Markovnikov* addition of water to the carbon–carbon double bond. For example:



Oxymercuration involves electrophilic addition to the carbon–carbon double bond, with the mercuric ion acting as electrophile. The absence of rearrangement and the high degree of stereospecificity (typically *anti*)—*in the oxymercuration step*—argues against an open carbonium ion as intermediate. Instead, it has been proposed, there is formed a cyclic *mercurinium ion*, analogous to the bromonium



and chloronium ions involved in the addition of halogens. In 1971, Olah (p. 160) reported spectroscopic evidence for the preparation of stable solutions of such mercurinium ions.

The mercurinium ion is attacked by the nucleophilic solvent—water, in the present case—to yield the addition product. This attack is back-side (unless prevented by some structural feature) and the net result is *anti* addition, as in the addition of halogens (Sec. 7.12). Attack is thus of the S_N2 type; yet the orientation of addition shows that the nucleophile becomes attached to the more highly substituted carbon—as though there were a free carbonium ion intermediate. As we shall see (Sec. 17.15), the transition state in reactions of such unstable three-membered rings has much S_N1 character.

Although the demercuration reaction is not really understood, free radicals have been proposed as intermediates. Whatever the mechanism, demercuration is generally not stereospecific and can, in certain special cases, be accompanied by rearrangement.

Despite the stereospecificity of the first stage, then, the overall process is not,

in general, stereospecific. Rearrangements *can* occur, but are not common. The reaction of 3,3-dimethyl-1-butene illustrates the absence of the rearrangements that are typical of intermediate carbonium ions.

Mercuration can be carried out in different solvents to yield products other than alcohols. This use of *solvomercuration* as a general synthetic tool is due largely to H. C. Brown (p. 507).

Problem 15.8 Predict the product of the reaction of styrene with mercuric acetate in methanol solution, followed by reduction with $NaBH_4$.

15.9 Hydroboration-oxidation

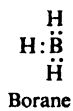
With the reagent *diborane*, $(BH_3)_2$, alkenes undergo *hydroboration* to yield alkylboranes, R_3B, which on oxidation give alcohols. For example:

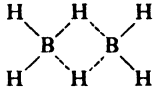
$$\underset{\text{Diborane}}{(BH_3)_2} \xrightarrow{H_2C{=}CH_2} CH_3CH_2BH_2 \xrightarrow{H_2C{=}CH_2} (CH_3CH_2)_2BH \xrightarrow{H_2C{=}CH_2} \underset{\text{Triethylboron}}{(CH_3CH_2)_3B}$$

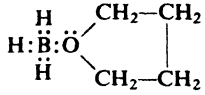
$$\underset{\text{Triethylboron}}{(CH_3CH_2)_3B} + \underset{\text{Hydrogen peroxide}}{3H_2O_2} \xrightarrow{OH^-} \underset{\text{Ethyl alcohol}}{3CH_3CH_2OH} + \underset{\text{Boric acid}}{3B(OH)_3}$$

The reaction procedure is simple and convenient, the yields are exceedingly high, and, as we shall see, the products are ones difficult to obtain from alkenes in any other way.

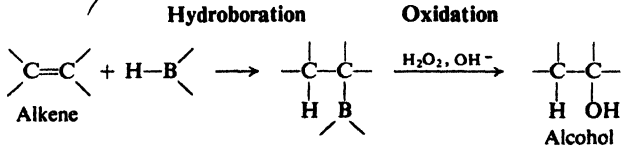
Diborane is the dimer of the hypothetical BH_3 (*borane*) and, in the reactions that concern us, acts much as though it were BH_3. Indeed, in tetrahydrofuran, one of the solvents used for hydroboration, the reagent exists as the monomer, in the form of an acid–base complex with the solvent.


Borane


Diborane


Borane-tetrahydrofuran complex

Hydroboration involves addition to the double bond of BH_3 (or, in following stages, BH_2R and BHR_2), with hydrogen becoming attached to one doubly-bonded carbon, and boron to the other. The alkylborane can then undergo oxidation, in which the boron is replaced by —OH (by a mechanism we shall encounter in Sec. 28.6).



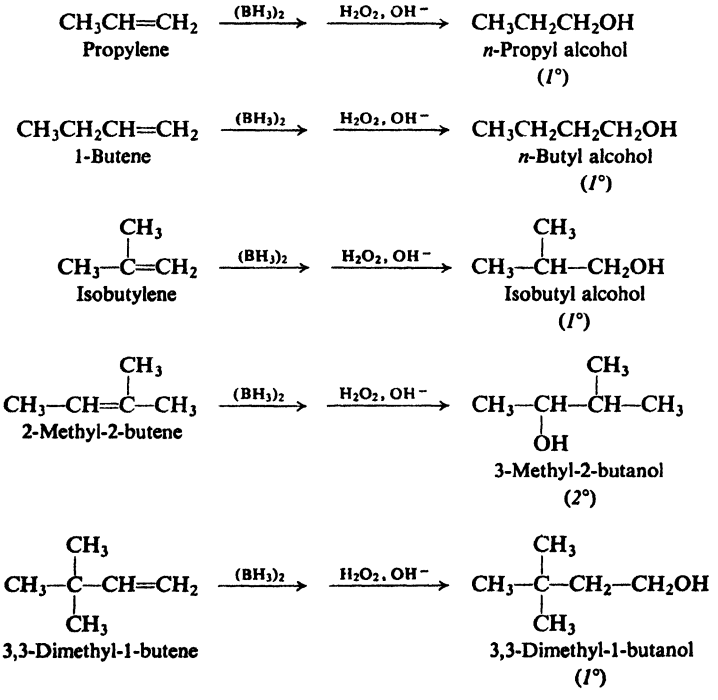
$$H{-}B\!\!\!\diagup\!\!\!\diagdown = H{-}BH_2,\ H{-}BHR,\ H{-}BR_2$$

Thus, the two-stage reaction process of hydroboration-oxidation permits, in effect, the addition to the carbon–carbon double bond of the elements of H—OH.

Reaction is carried out in an ether, commonly tetrahydrofuran or "diglyme" (*di*ethylene *gly*col *me*thyl ether, $CH_3OCH_2CH_2OCH_2CH_2OCH_3$). Diborane is commercially available in tetrahydrofuran solution. The alkylboranes are not isolated, but are simply treated *in situ* with alkaline hydrogen peroxide.

15.10 Orientation and stereochemistry of hydroboration

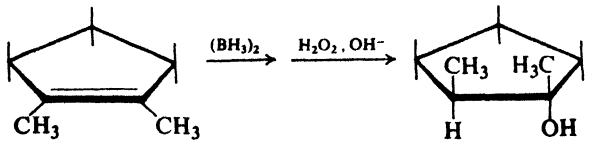
Hydroboration-oxidation, then, converts alkenes into alcohols. Addition is highly regiospecific; the preferred product here, however, is exactly *opposite* to the one formed by oxymercuration-demercuration or by direct acid-catalyzed hydration. For example:



The hydroboration-oxidation process gives products corresponding to **anti-Markovnikov** *addition of water to the carbon–carbon double bond.*

The reaction of 3,3-dimethyl-1-butene illustrates a particular advantage of the method. *Rearrangement does not occur in hydroboration*—evidently because carbonium ions are not intermediates—and hence the method can be used without the complications that often accompany other addition reactions.

The reaction of 1,2-dimethylcyclopentene illustrates the stereochemistry of the synthesis: *hydroboration-oxidation involves overall syn addition.*

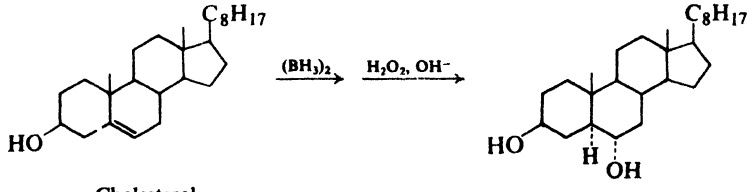


1,2-Dimethylcyclopentene *cis*-1,2-Dimethylcyclopentanol

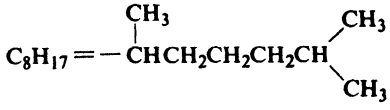
Through a combination of features of which we take up only three—orientation, stereochemistry, and freedom from rearrangements—hydroboration-oxidation gains its great synthetic utility: it gives a set of alcohols not obtainable from alkenes by other methods and, through these alcohols (Sec. 16.10), provides a convenient route to corresponding members of many chemical families.

We catch here a brief glimpse of just one of the many applications of hydroboration to organic synthesis that have been discovered by H. C. Brown (of Purdue University). Although generally recognized as an outstanding organic chemist, Professor Brown was originally trained as an inorganic chemist, in the laboratory of H. I. Schlesinger at the University of Chicago. It was in this laboratory—in the course of a search for volatile uranium compounds, during World War II—that lithium aluminum hydride and sodium borohydride (Sec. 19.10) were first made and their reducing properties first observed; and it was here that Brown's interest in borohydrides originated.

The examples we have used to show the fundamentals of hydroboration-oxidation have been, necessarily, simple ones. In practice, synthesis generally involves more complicated molecules, but the principles remain the same. For example:



Cholesterol Cholestane-3β,6α-diol



Problem 15.9 Predict the products of hydroboration-oxidation of: (a) *cis*-2-phenyl-2-butene; (b) *trans*-2-phenyl-2-butene; (c) 1-methylcyclohexene.

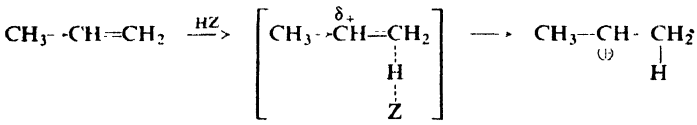
Problem 15.10 The stereochemistry of hydroboration-oxidation is the *net* result of the stereochemistry of the two steps, and is consistent with either of two combinations of stereochemistry for the individual steps. What are these two combinations?

15.11 Mechanism of hydroboration

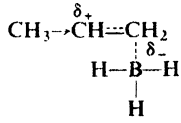
Much of the usefulness of hydroboration-oxidation lies in the "unusual" orientation of the hydration. The —OH simply takes the position occupied by

boron in the intermediate alkylborane, and hence the final product reflects the orientation of the hydroboration step. Is this orientation really "unusual"?

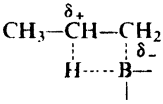
The orientation appears to be unusual because hydrogen adds to the opposite end of the double bond from where it adds in ordinary electrophilic addition. But the fundamental idea in electrophilic addition is that the *electrophilic* part of the reagent—the *acidic* part—becomes attached, using the π electrons, in such a way that the carbon being deprived of the π electrons is the one best able to stand the deprivation. Thus, with propylene as an example:



Now, what is the center of acidity in BH_3? Clearly, *boron*, with only six electrons. It is not at all surprising that boron should seek out the π electrons of the double bond and begin to attach itself to carbon. In doing this, it attaches itself in such a way that the positive charge can develop on the carbon best able to accommodate it. Thus:



Unlike ordinary electrophilic addition, however, the reaction does not proceed to give a carbonium ion. As the transition state is approached, the carbon that is losing the π electrons becomes itself increasingly acidic: electron-deficient boron is acidic but so, too, is electron-deficient carbon. Not too far away is a hydrogen atom held to boron by a pair of electrons. Carbon begins to take that hydrogen, with its electron pair; boron, as it gains the π electrons, is increasingly willing to release that hydrogen. Boron and hydrogen both add to the doubly-bonded carbons in the same transition state:



Transition state for hydroboration

In view of the basic nature of alkenes and the acidic nature of BH_3, the principal driving force of the reaction is almost certainly *attachment of boron to carbon.* In the transition state attachment of boron to C–1 has proceeded to a greater extent than attachment of hydrogen to C–2. Thus loss of (π) electrons by C–2 to the C_1–B bond exceeds its gain of electrons from hydrogen, and so C–2, the carbon that can best accommodate the charge, has become positive.

On theoretical grounds (Chap. 29) it has been postulated that the step we have described must follow a preliminary step in which boron attaches itself to both carbon atoms, or perhaps to the π electrons.

Thus orientation of addition in hydroboration is controlled in fundamentally the same way as in two-step electrophilic addition. Hydrogen becomes attached

to opposite ends of the double bond in the two reactions because it adds without electrons in one case (as a *proton*, an acid), and with electrons in the other case (as a *hydride ion*, a base).

Because of the Lowry-Brønsted treatment of acids and bases, we tend to think of hydrogen chiefly in its proton character. Actually, its hydride character has considerably more *reality*. Solid lithium hydride, for example, has an ionic crystalline lattice made up of Li^+ and H^-; by contrast, a naked unsolvated proton is not encountered by the organic chemist.

We are already familiar with the facile transfer of hydride from carbon to carbon: within a single molecule (hydride shift in rearrangements), and between molecules (abstraction by carbonium ion, Sec. 6.16). Later on we shall encounter a set of remarkably versatile reducing agents (hydrides like *lithium aluminum hydride*, $LiAlH_4$, and *sodium borohydride*, $NaBH_4$) that function by transfer of hydride ion to organic molecules.

Problem 15.11 Identify the acids and bases (Lewis or Lowry-Brønsted) in each of the following reactions:

(a) $Li^+H^- + H_2O \longrightarrow H_2 + Li^+OH^-$

(b) $(C_2H_5)_3B + NH_3 \longrightarrow (C_2H_5)_3\bar{B}:\overset{+}{N}H_3$

(c) $(BH_3)_2 + 2(CH_3)_3N \longrightarrow 2H_3\bar{B}:\overset{+}{N}(CH_3)_3$

(d) $2Li^+H + (BH_3)_2 \longrightarrow 2Li^+BH_4^-$

Problem 15.12 In light of the mechanism, what stereochemistry would you expect for the hydroboration step? On this basis, which of the two combinations in Problem 15.10 (p. 507) would be the correct one? What would the stereochemistry of the oxidation step be?

(Actually, the stereochemistry, worked out in a way we cannot go into here, is part of the basis for the mechanism, and not the other way around.)

15.12 Grignard synthesis of alcohols

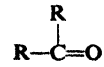
The Grignard reagent, we recall, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide (Sec. 3.16). This halide can be alkyl (1°, 2°, 3°), allylic, aralkyl (e.g., benzyl), or aryl (phenyl

$$RX + Mg \xrightarrow{\text{anhydrous ether}} \underset{\substack{\text{A Grignard}\\ \text{reagent}}}{RMgX}$$

or substituted phenyl). The halogen may be —Cl, —Br or —I. (Arylmagnesium *chlorides* must be made in the cyclic ether tetrahydrofuran instead of ethyl ether.)

One of the most important uses of the Grignard reagent is its reaction with aldehydes and ketones to yield alcohols. Aldehydes and ketones have the general formulas:

An aldehyde



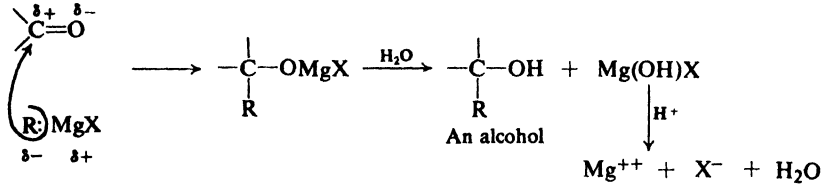
A ketone

The functional group of both is the **carbonyl group**, $-\overset{|}{C}=O$, and, as we shall see later (Chap. 19), aldehydes and ketones resemble each other closely in most of

their reactions. Like the carbon–carbon double bond, the carbonyl group is unsaturated, and like the carbon–carbon bond, it undergoes addition. One of its typical reactions is addition of the Grignard reagent.

Since the electrons of the carbonyl double bond hold together atoms of quite different electronegativity, we would not expect the electrons to be equally shared; in particular, the mobile π cloud should be pulled strongly toward the more electronegative atom, oxygen. Whatever the mechanism involved, addition of an unsymmetrical reagent is oriented so that the nucleophilic (basic) portion attaches itself to carbon, and the electrophilic (acidic) portion attaches itself to oxygen.

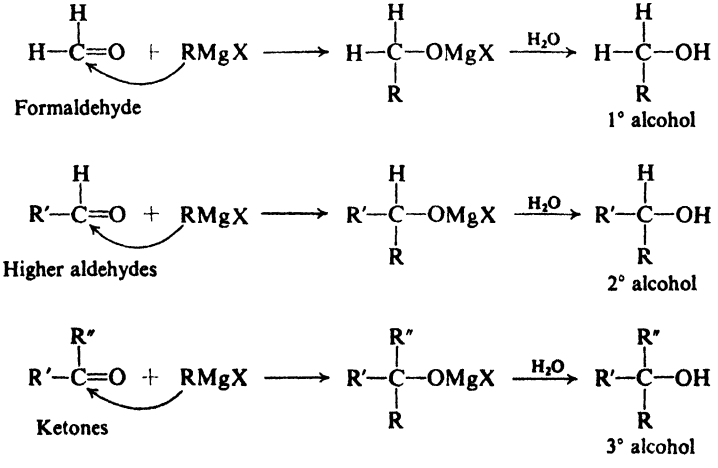
The carbon–magnesium bond of the Grignard reagent is a highly polar bond, carbon being negative relative to electropositive magnesium. It is not surprising, then, that in the addition to carbonyl compounds, the organic group becomes attached to carbon and magnesium to oxygen. The product is the magnesium



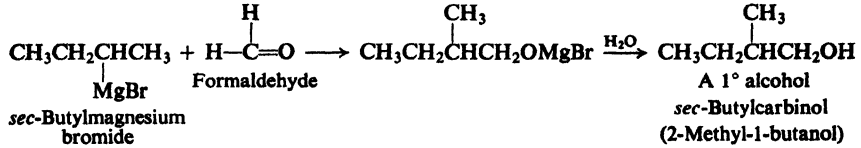
salt of the weakly acidic alcohol and is easily converted into the alcohol itself by the addition of the stronger acid, water. Since the Mg(OH)X thus formed is a gelatinous material difficult to handle, dilute mineral acid (HCl, H_2SO_4) is commonly used instead of water, so that water-soluble magnesium salts are formed.

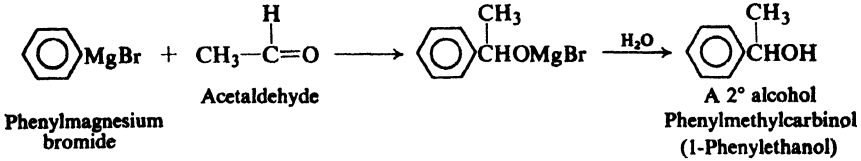
15.13 Products of the Grignard synthesis

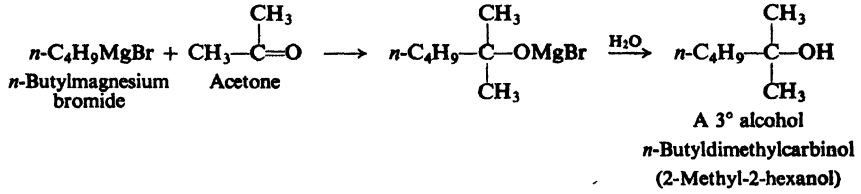
The class of alcohol that is obtained from a Grignard synthesis depends upon the type of carbonyl compound used: *formaldehyde*, HCHO, *yields primary alcohols; other aldehydes*, RCHO, *yield secondary alcohols; and ketones*, R_2CO, *yield tertiary alcohols.*



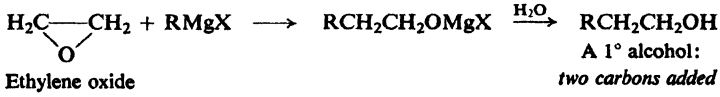
This relationship arises directly from our definitions of aldehydes and ketones, and our definitions of primary, secondary, and tertiary alcohols. The number of hydrogens attached to the carbonyl carbon defines the carbonyl compound as formaldehyde, higher aldehyde, or ketone. The carbonyl carbon is the one that finally bears the —OH group in the product; here the number of hydrogens defines the alcohol as primary, secondary, or tertiary. For example:



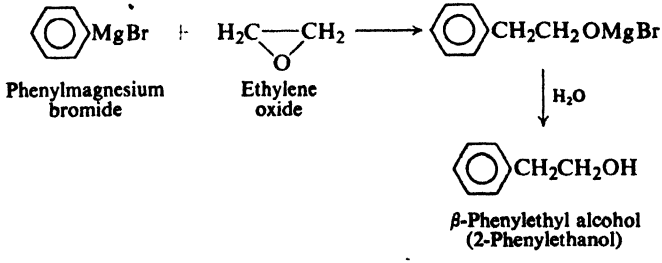




A related synthesis utilizes *ethylene oxide* (Sec. 17.14) to make *primary alcohols containing two more carbons* than the Grignard reagent. Here, too, the organic



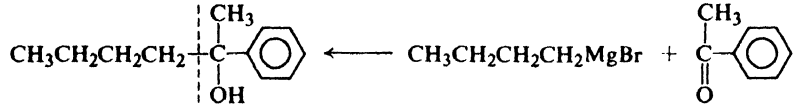
group becomes attached to carbon and magnesium to oxygen, this time with the breaking of a carbon–oxygen σ bond in the highly strained three-membered ring (Sec. 9.9). For example:



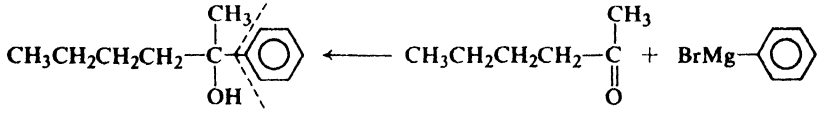
15.14 Planning a Grignard synthesis

How do we decide which Grignard reagent and which carbonyl compound to use in preparing a particular alcohol? We have only to look at the structure of the alcohol we want. Of the groups attached to the carbon bearing the —OH group, one must come from the Grignard reagent, the other two (including any hydrogens) must come from the carbonyl compound.

Most alcohols can be obtained from more than one combination of reagents; we usually choose the combination that is most readily available. Consider, the example, the synthesis of 2-phenyl-2-hexanol:



2-Phenyl-2-hexanol — *n*-Butylmagnesium bromide — Acetophenone



2-Phenyl-2-hexanol — Methyl *n*-butyl ketone — Phenylmagnesium bromide

As shown, we could make this either from the four-carbon Grignard reagent and the aromatic ketone, or from the phenyl Grignard reagent and the six-carbon aliphatic ketone. As we shall know when we have studied aldehydes and ketones (Chap. 19), the first route uses the more readily available carbonyl compound and is the one actually used to make this alcohol.

15.15 Limitations of the Grignard synthesis

The very reactivity that makes a Grignard reagent so useful strictly limits how we may use it. We must keep this reactivity in mind when we plan the experimental conditions of the synthesis, when we select the halide that is to become the Grignard reagent, and when we select the compound with which it is to react.

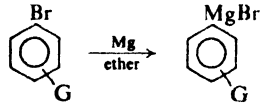
In our first encounter with the Grignard reagent (Sec. 3.16), we allowed it to react with water to form an alkane; the stronger acid, water, displaced the extremely weak acid, the alkane, from its salt. In the same way, *any* compound containing hydrogen attached to an electronegative element—oxygen, nitrogen, sulfur, or even triply-bonded carbon—is acidic enough to decompose a Grignard reagent. A Grignard reagent reacts rapidly with oxygen and carbon dioxide, and with nearly every organic compound containing a carbon–oxygen or carbon–nitrogen multiple bond.

How does all this affect our reaction between a Grignard reagent and, say, an aldehyde? First of all, alkyl halide, aldehyde, and the ether used as solvent must be scrupulously dried and freed of the alcohol from which each was very probably made; a Grignard reagent will not even form in the presence of water. Our apparatus must be completely dry before we start. We must protect the reaction

system from the water vapor, oxygen, and carbon dioxide of the air: water vapor can be kept out by use of calcium chloride tubes, and oxygen and carbon dioxide can be swept out of the system with dry nitrogen. Having done all this we may hope to obtain a good yield of product—providing we have properly chosen the halide and the aldehyde.

We cannot prepare a Grignard reagent from a compound (e.g., $HOCH_2CH_2Br$) that contains, in addition to halogen, some group (e.g., —OH) that will react with a Grignard reagent; if this were tried, as fast as a molecule of Grignard reagent formed it would react with the active group (—OH) in another molecule to yield an undesired product ($HOCH_2CH_2$—H).

We must be particularly watchful in the preparation of an arylmagnesium halide, in view of the wide variety of substituents that might be present on the benzene ring. Carboxyl (—COOH), hydroxyl (—OH), amino ($—NH_2$), and $—SO_3H$ all contain hydrogen attached to oxygen or nitrogen, and therefore are so acidic that they will decompose a Grignard reagent. We have just learned that a Grignard reagent adds to the carbonyl group (C=O), and we shall learn that it adds similarly to —COOR and —C≡N groups. The nitro ($—NO_2$) group oxidizes a Grignard reagent. It turns out that only a comparatively few groups may be present in the halide molecule from which we prepare a Grignard reagent; among these are —R, —Ar, —OR, and —Cl (of an aryl chloride).



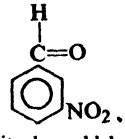
G *may not be.*

—COOH —C(=O)H
—OH —COOR
$—NH_2$ —C≡N
$—SO_3H$ $—NO_2$
and many others

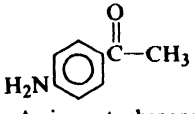
G *may be:*

—R —OR
—Ar(aryl) —Cl

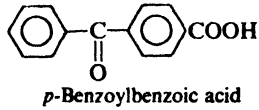
By the same token, the aldehyde (or other compound) with which a Grignard reagent is to react may not contain other groups that are reactive toward a Grignard reagent. For example, a Grignard reagent would be decomposed before it could add to the carbonyl group of:



m-Nitrobenzaldehyde



p-Aminoacetophenone

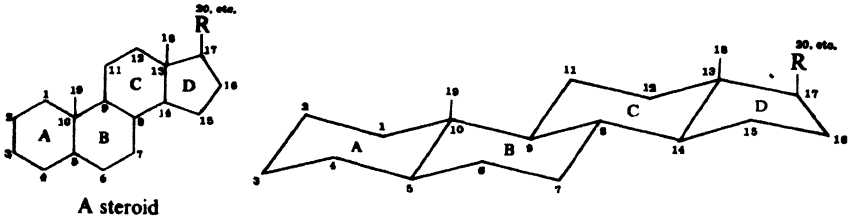


p-Benzoylbenzoic acid

These may seem like severe limitations, and they are. Nevertheless, the number of acceptable combinations is so great that the Grignard reagent is one of our most valuable synthetic tools. The kind of precautions described here must be taken in any kind of organic synthesis: we must not restrict our attention to the group we happen to be interested in, but must look for possible interference by other functional groups.

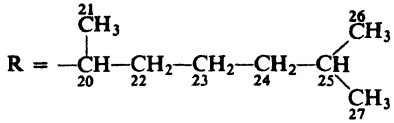
15.16 Steroids

Cholesterol (p. 507), notorious as the substance deposited on the walls of arteries and as the chief constituent of gallstones, is the kind of alcohol called a *sterol*. Sterols belong, in turn, to the class of compounds called **steroids**: compounds of the general formula

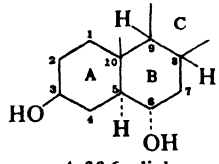


A steroid

The rings are (generally) aliphatic. Lines like the vertical ones attached to the 10- and 13-positions represent *angular methyl* groups. Commonly, in cholesterol, for example,



Stereochemistry is indicated by solid lines (β-bonds, coming *out* of the plane of the paper) and dotted lines (α-bonds, going *behind* the plane of the paper).

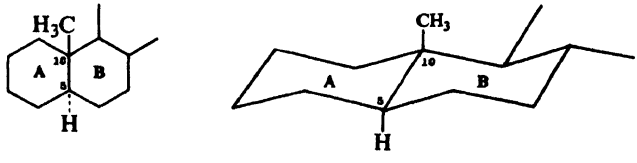


A 3β,6α-diol

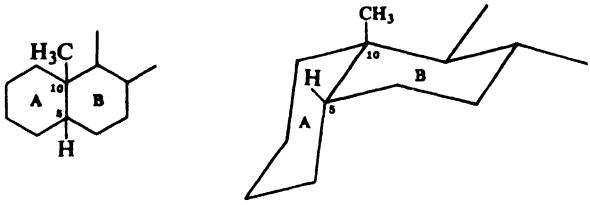
I

Thus in I the —H and —OH at the 5- and 6-positions are *cis* to each other, but *trans* to the 3-OH and to the angular methyl at the 10-position. Fusion of the rings to each other can be *cis* or *trans*, thus increasing the complications of the stereochemistry.

Finally, in any rigid cyclic system like this, conformational effects are marked, and often completely control the course of reaction.

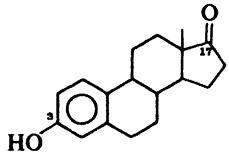


trans-Fusion



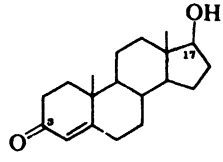
cis-Fusion

Steroids include sex hormones and adrenal cortical hormones (*cortisone* is one), cardiac glycosides, and bile acids. Because of their biological importance—and, undoubtedly, because of the fascinating complexity of the chemistry—the study of steroids has been, and is now, one of the most active areas of organic chemical research.



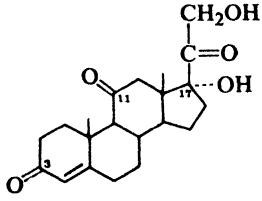
Estrone

An *estrogen*, or female sex hormone



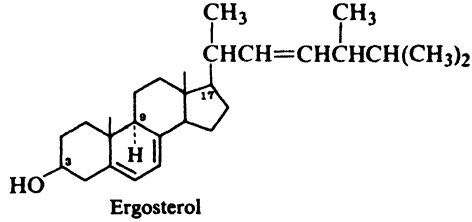
Testosterone

An *androgen*, or male sex hormone



Cortisone

An adrenocortical hormone



Ergosterol

A precursor of Vitamin D

PROBLEMS

1. (a) Ignoring enantiomerism, draw the structures of the eight isomeric pentyl alcohols, $C_5H_{11}OH$. (b) Name each by the IUPAC system and by the carbinol system. (c) Label each as primary, secondary, or tertiary. (d) Which one is isopentyl alcohol? *n*-Pentyl alcohol? *tert*-Pentyl alcohol? (e) Give the structure of a primary, a secondary, and a tertiary alcohol of the formula $C_6H_{13}OH$. (f) Give the structure of a primary, a secondary, and a tertiary *cyclic* alcohol of the formula C_5H_9OH.

2. Without referring to tables, arrange the following compounds in order of decreasing boiling point: (a) 3-hexanol; (b) *n*-hexane; (c) dimethyl-*n*-propylcarbinol; (d) *n*-octyl alcohol; (e) *n*-hexyl alcohol.

3. Looking at the beginning of each chapter for the structure involved, tell which families of compounds discussed in this book can: (a) form hydrogen bonds with other molecules of the same kind; (b) form hydrogen bonds with water.

4. Which compound would you expect to have the higher boiling point? (Check your answers in the proper tables.)

(a) *p*-cresol (*p*-$CH_3C_6H_4OH$) or anisole ($C_6H_5OCH_3$)

(b) methyl acetate, $CH_3C(=O)OCH_3$, or propionic acid, $CH_3CH_2C(=O)OH$

(c) propionic acid or *n*-pentyl alcohol.

5. Write equations to show how isopropyl alcohol might be prepared: (a) from an olefin; (b) from an alkyl halide; (c) by a Grignard reaction. (d) Which method is used industrially? Why?

6. Give structures of the Grignard reagent and the aldehyde or ketone that would react to yield each of the following alcohols. If more than one combination of reactants is possible, show each of the combinations.

(a) (h) each of the isomeric pentyl alcohols of Problem 1(a)
(i) 1-phenyl-1-propanol
(j) 2-phenyl-2-propanol
(k) 1-phenyl-2-propanol
(l) 3-phenyl-1-propanol
(m) 1-methylcyclohexanol
(n) cyclohexylcarbinol
(o) 1-cyclohexylethanol
(p) 2,4-dimethyl-3-pentanol
(q) 1-(*p*-tolyl)ethanol, *p*-$CH_3C_6H_4CHOHCH_3$
(r) triphenylcarbinol, $(C_6H_5)_3COH$

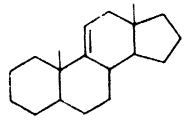
7. For many 2-substituted ethanols, GCH_2CH_2OH, the *gauche* conformation is more stable than the *anti*:

G = $-OH$, $-NH_2$, $-F$, $-Cl$, $-Br$, $-OCH_3$, $NHCH_3$, $-N(CH_3)_2$, and $-NO_2$.

How might this be accounted for?

8. (a) As shown on p. 507, cholesterol is converted into cholestane-3β,6α-diol through *cis*-hydration by hydroboration-oxidation. What stereoisomeric product could also have been formed by *cis*-hydration? Actually, the reaction gives a 78% yield of cholestane-3β,6α-diol, and only a small amount of its stereoisomer. What factor do you think is responsible for this particular stereospecificity? (*Hint:* See pp. 514–515.)

(b) Hydroboration of androst-9(11)-ene gives 90% of a single stereoisomer. Which would you expect this to be?

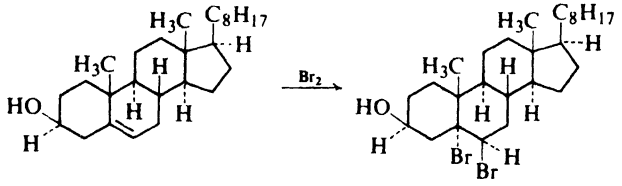


Androst-9(11)-ene

9. (a) Using models and then drawing formulas, show the possible chair conformations for *cis*-1,3-cyclohexanediol. (b) On the basis solely of 1,3-interaction, which would you expect to be the more stable conformation? (c) Infrared evidence indicates intramolecular hydrogen bonding in *cis*-1,3-cyclohexanediol. Just how would the infrared spectrum show this? Which conformation in (a) is indicated by this evidence, and what is the source of its stability?

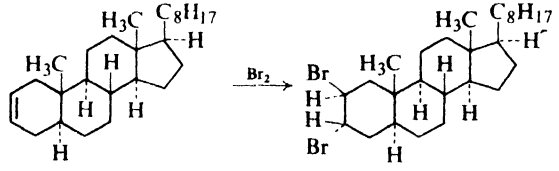
10. The infrared spectrum of the stereoisomer of 2,5-di-*tert*-butyl-1,4-cyclohexanediol in which all four substituents are *cis* to each other shows the presence of an intramolecular hydrogen bond. In what conformation does the molecule exist? (*Hint:* Use models.)

11. (a) What are the two diastereomeric products that could be formed by *anti*-addition of bromine to cholesterol? to 2-cholestene? (b) Actually, one product greatly predominates in each case, as shown:



Cholesterol

5α,6β-Dibromo-3β-hydroxycholestane
85% yield



2-Cholestene

2β,3α-Dibromocholestane
70% yield

How do you account for the observed stereochemistry? (It is *not* a matter of relative stability of the diastereomers.) (*Hint:* Consider carefully the stereochemical possibilities at each step of the mechanism.)

12. On treatment with a variety of reagents (water, acetylide ion), borate esters of the kind shown are converted into alkenes:

$$(RO)_2BCH_2CH_2Br \longrightarrow CH_2{=}CH_2$$

The *cis* and *trans* esters (I) were prepared, and their configurations were assigned by nmr. Each ester was treated with bromine, and the resulting dibromide was treated with water. *cis*-I gave only *trans*-II as the final product, and *trans*-I gave only *cis*-II.

$CH_3CH{=}C(CH_3)B(OR)_2$ — I (*cis* or *trans*)

$CH_3CH{=}CBrCH_3$ — II (*cis* or *trans*)

Making use of what you know about the addition of bromine to alkenes, what do you conclude about the stereochemistry of this elimination reaction? Show the most likely mechanism for the elimination, including the part played by water (or acetylide ion).