Organic chemistry IV

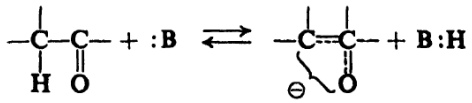
Chapter 21 Carbanions I

Aldol and Claisen Condensations

21.1 Acidity of α-hydrogens

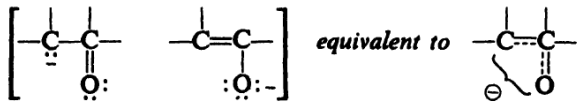
In our introduction to aldehydes and ketones, we learned that it is the carbonyl group that largely determines the chemistry of aldehydes and ketones. At that time, we saw in part how the carbonyl group does this: by providing a site at which nucleophilic addition can take place. Now we are ready to learn another part of the story: how the carbonyl group strengthens the acidity of the hydrogen atoms attached to the α-carbon and, by doing this, gives rise to a whole set of chemical reactions.

Ionization of an α-hydrogen,



I

yields a carbanion I that is a resonance hybrid of two structures II and III,



II III I

resonance that is possible only through participation by the carbonyl group. Resonance of this kind is *not* possible for carbanions formed by ionization of β-hydrogens, γ-hydrogens, etc., from saturated carbonyl compounds.

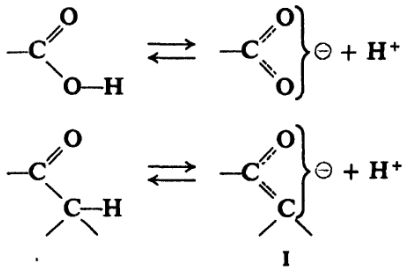
Problem 21.1 Which structure, II or III, would you expect to make the larger contribution to the carbanion I? Why?

Problem 21.2 Account for the fact that the diketone acetylacetone (2,4-pentanedione) is about as acidic as phenol, and much more acidic than, say, acetone. Which hydrogens are the most acidic?

Problem 21.3 How do you account for the following order of acidity?

$$(C_6H_5)_3CH > (C_6H_5)_2CH_2 > C_6H_5CH_3 > CH_4$$

The carbonyl group thus affects the acidity of α-hydrogens in just the way it affects the acidity of carboxylic acids: by helping to accommodate the negative charge of the anion.

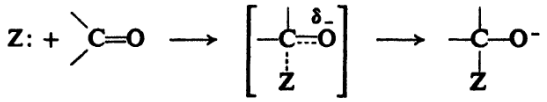


I

Resonance in I involves structures (II and III) of quite different stabilities, and hence is much less important than the resonance involving equivalent structures in a carboxylate ion. Compared with the hydrogen of a —COOH group, the α-hydrogen atoms of an aldehyde or ketone are very weakly acidic; the important thing is that they are considerably more acidic than hydrogen atoms anywhere else in the molecule, and that they are acidic enough for *significant*—even though very low—concentrations of carbanions to be generated.

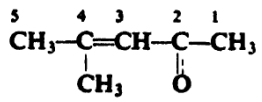
We shall use the term *carbanion* to describe ions like I since *part* of the charge is carried by carbon, even though the stability that gives these ions their importance is due to the very fact that most of the charge is *not* carried by carbon but by oxygen.

We saw before (Sec. 19.8) that the susceptibility of the carbonyl group to nucleophilic attack is due to the ability of oxygen to accommodate the negative charge that develops as a result of the attack,



precisely the same property of oxygen that underlies the acidity of α-hydrogens. We have started with two apparently unrelated chemical properties of carbonyl compounds and have traced them to a common origin—an indication of the simplicity underlying the seeming confusion of organic chemistry.

Problem 21.4 In the reaction of aqueous NaCN with an α,β-unsaturated ketone like



CN^- adds, not to C-2, but to C-4. (a) How do you account for this behavior?

(b) What product would you expect to isolate from the reaction mixture? (*Hint:* See Secs. 19.12 and 8.20.) (Check your answers in Sec. 27.5.)

21.2 Reactions involving carbanions

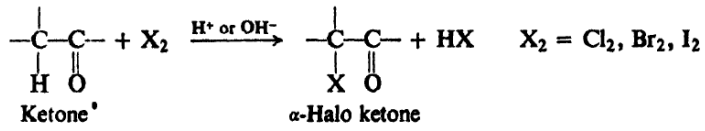
The carbonyl group occurs in compounds other than aldehydes and ketones—in esters, for example—and, wherever it is, it makes any α-hydrogens acidic and thus aids in formation of carbanions. Since these α-hydrogens are only weakly acidic, however, the carbanions are highly basic, exceedingly reactive particles. In their reactions they behave as we would expect: as *nucleophiles*. As nucleophiles, carbanions can attack carbon and, in doing so, form carbon–carbon bonds. *From the standpoint of synthesis, acid-strengthening by carbonyl groups is probably the most important structural effect in organic chemistry.*

We shall take up first the behavior of ketones toward the halogens, and see evidence that carbanions do indeed exist; at the same time, we shall see an elegant example of the application of kinetics, stereochemistry, and isotopic tracers to the understanding of reaction mechanisms. And while we are at it, we shall see something of the role that keto–enol tautomerism plays in the chemistry of carbonyl compounds.

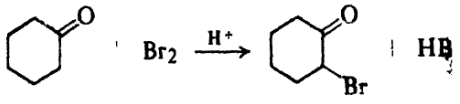
Next, we shall turn to reactions in which the carbonyl group plays *both* its roles: the *aldol condensation*, in which a carbanion generated from one molecule of aldehyde or ketone adds, as a nucleophile, to the carbonyl group of a second molecule; and the *Claisen condensation*, in which a carbanion generated from one molecule of ester attacks the carbonyl group of a second molecule, with acyl substitution as the final result.

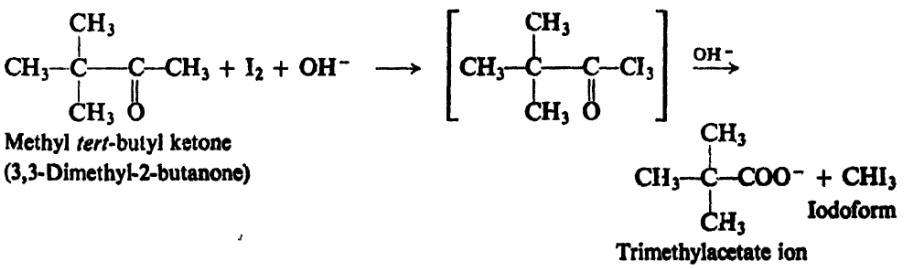
REACTIONS INVOLVING CARBANIONS

1. Halogenation of ketones. Discussed in Secs. 21.3–21.4.



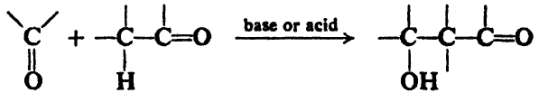
Examples:





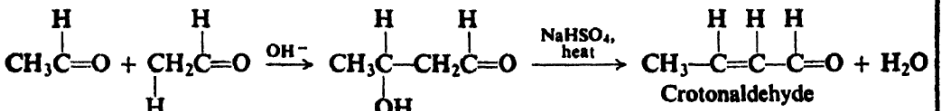
2. Nucleophilic addition to carbonyl compounds.

(a) Aldol condensation. Discussed in Secs. 21.5–21.8.

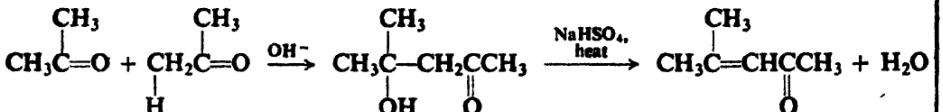


An aldol
(A β-hydroxy carbonyl compound)

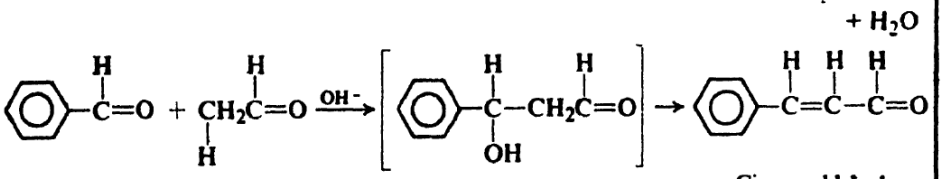
Examples:



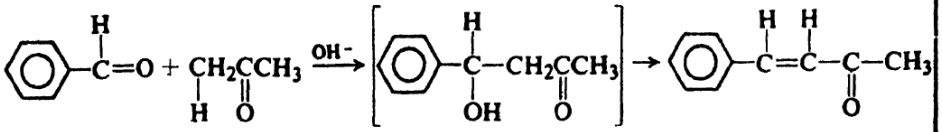
Acetaldehyde
2 moles
Acetaldol
(3-Hydroxybutanal)
Crotonaldehyde
(2-Butenal)



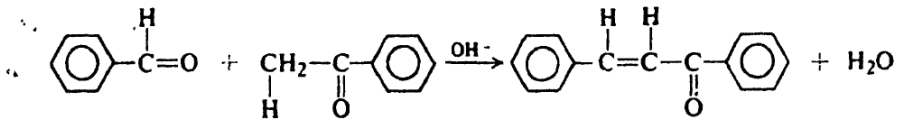
Acetone
2 moles
Diacetone alcohol
Mesityl oxide
(4-Methyl-3-penten-2-one)



Benzaldehyde
Acetaldehyde
Cinnamaldehyde
(3-Phenyl-2-propenal)



Benzaldehyde
Acetone
Benzalacetone
(*Benzal* is $C_6H_5CH=$)
(4-Phenyl-3-buten-2-one)



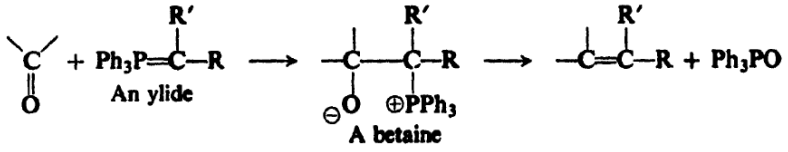
Benzaldehyde
Acetophenone
Benzalacetophenone
(1,3-Diphenyl-2-propen-1-one)

(b) Reactions related to aldol condensation. Discussed in Sec. 21.9.

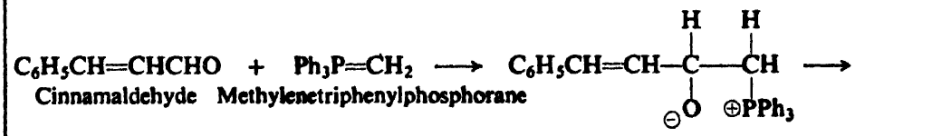
(c) Addition of Grignard reagents. Discussed in Sec. 19.11.

(d) Addition of organozinc compounds. Reformatsky reaction. Discussed in Sec. 21.13.

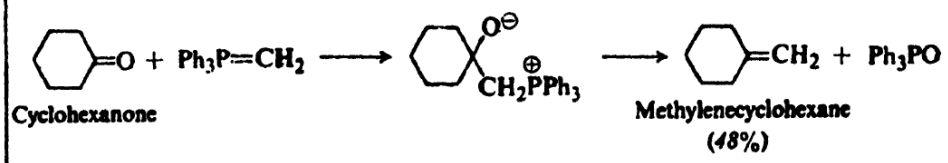
(e) **Wittig reaction.** Discussed in Sec. 21.10.



Examples:

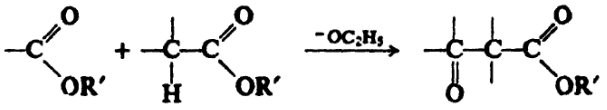


$C_6H_5CH{=}CH{-}CH{=}CH_2$
1-Phenyl-1,3-butadiene
(69%)

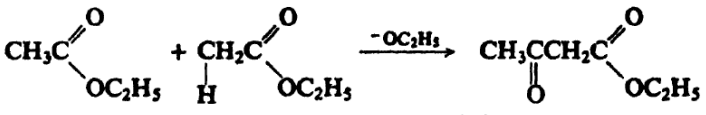


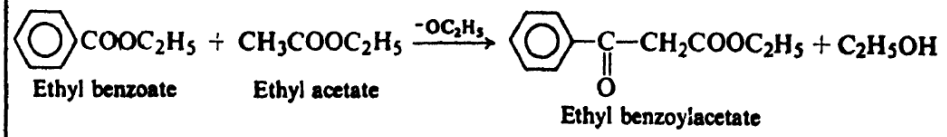
3. Nucleophilic acyl substitution.

(a) **Claisen condensation.** Discussed in Secs. 21.11–21.12.



Examples:





(b) **Acylation of organocadmium compounds.** Discussed in Sec. 19.7.

4. Nucleophilic aliphatic substitution.

(a) **Coupling of alkyl halides with organometallic compounds.** Discussed in Sec. 3.17.

(b) Synthesis of acetylides. Discussed in Sec. 8.12.

(c) Alkylation of malonic ester and acetoacetic ester. Discussed in Secs. 26.2–26.3.

5. Addition to α,β-unsaturated carbonyl compounds. Michael addition. Discussed in Sec. 27.7.

21.3 Base-promoted halogenation of ketones

Acetone reacts with bromine to form bromoacetone; the reaction is accelerated by bases (e.g., hydroxide ion, acetate ion, etc.). Study of the kinetics shows that

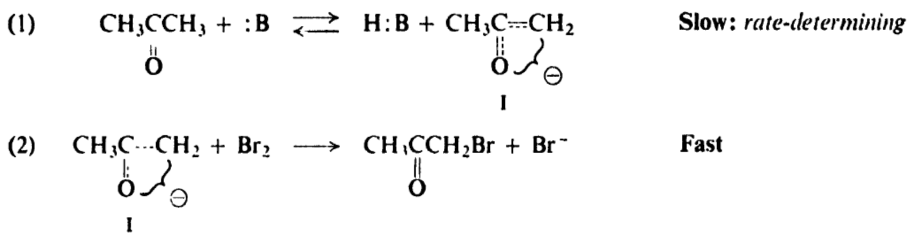
$$\underset{\text{Acetone}}{CH_3COCH_3} + Br_2 + :B \longrightarrow \underset{\text{Bromoacetone}}{CH_3COCH_2Br} + Br^- + H:B$$

the rate of reaction depends upon the concentration of acetone, [acetone], and of base, [:B], but is *independent of bromine concentration*:

$$\text{rate} = k\,[\text{acetone}][:B]$$

We have encountered this kind of situation before (Sec. 14.12) and know, in a general way, what it must mean: if the rate of reaction does not depend upon $[Br_2]$, it can only mean that the reaction *whose rate we are measuring* does not involve Br_2.

The kinetics is quite consistent with the following mechanism. The base



slowly abstracts a proton (step 1) from acetone to form carbanion I, which then reacts rapidly with bromine (step 2) to yield bromoacetone. Step (1), generation of the carbanion. is the rate-determining step, since its rate determines the overall rate of the reaction sequence. As fast as carbanions are generated, they are snapped up by bromine molecules.

Strong support for this interpretation comes from the kinetics of iodination. Here. too, the rate of reaction depends upon [acetone] and [:B] but is independent of $[I_2]$. Furthermore, and most significant, at a given [acetone] and [:B], bromination and iodination *proceed at identical rates*. That is to say, in the rate expression

$$\text{rate} = k\,[\text{acetone}][:B]$$

the value of k is the same regardless of which halogen is involved. It *should* be, of course, according to the proposed mechanism, since in both cases it is the rate constant for the same reaction, abstraction of a proton from the ketone.

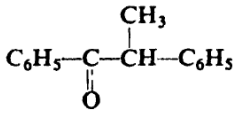
Study of the bromination of acetone, done by A. Lapworth (of the University of

Manchester) in 1904, showed for the first time how kinetics could be used to reveal the mechanism of an organic reaction. The carbanion mechanism has since been confirmed not only by the iodination work, but also by studies of stereochemistry and isotopic exchange.

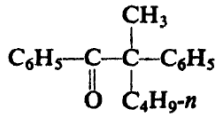
Problem 21.5 Show in detail exactly how each of the following facts provides evidence for the carbanion mechanism of base-promoted halogenation of ketones.

(a) In basic solution, (+)-phenyl *sec*-butyl ketone undergoes racemization; the rate constant for loss of optical activity is identical with the rate constant for bromination of this ketone.

(b) Ketone II undergoes racemization in basic solution, but ketone III does not.



II



III

(c) When (+)-phenyl *sec*-butyl ketone is allowed to stand in D_2O containing OD^-, it not only undergoes racemization, but also becomes labeled with deuterium at the α-position; the rate constants for racemization and hydrogen exchange are identical.

Problem 21.6 (a) Suggest a mechanism for the base-catalyzed racemization of the optically active ester, ethyl mandelate, $C_6H_5CHOHCOOC_2H_5$. (b) How do you account for the fact that optically active mandelic acid undergoes racemization in base *much more slowly* than the ester? (*Hint:* See Sec. 18.20.) (c) What would you predict about the rate of base-catalyzed racemization of α-methylmandelic acid, $C_6H_5C(CH_3)(OH)COOH$?

Problem 21.7 Suppose, as an alternative to the carbanion mechanism, that hydrogen exchange and racemization were both to arise by some kind of direct displacement of one hydrogen (H) by another (D) with inversion of configuration. What relationship would you then expect between the rates of racemization and exchange? (*Hint:* Take one molecule at a time, and see what happens when H is replaced by D with inversion.)

21.4 Acid-catalyzed halogenation of ketones. Enolization

Acids, like bases, speed up the halogenation of ketones. Acids are not, however, consumed, and hence we may properly speak of acid-*catalyzed* halogenation (as contrasted to base-*promoted* halogenation). Although the reaction is not,

$$\underset{\text{Acetone}}{CH_3COCH_3} + Br_2 \xrightarrow{\text{acid}} \underset{\text{Bromoacetone}}{CH_3COCH_2Br} + HBr$$

strictly speaking, a part of carbanion chemistry, this is perhaps the best place to take it up, since it shows a striking parallel in every aspect to the base-promoted reaction we have just left.

Here, too, the kinetics show the rate of halogenation to be independent of halogen concentration, but dependent upon ketone concentration and, this time, acid concentration. Here, too, we find the remarkable identity of rate constants for apparently different reactions: for bromination and iodination of acetone, and exchange of its hydrogens for deuterium; for iodination and racemization of phenyl *sec*-butyl ketone.

The interpretation, too, is essentially the same as the one we saw before: *preceding* the step that involves halogen, there is a rate-determining reaction that can lead not only to halogenation but also to racemization and to hydrogen exchange.

The rate-determining reaction here is the formation of the *enol*, which involves two steps: rapid, reversible protonation (step 1) of the carbonyl oxygen, followed by the slow loss of an α-hydrogen (step 2).

(1) $CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + H{:}B \rightleftharpoons CH_3-\underset{\underset{+OH}{\|}}{C}-CH_3 + {:}B$ **Fast**

(2) $CH_3-\underset{\underset{+OH}{\|}}{C}-CH_3 + {:}B \longrightarrow CH_3-\underset{\underset{OH}{|}}{C}=CH_2 + H{:}B$ **Slow**

Enol

(3) $CH_3-\underset{\underset{OH}{|}}{C}=CH_2 + X_2 \longrightarrow CH_3-\underset{\underset{+OH}{\|}}{C}-CH_2X + X^-$ **Fast**

I

(4) $CH_3-\underset{\underset{+OH}{\|}}{C}-CH_2X + {:}B \rightleftharpoons CH_3-\underset{\underset{O}{\|}}{C}-CH_2X + H{:}B$ **Fast**

Once formed, the enol reacts rapidly with halogen (step 3). We might have expected the unsaturated enol to undergo addition and, indeed, the reaction starts out exactly as though this were going to happen: positive halogen attaches itself to form a cation. As usual (Sec. 6.11), attachment occurs in the way that yields the more stable cation.

The ion formed in this case, I, is an exceedingly stable one, owing its stability to the fact that it is hardly a "carbonium" ion at all, since oxygen can carry the charge and still have an octet of electrons. The ion is, actually, a protonated ketone; loss of the proton yields the product, bromoacetone.

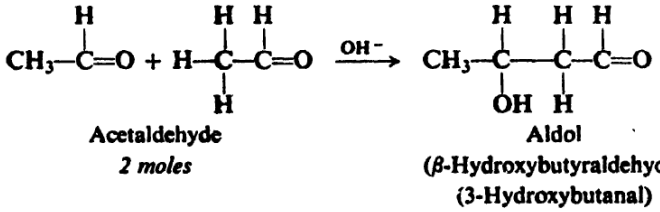
We may find it odd, considering that we call this reaction "acid-catalyzed," that the rate-determining step (2) is really the same as in the base-promoted reaction: abstraction of an α-hydrogen by a base—here, by the conjugate base of the catalyzing acid. Actually, what we see here must always hold true: a reaction that is truly *catalyzed* by acid or base is catalyzed by *both acid and base*. In our case, transfer of the proton from the acid H:B to carbonyl oxygen (step 1) makes the ketone more reactive and hence speeds up enolization. But, if this is truly catalysis, the acid must not be *consumed*. Regeneration of the acid H:B requires that the conjugate base :B get a proton from somewhere; it takes it from the α-carbon (step 2), and thus completes the enolization. Both acid and base speed up the rate-determining step (2): base directly, as one of the reactants, and acid indirectly, by increasing the concentration of the other reactant, the protonated ketone. Using a strong mineral acid in aqueous solution, we would not be aware of the role played by the base; the acid is H_3O^+ and the conjugate base, H_2O, is the solvent.

Problem 21.8 Show in detail how the enolization mechanism accounts for the following facts: (a) the rate constants for acid-catalyzed hydrogen–deuterium exchange and bromination of acetone are identical; (b) the rate constants for acid-catalyzed racemization and iodination of phenyl *sec*-butyl ketone are identical.

Problem 21.9 (a) In the acid-catalyzed dehydration of alcohols (Sec. 5.20), what is the base involved? (b) In the base-catalyzed racemization and hydrogen exchange of phenyl *sec*-butyl ketone (Problem 21.5, p. 707), what is the acid involved?

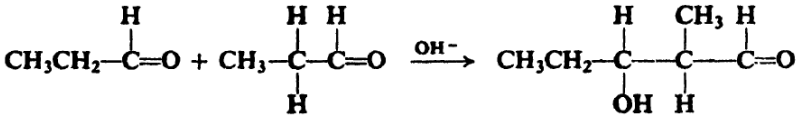
21.5 Aldol condensation

Under the influence of dilute base or dilute acid, two molecules of an aldehyde or a ketone may combine to form a β-hydroxyaldehyde or β-hydroxyketone. This reaction is called the **aldol condensation**. In every case the product results from addition of one molecule of aldehyde (or ketone) to a second molecule in such a way that the α-carbon of the first becomes attached to the carbonyl carbon of the second. For example:



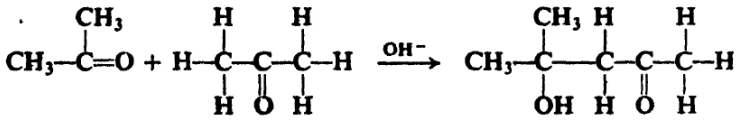
Acetaldehyde
2 moles

Aldol
(β-Hydroxybutyraldehyde)
(3-Hydroxybutanal)



Propionaldehyde
2 moles

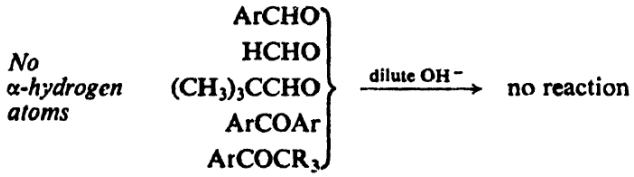
β-Hydroxy-α-methylvaleraldehyde
(3-Hydroxy-2-methylpentanal)



Acetone
2 moles

4-Hydroxy-4-methyl-2-pentanone
(Diacetone alcohol)

If the aldehyde or ketone does not contain an α-hydrogen, a simple aldol condensation cannot take place. For example:



No α-hydrogen atoms

ArCHO
HCHO
$(CH_3)_3CCHO$
ArCOAr
$ArCOCR_3$

dilute OH^- → no reaction

(In concentrated base, however, these may undergo the Cannizzaro reaction, Sec. 19.16.)

The generally accepted mechanism for the base-catalyzed condensation involves the following steps, acetaldehyde being used as an example. Hydroxide ion

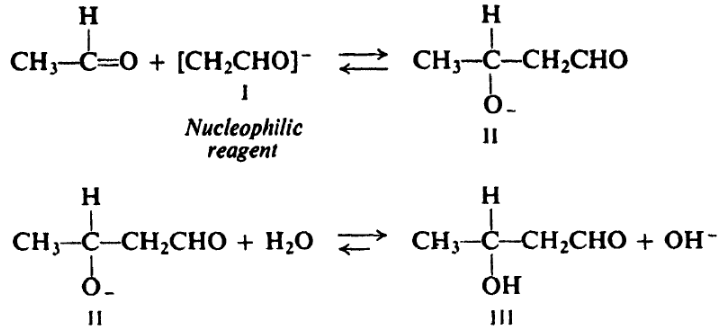
(1) $$CH_3CHO + OH^- \rightleftharpoons H_2O + [CH_2CHO]^-$$

Basic catalyst

I

(2)

(3)



abstracts (step 1) a hydrogen ion from the α-carbon of the aldehyde to form carbanion I, which attacks (step 2) carbonyl carbon to form ion II. II (an alkoxide) abstracts (step 3) a hydrogen ion from water to form the β-hydroxyaldehyde III, regenerating hydroxide ion. The purpose of hydroxide ion is thus to produce the carbanion I, which is the actual nucleophilic reagent.

Problem 21.10 Illustrate these steps for:

(a) propionaldehyde
(b) acetone
(c) acetophenone
(d) cyclohexanone
(e) phenylacetaldehyde

Problem 21.11 The aldol condensation of unsymmetrical ketones (methyl ethyl ketone, for example) is usually of little value in synthesis. Why do you think this is so?

The carbonyl group plays two roles in the aldol condensation. It not only provides the unsaturated linkage at which addition (step 2) occurs, but also makes the α-hydrogens acidic enough for carbanion formation (step 1) to take place.

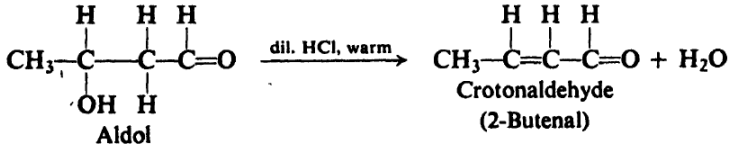
Problem 21.12 In *acid-catalyzed aldol condensations*, acid is believed to perform two functions: to catalyze conversion of carbonyl compound into the enol form, and to provide protonated carbonyl compound with which the enol can react. The reaction that then takes place can, depending upon one's point of view, be regarded either as acid-catalyzed nucleophilic addition to a carbonyl group, or as electrophilic addition to an alkene. On this basis, write all steps in the mechanism of acid-catalyzed aldol condensation of acetaldehyde. In the actual *condensation* step, identify the nucleophile and the electrophile.

Problem 21.13 (a) When acetaldehyde at fairly high concentration was allowed to undergo base-catalyzed aldol condensation in heavy water (D_2O), the product was found to contain almost no deuterium bound to carbon. This finding has been taken as one piece of evidence that the slow step in this aldol condensation is formation of the carbanion. How would you justify this conclusion? (b) The kinetics also supports this conclusion. What kinetics would you expect if this were the case? (*Remember:* Two molecules of acetaldehyde are involved in aldol condensation.) (c) When the experiment in part (a) was carried out at low acetaldehyde concentration, the product was found to contain considerable deuterium bound to carbon. How do you account for this? (*Hint:* See Sec. 14.20.) (d) In contrast to acetaldehyde, acetone was found to undergo base-catalyzed hydrogen–deuterium exchange much faster than aldol condensation. What is one important factor contributing to this difference in behavior?

Problem 21.14 In alkaline solution, 4-methyl-4-hydroxy-2-pentanone is partly converted into acetone. What does this reaction amount to? Show all steps in the most likely mechanism. (*Hint:* See Problem 5.8, p. 170.)

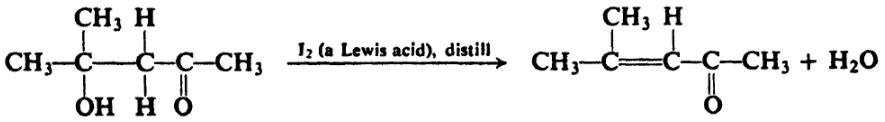
21.6 Dehydration of aldol products

The β-hydroxyaldehydes and β-hydroxyketones obtained from aldol condensations are very easily dehydrated; the major products have the carbon–carbon double bond between the α- and β-carbon atoms. For example:



Aldol

Crotonaldehyde
(2-Butenal)



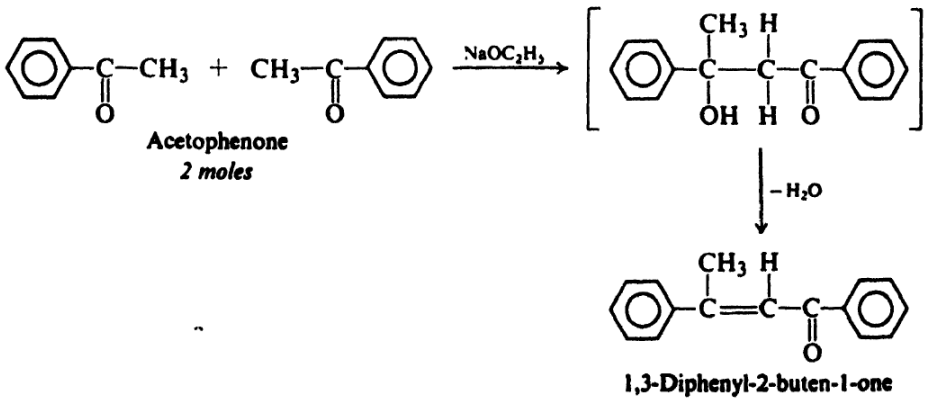
Diacetone alcohol
(4-Hydroxy-4-methyl-2-pentanone)

Mesityl oxide
(4-Methyl-3-penten-2-one)

Both the ease and the orientation of elimination are related to the fact that the alkene obtained is a particularly stable one, since the carbon–carbon double bond is conjugated with the carbon–oxygen double bond of the carbonyl group (compare Sec. 8.16).

Problem 21.15 Draw resonance structures to account for the unusual stability of an α,β-unsaturated aldehyde or ketone. What is the significance of these structures in terms of orbitals? (See Sec. 8.17.)

As we know, an alkene in which the carbon–carbon double bond is conjugated with an aromatic ring is particularly stable (Sec. 12.17); in those cases where elimination of water from the aldol product can form such a conjugated alkene, the unsaturated aldehyde or ketone is the product actually isolated from the reaction. For example:

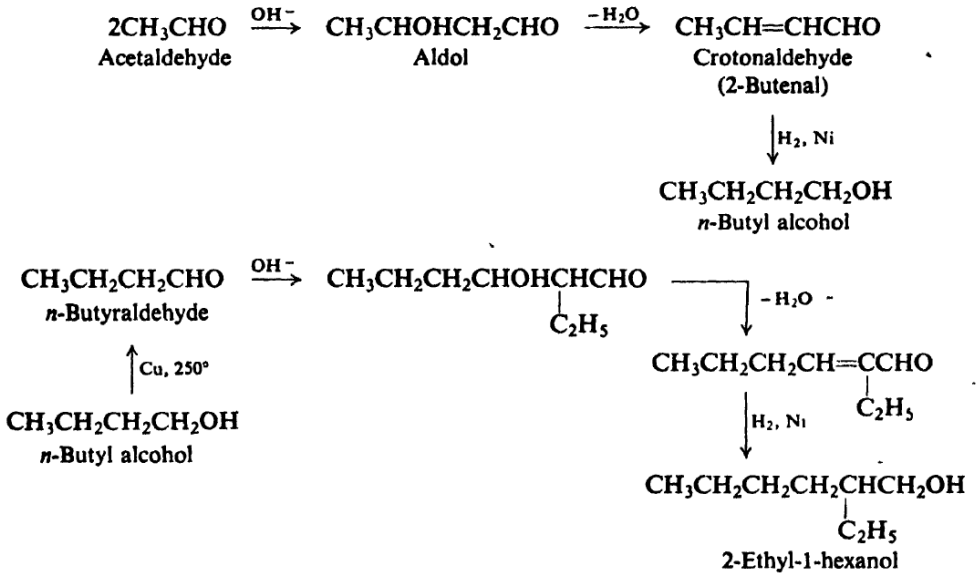


Acetophenone
2 moles

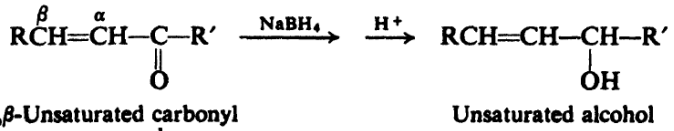
1,3-Diphenyl-2-buten-1-one

21.7 Use of aldol condensation in synthesis

Catalytic hydrogenation of α,β-unsaturated aldehydes and ketones yields saturated alcohols, addition of hydrogen occurring both at carbon–carbon and at carbon–oxygen double bonds. It is for the purpose of ultimately preparing saturated alcohols that the aldol condensation is often carried out. For example, *n*-butyl alcohol and 2-ethyl-1-hexanol are both prepared on an industrial scale in this way:



Unsaturated alcohols can be prepared if a reagent is selected that reduces only the carbonyl group and leaves the carbon–carbon double bond untouched; one such reagent is sodium borohydride, $NaBH_4$.



Problem 21.16 Outline the synthesis of the following alcohols starting from alcohols of smaller carbon number:

(a) 2-methyl-1-pentanol
(b) 4-methyl-2-pentanol
(c) 2-cyclohexylcyclohexanol
(d) 2,4-diphenyl-1-butanol
(e) 1,3-diphenyl-2-buten-1-ol

Problem 21.17 The insect repellent "6-12" (2-ethyl-1,3-hexanediol) is produced by the same chemical company that produces *n*-butyl alcohol and 2-ethyl-1-hexanol; suggest a method for its synthesis. How could you synthesize 2-methyl-2,4-pentanediol?

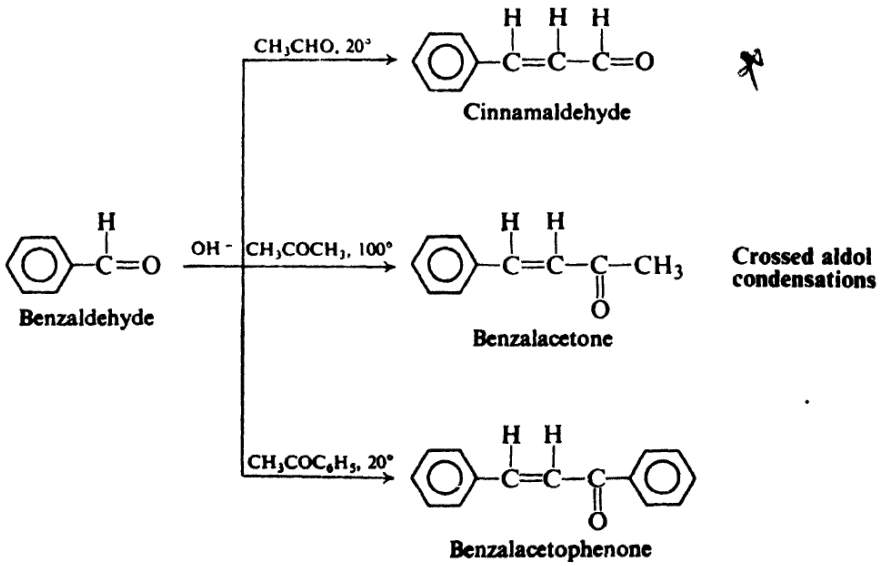
21.8 Crossed aldol condensation

An aldol condensation between two different carbonyl compounds—a so-called **crossed aldol condensation**—is not always feasible in the laboratory, since a

mixture of the four possible products may be obtained. On a commercial scale, however, such a synthesis may be worthwhile if the mixture can be separated and the components marketed.

Problem 21.18 *n*-Butyl alcohol, *n*-hexyl alcohol, 2-ethyl-1-hexanol, and 2-ethyl-1-butanol are marketed by the same chemical concern; how might they be prepared from cheap, readily available compounds?

Under certain conditions, a good yield of a single product can be obtained from a crossed aldol condensation: (a) one reactant contains no α-hydrogens and therefore is incapable of condensing with itself (e.g., aromatic aldehydes or formaldehyde); (b) this reactant is mixed with the catalyst; and then (c) a carbonyl

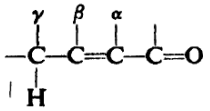


compound that contains α-hydrogens is added slowly to this mixture. There is thus present at any time only a very low concentration of the ionizable carbonyl compound, and the carbanion it forms reacts almost exclusively with the other carbonyl compound, which is present in large excess.

Problem 21.19 Outline the synthesis of each of the following from benzene or toluene and any readily available alcohols:

(a) 4-phenyl-2-butanol
(b) 1,3-diphenyl-1-propanol
(c) 1,3-diphenylpropane
(d) 2,3-diphenyl-1-propanol
(e) 1,5-diphenyl-1,4-pentadien-3-one (dibenzalacetone)

Problem 21.20 (a) What prediction can you make about the acidity of the γ-hydrogens of α,β-unsaturated carbonyl compounds,



as, for example, in crotonaldehyde? (b) In view of your answer to (a), suggest a way to synthesize 5-phenyl-2,4-pentadienal, $C_6H_5CH{=}CH{-}CH{=}CH{-}CHO$.

21.9 Reactions related to the aldol condensation

There are a large number of condensations that are closely related to the aldol condensation. Each of these reactions has its own name—*Perkin*, *Knoevenagel*, *Doebner*, *Claisen*, *Dieckmann*, for example—and at first glance each may seem quite different from the others. Closer examination shows, however, that like the aldol condensation each of these involves attack by a carbanion on a carbonyl group. In each case the carbanion is generated in very much the same way: the abstraction by base of a hydrogen ion *alpha* to a carbonyl group. Different bases may be used—sodium hydroxide, sodium ethoxide, sodium acetate, amines—and the carbonyl group to which the hydrogen is *alpha* may vary—aldehyde, ketone, anhydride, ester—but the chemistry is essentially the same as that of the aldol condensation. We shall take up a few of these condensations in the following problems and in following sections; in doing this, we must not lose sight of the fundamental resemblance of each of them to the aldol condensation.

Problem 21.21 Esters can be condensed with aromatic aldehydes in the presence of alkoxides; thus benzaldehyde and ethyl acetate, in the presence of sodium ethoxide, give ethyl cinnamate, $C_6H_5CH{=}CHCOOC_2H_5$. Show all steps in the most likely mechanism for this condensation.

Problem 21.22 Account for the following reactions:

(a) $C_6H_5CHO + CH_3NO_2 \xrightarrow{KOH} C_6H_5CH{=}CHNO_2 + H_2O$

(b) $C_6H_5CHO + C_6H_5CH_2CN \xrightarrow{NaOC_2H_5} C_6H_5CH{=}\underset{\displaystyle C_6H_5}{\underset{|}{C}}{-}CN + H_2O$

(c) $C_6H_5CHO + CH_3(C_6H_3(NO_2)_2) \xrightarrow{2^\circ\ \text{amine}} C_6H_5CH{=}CH(C_6H_3(NO_2)_2) + H_2O$

(d) $CH_3CHO + NaC{\equiv}CH \xrightarrow{NH_3(l)} \underset{\displaystyle ONa}{\underset{|}{CH_3CHC}}{\equiv}CH \xrightarrow{NH_4Cl} \underset{\displaystyle OH}{\underset{|}{CH_3CHC}}{\equiv}CH$

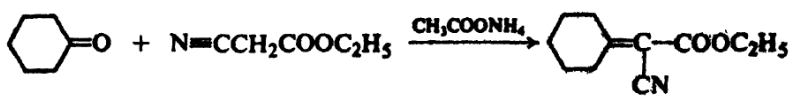
(e) **A Perkin condensation:**

$$\underset{\text{Acetic anhydride}}{C_6H_5CHO + (CH_3CO)_2O} \xrightarrow{CH_3COONa} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

(f) **A Knoevenagel reaction:**

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow{2^\circ\ \text{amine}} C_6H_5CH{=}C(COOC_2H_5)_2$$

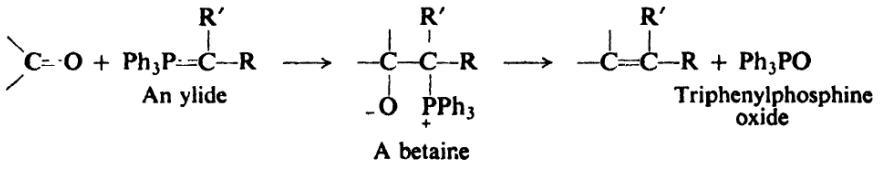
(g) **A Cope reaction:**



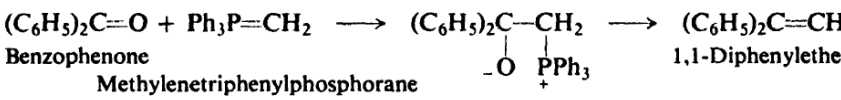
21.10 The Wittig reaction

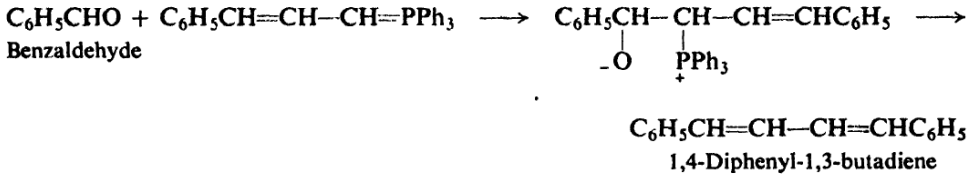
In 1954, Georg Wittig (then at the University of Tübingen) reported a method of synthesizing alkenes from carbonyl compounds, which amounts to the replace-

ment of carbonyl oxygen, =O, by the group =CRR′. The heart of the synthesis



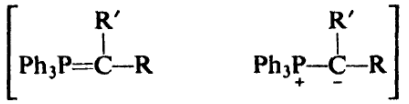
is the nucleophilic attack on carbonyl carbon by an *ylide* to form a *betaine* which—often spontaneously—undergoes elimination to yield the product. For example:





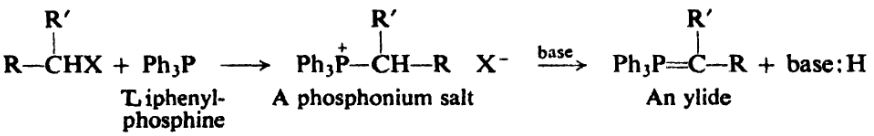
The reaction is carried out under mild conditions, and the position of the carbon–carbon double bond is not in doubt. Carbonyl compounds may contain a wide variety of substituents, and so may the ylide. (Indeed, in its broadest form, the Wittig reaction involves reactants other than carbonyl compounds, and may lead to products other than substituted alkenes.)

The phosphorus ylides have hybrid structures, and it is the negative charge on

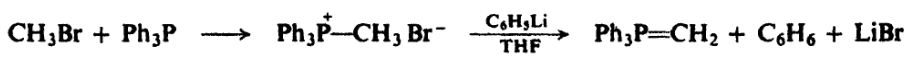


carbon—the carbanion character of ylides—that is responsible for their characteristic reactions: in this case, nucleophilic attack on carbonyl carbon.

The preparation of ylides is a two-stage process, each stage of which belongs to a familiar reaction type: nucleophilic attack on an alkyl halide, and abstraction of a proton by a base.



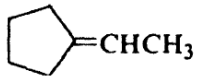
Many different bases have been used—chiefly alkoxides and organometallics—and in a variety of solvents. For example:



$$CH_2{=}CHCH_2Cl + Ph_3P \longrightarrow Ph_3\overset{+}{P}{-}CH_2CH{=}CH_2\ Cl^- \xrightarrow[DMF]{NaOEt} Ph_3P{=}CHCH{=}CH_2$$

Problem 21.23 What side reactions would you expect to encounter in the preparation of an ylide like $Ph_3P{=}C(CH_3)CH_2CH_3$?

Problem 21.24 Give the structure of an ylide and a carbonyl compound from which each of the following could be made.

(a) $CH_3CH_2CH_2CH{=}C(CH_3)CH_2CH_3$
(b) $C_6H_5C(CH_3){=}CHCH_2C_6H_5$
(c) $C_6H_5CH{=}CHC_6H_5$
(d) 
(e) 1,4-diphenyl-1,3-butadiene (an alternative to the set of reagents used on p. 715)
(f) $CH_2{=}CHCH{=}C(CH_3)COOCH_3$

Problem 21.25 Outline all steps in a possible laboratory synthesis of each ylide and each carbonyl compound in the preceding problem, starting from benzene, toluene, alcohols of four carbons or fewer, acetic anhydride, triphenylphosphine, and cyclopentanol, and using any needed inorganic reagents.

Problem 21.26 Give the structures of compounds A–C.

$C_6H_5OCH_2Cl + Ph_3P$, then t-BuOK $\longrightarrow$ A ($C_{25}H_{21}OP$)
A + methyl ethyl ketone $\longrightarrow$ Ph_3PO + B ($C_{11}H_{14}O$)
B + dilute aqueous acid $\longrightarrow$ C ($C_5H_{10}O$)

The above sequence offers a general route to what class of compounds?

Problem 21.27 Give the structures of compounds D–F.

(a) $C_6H_5COCH_2CH_2CH_2CH_2Br + Ph_3P$, then NaOEt $\longrightarrow$ D ($C_{11}H_{12}$)
(b) $BrCH_2CH_2CH_2CH_2Br + Ph_3P$, then base $\longrightarrow$ E ($C_{39}H_{34}P_2$)
E + o-$C_6H_4(CHO)_2$ $\longrightarrow$ F ($C_{11}H_{10}$)

Problem 21.28 Give the structures of compounds G and H, and account for the stereochemistry of each step.

trans-2-octene + $C_6H_5CO_2OH$ $\longrightarrow$ G ($C_8H_{16}O$)
G + Ph_2PLi, then CH_3I $\longrightarrow$ H ($C_{21}H_{29}OP$)
H $\longrightarrow$ *cis*-2-octene

21.11 Claisen condensation. Formation of β-keto esters

An α-hydrogen in an ester, like an α-hydrogen in an aldehyde or ketone, is weakly acidic, and for the same reason: through resonance, the carbonyl group helps accommodate the negative charge of the carbanion. Let us look at an exceedingly important reaction of esters that depends upon the acidity of α-hydrogens. It is—for esters—the exact counterpart of the aldol condensation; reaction takes a different turn at the end, but a turn that is typical of the chemistry of acyl compounds.

When ethyl acetate is treated with sodium ethoxide, and the resulting mixture

is acidified, there is obtained ethyl β-ketobutyrate (ethyl 3-oxobutanoate), generally known as **ethyl acetoacetate** or **acetoacetic ester**:

$$\underset{\substack{\text{Ethyl acetate}\\ \textit{2 moles}}}{2CH_3COOC_2H_5} + \underset{\substack{\text{Sodium}\\ \text{ethoxide}}}{Na^+\ {}^-OC_2H_5} \xrightarrow{C_2H_5OH} \underset{\text{Sodioacetoacetic ester}}{CH_3COCHCOOC_2H_5{}^-Na^+} + 2C_2H_5OH$$

$$\downarrow H^+$$

$$\underset{\substack{\text{Ethyl acetoacetate}\\ \text{Acetoacetic ester}\\ \textit{A } \beta\textit{-keto ester}}}{CH_3\overset{\beta}{C}OCH_2COOC_2H_5}$$

Ethyl acetoacetate is the ester of a *β-keto acid*; its preparation illustrates the reaction known as the **Claisen condensation**.

The generally accepted mechanism for the Claisen condensation (shown here for ethyl acetate) is:

$$(1)\qquad CH_3COOC_2H_5 + {}^-OC_2H_5 \rightleftharpoons C_2H_5OH + \underset{\text{I}}{{}^-CH_2COOC_2H_5}$$

$$(2)\qquad CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5 + \underset{\text{I}}{{}^-CH_2COOC_2H_5} \rightleftharpoons CH_3-\underset{OC_2H_5}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}-CH_2COOC_2H_5$$

$$\updownarrow$$

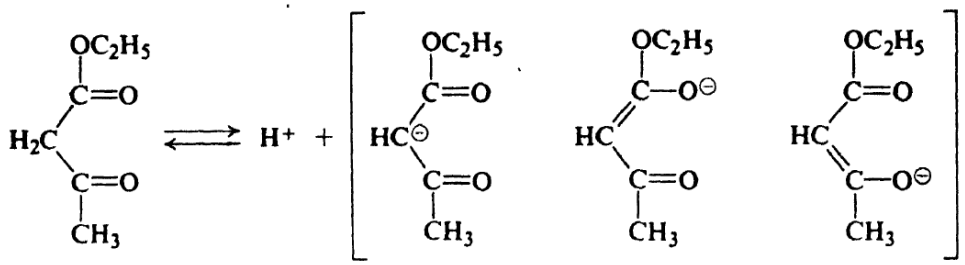
$$CH_3\overset{O}{\overset{\|}{C}}CH_2COOC_2H_5 + {}^-OC_2H_5$$

$$(3)\qquad \underset{\text{Stronger acid}}{CH_3\overset{O}{\overset{\|}{C}}CH_2COOC_2H_5} + {}^-OC_2H_5 \rightleftharpoons CH_3COCHCOOC_2H_5{}^- + \underset{\text{Weaker acid}}{C_2H_5OH}$$

Ethoxide ion abstracts (step 1) a hydrogen ion from the α-carbon of the ester to form carbanion I. The powerfully nucleophilic carbanion I attacks (step 2) the carbonyl carbon of a second molecule of ester to displace ethoxide ion and yield the keto ester.

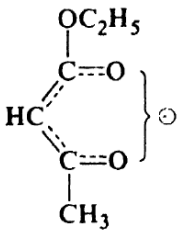
Like the aldol condensation and related reactions, the Claisen condensation involves nucleophilic attack by a carbanion on an electron-deficient carbonyl carbon. *In the aldol condensation, nucleophilic attack leads to addition, the typical reaction of aldehydes and ketones; in the Claisen condensation, nucleophilic attack leads to substitution, the typical reaction of acyl compounds* (Sec. 20.4).

When reaction is complete there is present, not acetoacetic ester, but its sodium salt, *sodioacetcacetic ester*. The α-hydrogens of acetoacetic ester are located *alpha* to *two* carbonyl groups, and hence ionization yields a particularly stable carbanion in which two carbonyl groups help accommodate the charge. As a result acetoacetic ester is a much stronger acid than ordinary esters or other compounds containing a single carbonyl group. It is considerably stronger than ethyl alcohol, and hence it reacts (step 3) with ethoxide ion to form ethyl alcohol and the anion



Acetoacetic ester

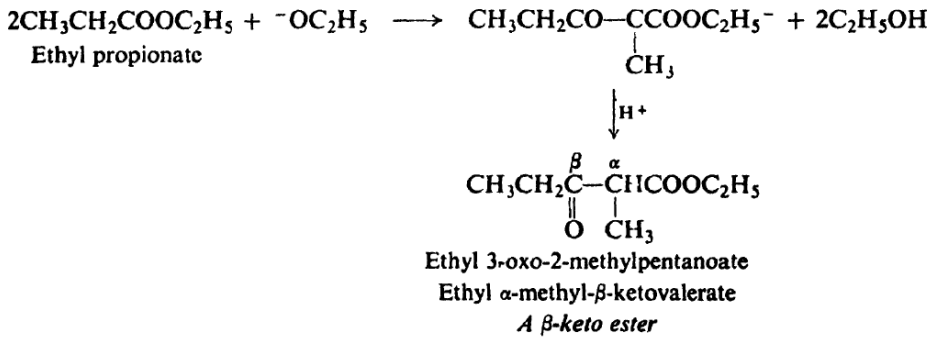
equivalent to



of sodioacetoacetic ester. Formation of the salt of acetoacetic ester is essential to the success of the reaction; of the various equilibria involved in the reaction, only (3) is favorable to the product we want.

Problem 21.29 Better yields are obtained if the Claisen condensation is carried out in ether with alcohol-free sodium ethoxide as catalyst instead of in ethyl alcohol solution. How do you account for this?

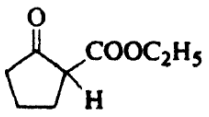
As we might expect, the Claisen condensation of more complicated esters yields the products resulting from ionization of an α-hydrogen of the ester; as a result, it is always the α-carbon of one molecule that becomes attached to the carbonyl carbon of another. For example:



Ethyl propionate

Ethyl 3-oxo-2-methylpentanoate
Ethyl α-methyl-β-ketovalerate
A β-keto ester

Problem 21.30 Sodium ethoxide converts ethyl adipate into 2-carbethoxycyclopentanone (II). This is an example of the **Dieckmann condensation.**

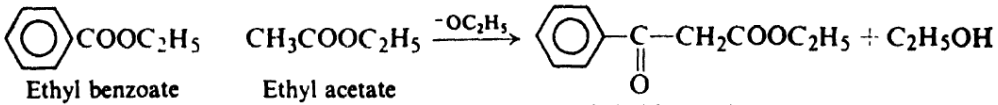


II

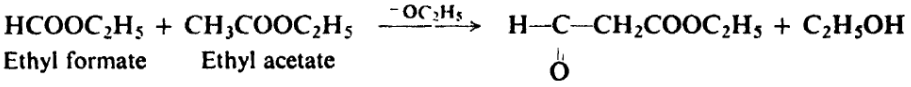
(a) How do you account for formation of II? (b) What product would you expect from the action of sodium ethoxide on ethyl pimelate (ethyl heptanedioate)? (c) Would you expect similar behavior from ethyl glutarate or ethyl succinate? Actually, ethyl succinate reacts with sodium ethoxide to yield a compound of formula $C_{12}H_{16}O_6$ containing a six-membered ring. What is the likely structure for this last product?

21.12 Crossed Claisen condensation

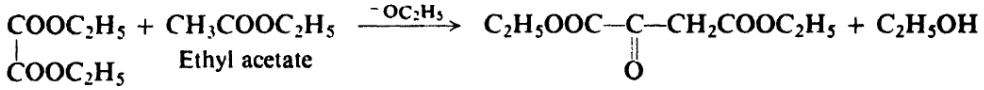
Like a crossed aldol condensation (Sec. 21.8), a **crossed Claisen condensation** is generally feasible only when one of the reactants has no α-hydrogens and thus is incapable of undergoing self-condensation. For example:



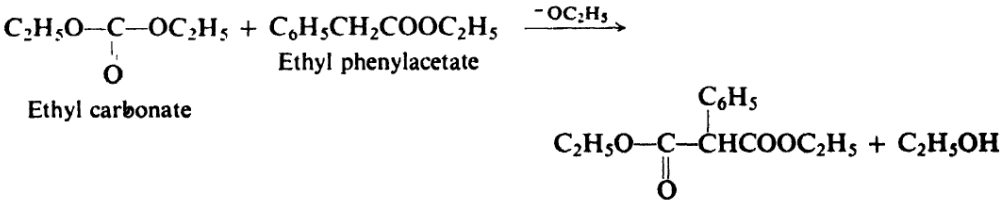
Ethyl benzoate — Ethyl acetate — Ethyl benzoylacetate



Ethyl formate — Ethyl acetate — Ethyl formylacetate (known only as the Na salt)



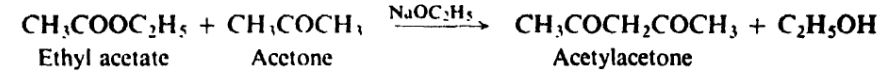
Ethyl oxalate — Ethyl acetate — Ethyl oxaloacetate



Ethyl carbonate — Ethyl phenylacetate — Ethyl phenylmalonate (Phenylmalonic ester)

Problem 21.31 In what order should the reactants be mixed in each of the above crossed Claisen condensations? (*Hint:* See Sec. 21.8.)

Problem 21.32 Ketones (but not aldehydes) undergo a crossed Claisen condensation with esters. For example:



Ethyl acetate — Acetone — Acetylacetone

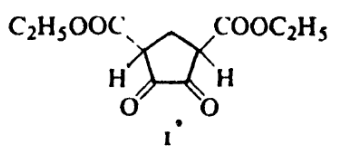
(a) Outline all steps in the most likely mechanism for this reaction. (b) Predict the principal products expected from the reaction in the presence of sodium ethoxide of ethyl propionate and acetone; (c) of ethyl benzoate and acetophenone; (d) of ethyl oxalate and cyclohexanone.

Problem 21.33 Outline the synthesis from simple esters of:

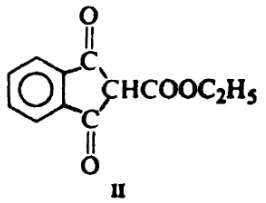
(a) ethyl α-phenylbenzoylacetate, $C_6H_5COCH(C_6H_5)COOC_2H_5$

(b) ethyl 2,3-dioxo-1,4-cyclopentanedicarboxylate (I). (*Hint:* Use ethyl oxalate as one ester.)

(c) ethyl 1,3-dioxo-2-indanecarboxylate (II)



I

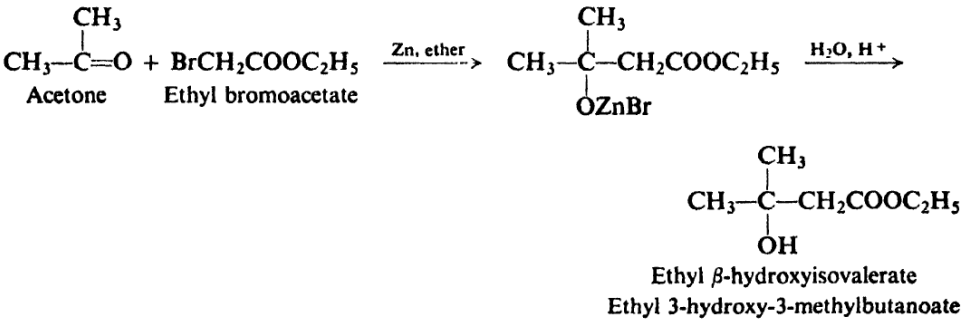


II

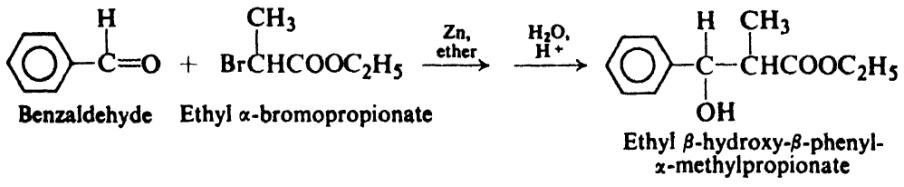
21.13 Reformatsky reaction. Preparation of β-hydroxy esters

In the Claisen condensation, we have just seen, carbanions are generated from esters through abstraction of an α-hydrogen by base. But we are familiar with another way of generating carbanions—or rather, groups with considerable carbanion character: through formation of organometallic compounds. This approach, too, plays a part in the chemistry of esters.

If an α-bromo ester is treated with metallic zinc in the presence of an aldehyde or ketone, there is obtained a β-hydroxy ester. This reaction, known as the **Reformatsky reaction**, is the most important method of preparing β-hydroxy acids and their derivatives. For example:

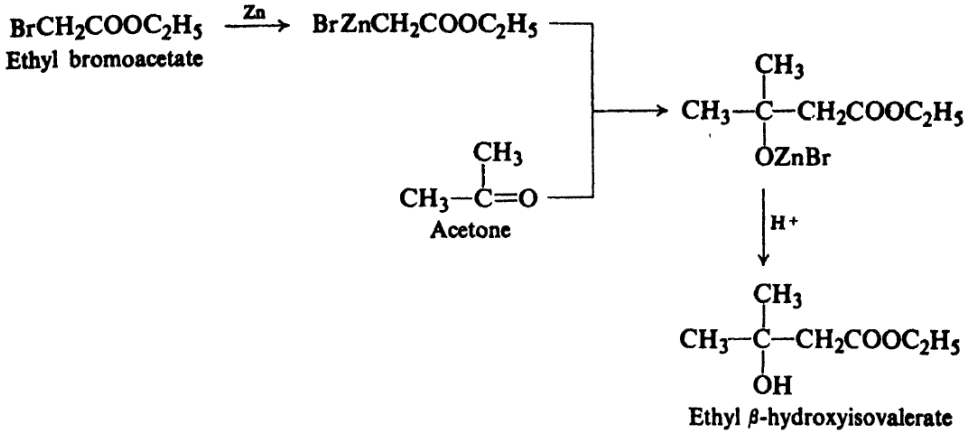


Acetone + Ethyl bromoacetate → $CH_3-C(CH_3)(OZnBr)-CH_2COOC_2H_5$ → Ethyl β-hydroxyisovalerate (Ethyl 3-hydroxy-3-methylbutanoate)

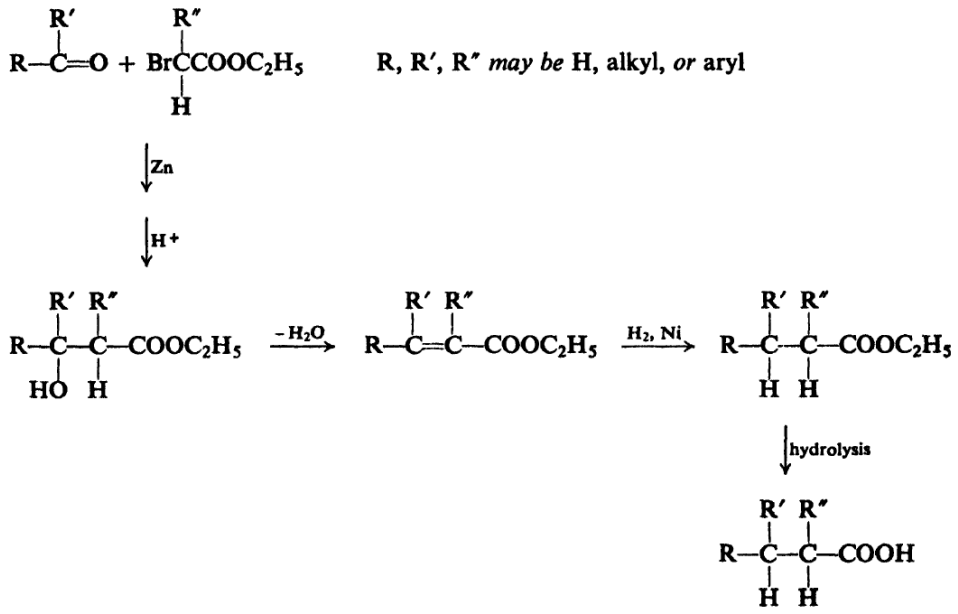


Benzaldehyde + Ethyl α-bromopropionate → Ethyl β-hydroxy-β-phenyl-α-methylpropionate

The α-bromo ester and zinc react in absolute ether to yield an intermediate organozinc compound, which then adds to the carbonyl group of the aldehyde or ketone. The formation and subsequent reaction of the organozinc compound is similar to the formation and reaction of a Grignard reagent. Zinc is used in place of magnesium simply because the organozinc compounds are less reactive than Grignard reagents; they do not react with the ester function but only with the aldehyde or ketone.



The Reformatsky reaction takes place only with esters containing bromine in the *alpha* position, and hence necessarily yields *beta*-hydroxy esters. By the proper

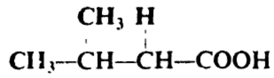
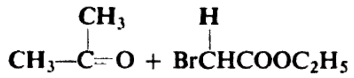
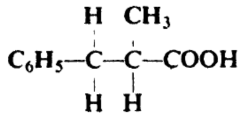
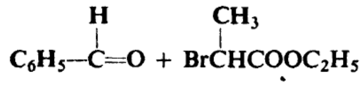


selection of ester and carbonyl compound, a wide variety of rather complicated β-hydroxy carboxylic acids can be prepared.

Like β-hydroxyaldehydes and -ketones, β-hydroxyesters and -acids are readily dehydrated. The unsaturated compounds thus obtained (chiefly α,β-unsaturated) can be hydrogenated to saturated carboxylic acids. Extended in this way, the Reformatsky reaction is a useful general method for preparing carboxylic acids, paralleling the aldol route to alcohols.

In planning the synthesis of a carboxylic acid by the Reformatsky reaction,

our problem is to select the proper starting materials; to do this, we have only to look at the structure of the product we want. For example:

Acid wanted:	*Requires:*	*Starting materials:*
	R = CH_3—, R′ = CH_3—, R″ = H—	
	R = C_6H_5—, R′ = H—, R″ = CH_3—	

Chapter 26 Carbanions II
Malonic Ester and Acetoacetic Ester Syntheses

26.1 Carbanions in organic synthesis

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

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

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

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

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

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

26.2 Malonic ester synthesis of carboxylic acids

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

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

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

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

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

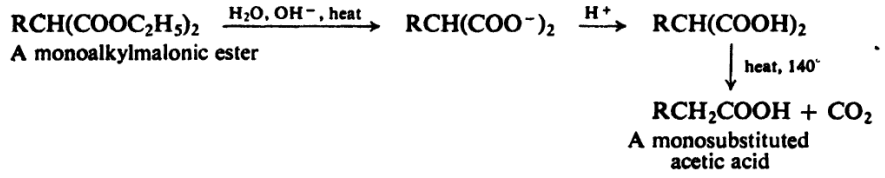
This reaction involves nucleophilic attack on the alkyl halide by the carbanion, $CH(COOC_2H_5)_2{}^-$, and, as we might expect, gives highest yields with primary alkyl halides, lower yields with secondary alkyl halides, and is worthless for tertiary alkyl halides and for aryl halides.

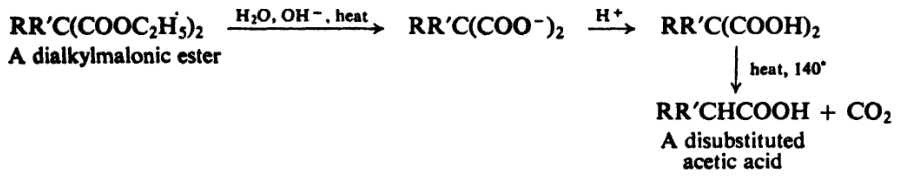
The alkylmalonic ester still contains one ionizable hydrogen, and on treatment with sodium ethoxide it, too, can be converted into its salt; this salt can react with an alkyl halide—which may be the same as, or different from, the first alkyl halide—to yield a dialkylmalonic ester:

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

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

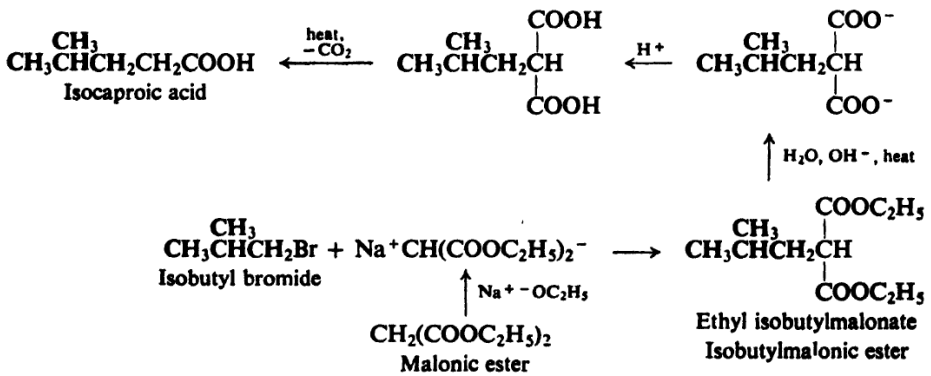
The acidity of malonic ester thus permits the preparation of substituted malonic esters containing one or two alkyl groups. How can these substituted malonic esters be used to make carboxylic acids? When heated above its melting point, malonic acid readily loses carbon dioxide to form acetic acid; in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



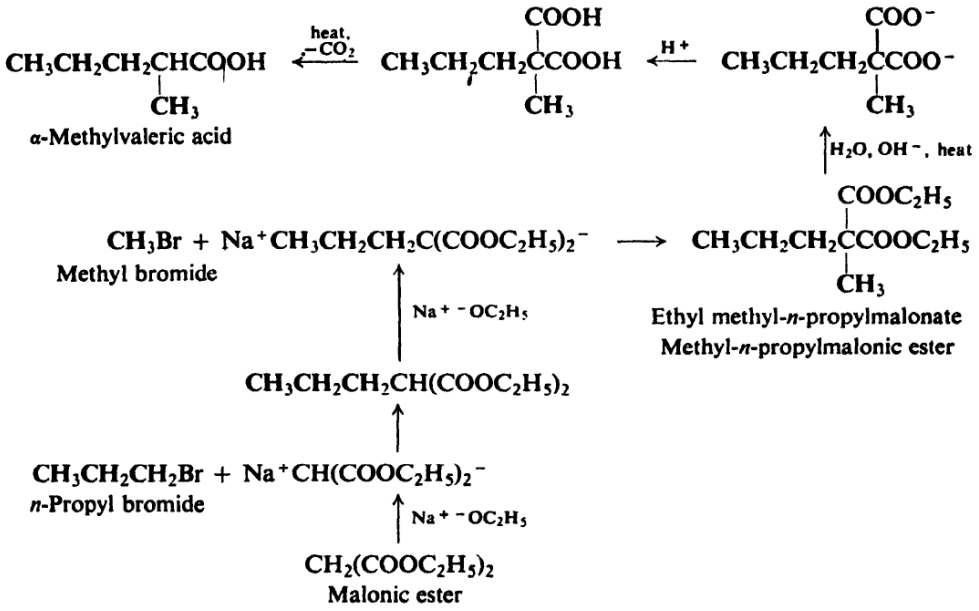


A malonic ester synthesis yields an acetic acid in which one or two hydrogens have been replaced by alkyl groups.

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



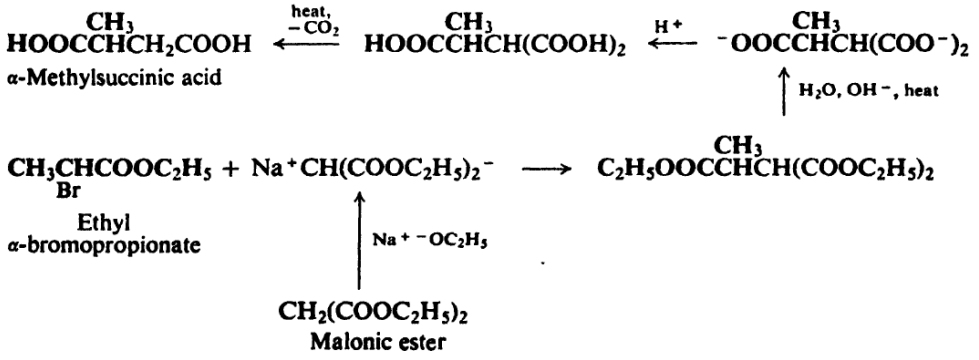
An isomer of isocaproic acid, α-methylvaleric acid, $CH_3CH_2CH_2CH(CH_3)COOH$, can be considered as acetic acid in which one hydrogen has been replaced by a



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

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

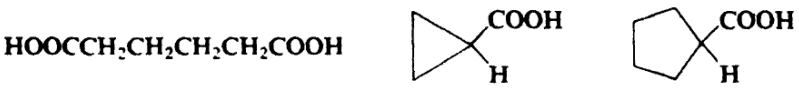
In place of simple alkyl halides, certain other halogen-containing compounds may be used, in particular the readily available α-bromo esters (why can α-bromo-*acids* not be used?), which yield substituted succinic acids by the malonic ester synthesis. For example:



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

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

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



Adipic acid | Cyclopropanecarboxylic acid | Cyclopentanecarboxylic acid

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

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

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

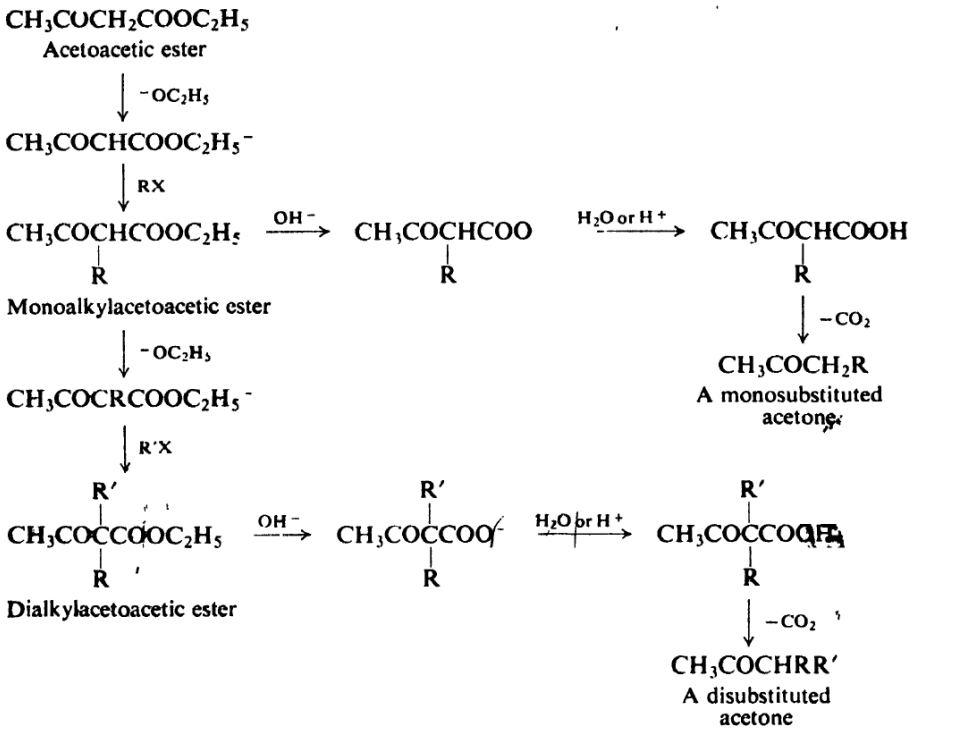
Problem 26.5 In an example of the **Michael condensation,** malonic ester reacts with ethyl 2-butenoate in the presence of sodium ethoxide to yield A, of formula $C_{13}H_{22}O_6$. The sequence of hydrolysis, acidification, and heating converts A into 3-methylpentanedioic acid. What is A, and how is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

26.3 Acetoacetic ester synthesis of ketones

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

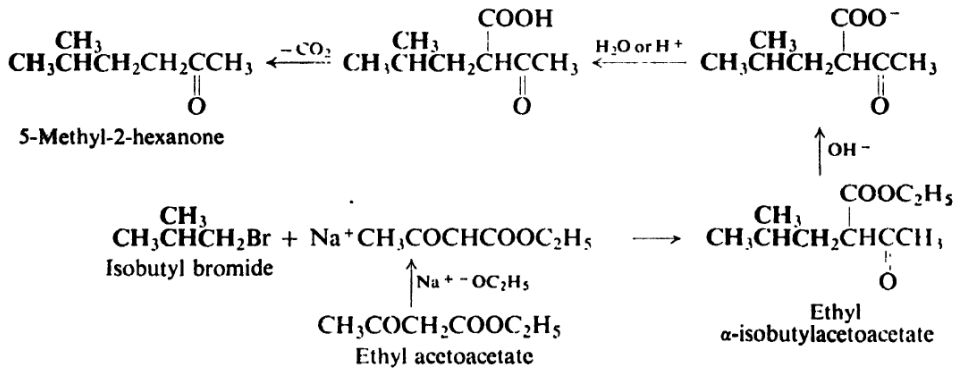
Acetoacetic ester is converted by sodium ethoxide into the sodioacetoacetic ester, which is then allowed to react with an alkyl halide to form an alkylacetoacetic ester (an ethyl alkylacetoacetate), $CH_3COCHRCOOC_2H_5$; if desired, the alkylation can be repeated to yield a dialkylacetoacetic ester,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

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



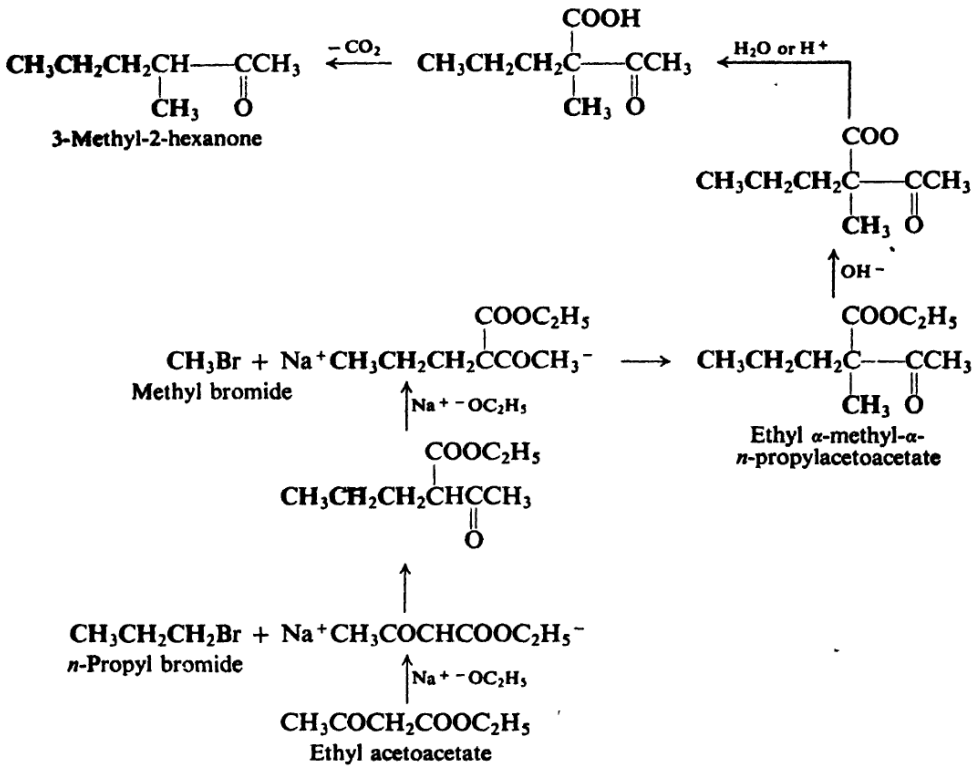
The acetoacetic ester synthesis of ketones yields an acetone molecule in which one or two hydrogens have been replaced by alkyl groups.

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



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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

Problem 26.10 Outline the synthesis from simple esters of:

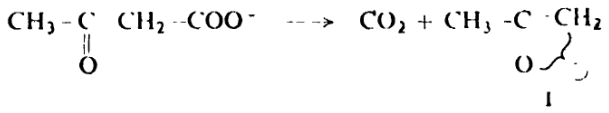
(a) α-ketoisocaproic acid
(b) α-keto-β-phenylpropionic acid
(c) α-ketoglutaric acid
(d) *leucine* (α-aminoisocaproic acid). (*Hint:* See Sec. 22.11.)
(e) *glutamic acid* (α-aminoglutaric acid)

26.4 Decarboxylation of β-keto acids and malonic acids

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

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

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

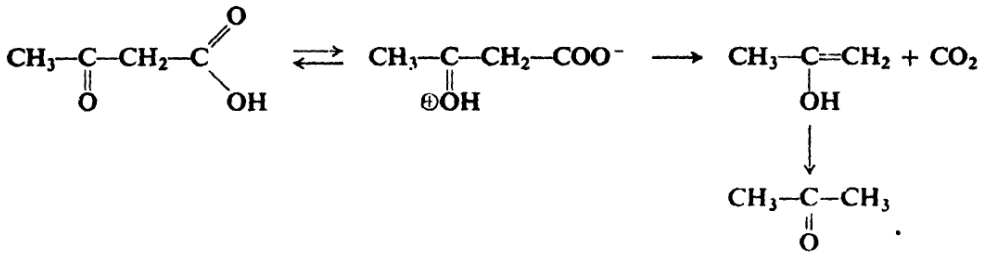


yields the carbanion I. This carbanion is formed faster than the simple carbanion ($R:^-$) that would be formed from a simple carboxylate ion ($RCOO^-$) because it is more stable. It is more stable, of course, due to the accommodation of the negative charge by the keto group.

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

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

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



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

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

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

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

26.5 Direct and indirect alkylation of esters and ketones

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

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

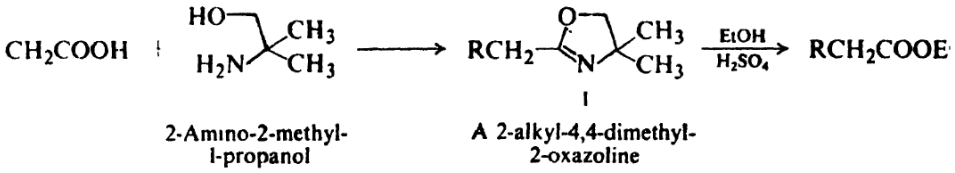
α-hydrogens, but only those on one particular α-carbon, so that alkylation will take place there. Then, when alkylation is over, the carbethoxy group is easily removed by hydrolysis and decarboxylation.

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

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

26.6 Synthesis of acids and esters via 2-oxazolines

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

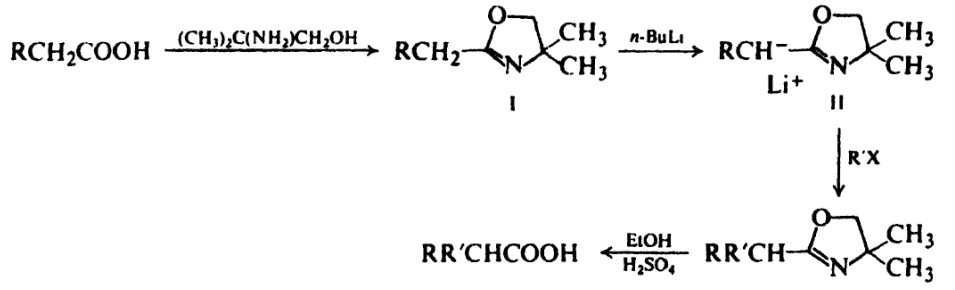


I

2-Amino-2-methyl-1-propanol

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

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



I II

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

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

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

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

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

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

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

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

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

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

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

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

26.7 Organoborane synthesis of acids and ketones

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

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

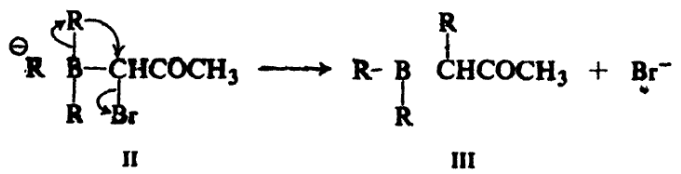
$$R_3B + \underset{\text{Bromoacetone}}{BrCH_2COCH_3} \xrightarrow{\text{base}} \underset{\text{An alkylacetone}}{RCH_2COCH_3}$$

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

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

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

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

(3) 

II III

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

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

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

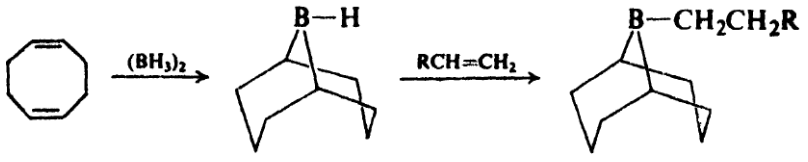
We have, then, three acid-base reactions and a 1,2-alkyl shift: all familiar reaction types. Step (1) involves formation of a carbanion; step (3) involves intramolecular nucleophilic (S_N2) attack by a carbanion-like alkyl group; and step (4) involves attachment of a proton to a carbanion or a carbanion-like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

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

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

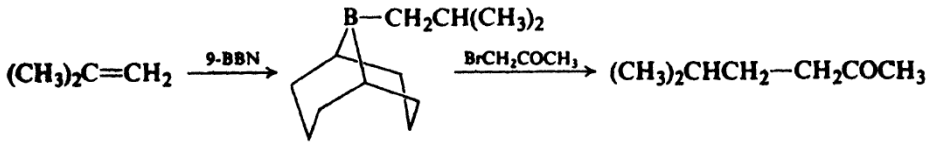
As a synthetic route, this organoborane synthesis parallels the acetoacetic ester and malonic ester syntheses. An acetone unit is furnished by acetoacetic ester or, here, by bromoacetone; an acetic acid unit is furnished by malonic ester or, here, by bromoacetic ester. In these syntheses, bromine plays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

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

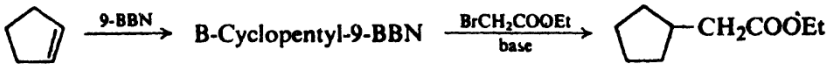


1,5-Cyclooctadiene 9-Borabicyclo[3.3.1]nonane (9-BBN) B-Alkyl-9-borabicyclo[3.3.1]nonane (B-Alkyl-9-BBN)

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



Isobutylene B-Isobutyl-BBN 5-Methyl-2-hexanone



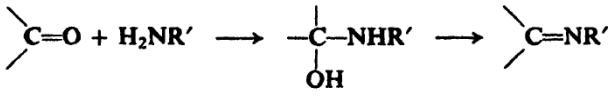
Cyclopentene Ethyl cyclopentylacetate

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

Problem 26.28 Using 9-BBN plus any alkenes and unhalogenated acids or ketones, outline all steps in the synthesis of: (a) 2-heptanone; (b) 4-methylpentanoic acid; (c) 4-methyl-2-hexanone; (d) 1-cyclohexyl-2-propanone; (e) ethyl (*trans*-2-methylcyclopentyl)acetate; (f) 1-phenyl-4-methyl-1-pentanone; (g) 1-cyclopentyl-3,3-dimethyl-2-butanone.

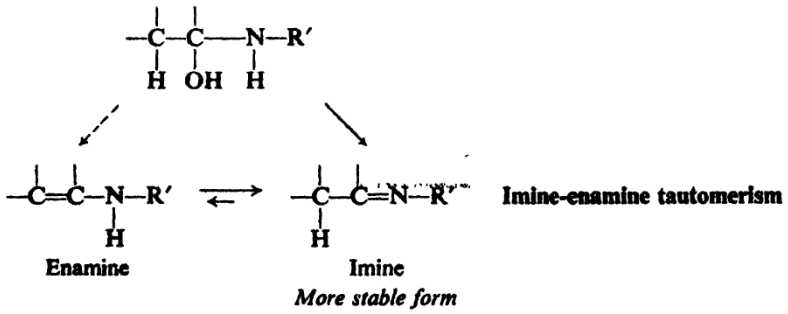
26.8 Alkylation of carbonyl compounds via enamines

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



A 1° amine An imine

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



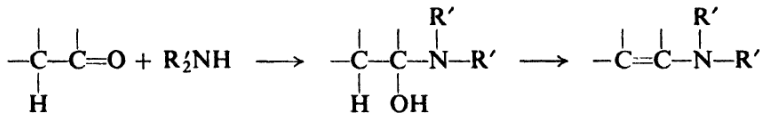
Enamine Imine

More stable form

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

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

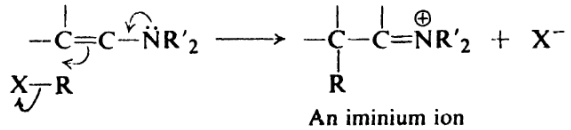
Now, a secondary amine, too, can react with a carbonyl compound, and to yield the same kind of initial product. But here there is no hydrogen left on nitrogen; if dehydration is to occur, it must be in the other direction, to form a carbon–carbon double bond. A stable enamine is the product.



A 2° imine — An enamine

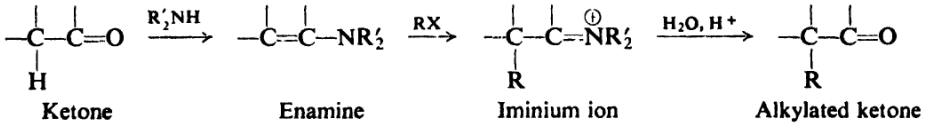
In 1954 Gilbert Stork (of Columbia University) showed how enamines could be used in the alkylation and acylation of aldehydes and ketones, and in the years since then enamines have been intensively studied and used in organic synthesis in a wide variety of ways. All we can do here is to try to understand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

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



An iminium ion

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



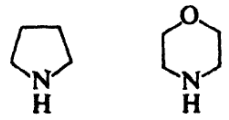
Ketone — Enamine — Iminium ion — Alkylated ketone

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

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

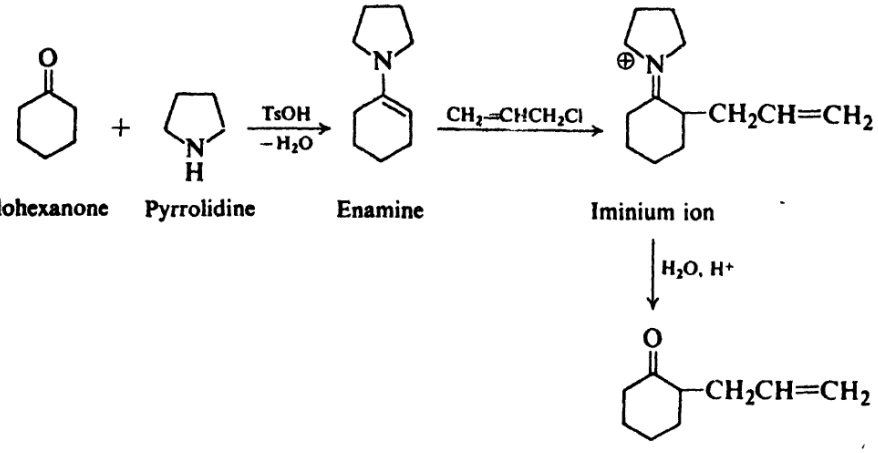
of aniline involves, we say, electrophilic attack by bromine on the aromatic ring; but from the opposite, and equally valid, point of view, it involves nucleophilic attack on bromine by carbons of the ring—with nitrogen furnishing the electrons.

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

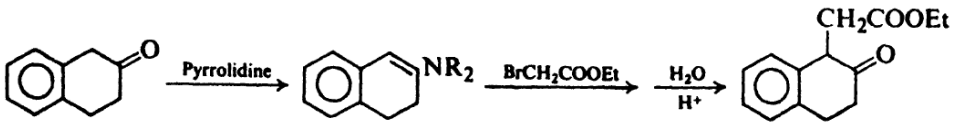


Pyrrolidine Morpholine

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



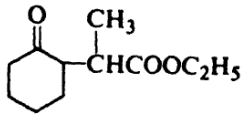
Cyclohexanone Pyrrolidine Enamine Iminium ion

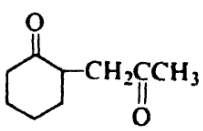


β-Tetralone Enamine

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

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

(c) 

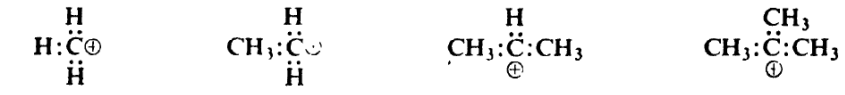
(d) 

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

5.15 Carbonium ions

To account for the observed facts, we saw earlier, a certain mechanism was advanced for the halogenation of alkanes; the heart of this mechanism is the fleeting existence of free radicals, highly reactive neutral particles bearing an odd electron.

Before we can discuss the preparation of alkenes by dehydration of alcohols, we must first learn something about another kind of reactive particle: the **carbonium ion**, *a group of atoms that contains a carbon atom bearing only six electrons.* Carbonium ions are classified as primary, secondary, or tertiary after the carbon bearing the positive charge. They are named by use of the word *cation.* For example:



Methyl cation | Ethyl cation (*primary*, 1°) | Isopropyl cation (*secondary*, 2°) | *tert*-Butyl cation (*tertiary*, 3°)

Like the free radical, the carbonium ion is an exceedingly reactive particle, and for the same reason: the tendency to complete the octet of carbon. Unlike the free radical, the carbonium ion carries a positive charge.

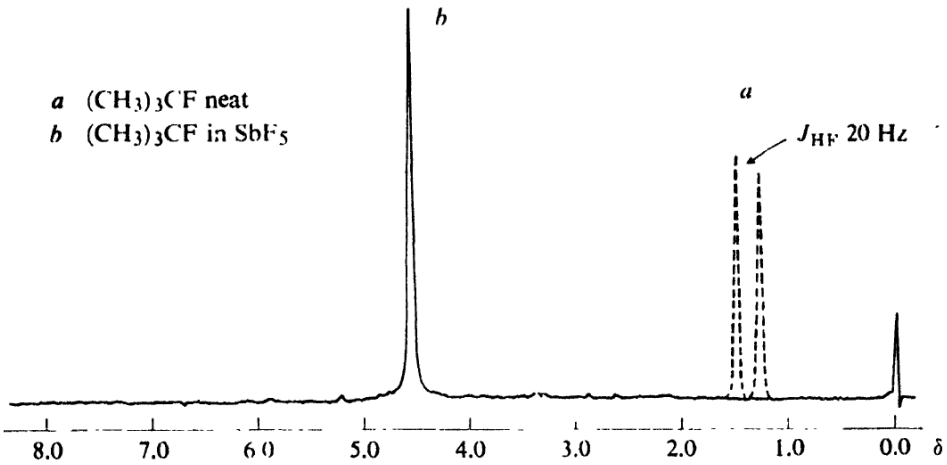
One kind of unusually stable carbonium ion (Sec. 12.19) was recognized as early as 1902 by the salt-like character of certain organic compounds. But direct observation of simple alkyl cations should be exceedingly difficult, by virtue of the very reactivity—and hence short life—that we attribute to them. Nevertheless, during the 1920's and 1930's, alkyl cations were proposed as intermediates in many organic reactions, and their existence was generally accepted, due largely to the work of three chemists: Hans Meerwein of Germany, "the father of modern carbonium ion chemistry;" Sir Christopher Ingold of England; and Frank Whitmore of the United States. The evidence consisted of a wide variety of observations made in studying the chemistry of alkenes, alcohols, alkyl halides, and many other kinds of organic compounds: observations that revealed a basically similar pattern of behavior most logically attributed to intermediate carbonium ions. A sizable part of this book will be devoted to seeing what that pattern is.

In 1963, George Olah (now at Case Western Reserve University) reported the *direct observation* of simple alkyl cations. Dissolved in the extremely powerful Lewis acid SbF_5, alkyl fluorides (and, later, other halides) were found to undergo ionization to form the cation, which could be studied at leisure. There was a

$$RF + SbF_5 \longrightarrow R^+ SbF_6^-$$

dramatic change in the nmr spectrum (Chap. 13), from the spectrum of the alkyl fluoride to the spectrum of a molecule that contained no fluorine but instead sp^2-hybridized carbon with a very low electron density. Figure 5.7 shows what was observed for the *tert*-butyl fluoride system: a simple spectrum but, by its very

simplicity, enormously significant. Although potentially very reactive, the *tert*-butyl cation can do little in this environment except try to regain the fluoride ion—and the SbF_5 is an even stronger Lewis acid than the cation.



Courtesy of *The Journal of American Chemical Society*

Figure 5.7. Proton nmr spectrum of (*a*) *tert*-butyl fluoride and (*b*) *tert*-butyl cation. In (*a*), proton signal split into two peaks by coupling with nearby fluorine. In (*b*), single peak, shifted far downfield; strong deshielding due to low electron density on positive carbon.

By methods like this, Olah has opened the door to the study not just of the existence of organic cations of many kinds, but of intimate details of their structure.

5.16 Structure of carbonium ions

In a carbonium ion, the electron-deficient carbon is bonded to three other atoms, and for this bonding uses sp^2 orbitals; the bonds are trigonal, directed to the corners of an equilateral triangle. This part of a carbonium ion is therefore

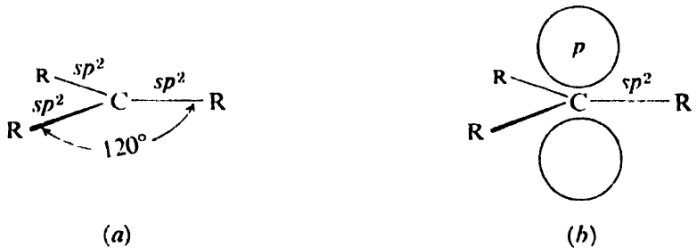


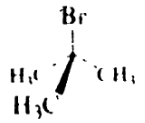
Figure 5.8. A carbonium ion. (*a*) Only σ bonds shown. (*b*) Empty *p* orbital above and below plane of σ bonds.

flat, the electron-deficient carbon and the three atoms attached to it lying in the same plane (Fig. 5.8*a*).

But our description of the molecule is not yet quite complete. Carbon has left a *p* orbital, with its two lobes lying above and below the plane of the σ bonds (Fig. 5.8*b*); in a carbonium ion, the *p* orbital is *empty*. Although formally empty, this *p* orbital, we shall find, is intimately involved in the chemistry of carbonium ions: in their stability, and the stability of various transition states leading to their formation.

There can be little doubt that carbonium ions actually are flat. The quantum mechanical picture of a carbonium ion is exactly the same as that of boron trifluoride (Sec. 1.10), a molecule whose flatness is firmly established. Nmr and infrared spectra of the stabilized carbonium ions studied by Olah are consistent with sp^2 hybridization and flatness: in particular, infrared and Raman spectra of the *tert*-butyl cation are strikingly similar to those of trimethylboron, known to be flat.

Evidence of another kind indicates that carbonium ions not only normally *are* flat, but have a strong *need to be* flat. Consider the three tertiary alkyl bromides: *tert*-butyl bromide; and I and II, which are *bicyclic* (two-ringed) compounds with



tert-Butyl bromide

I

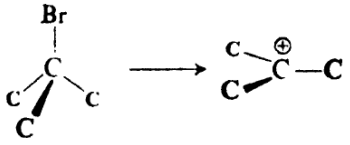
1-Bromobicyclo-[2.2.2]octane

II

1-Bromobicyclo-[2.2.1]heptane

bromine at the bridgehead. The impact of a high-energy electron can remove bromine from an alkyl bromide and generate a carbonium ion; the energy of the electron required to do the job can be measured. On electron impact, I requires 5 kcal mole more energy to form the carbonium ion than does *tert*-butyl bromide, and II requires 20 kcal mole more energy.

How are we to interpret these facts? On conversion into a carbonium ion, three carbons must move into the plane of the electron-deficient carbon: easy for



Alkyl bromide
Tetrahedral

Carbonium ion
Trigonal

the open-chain *tert*-butyl group; but difficult for I, where the three carbons are tied back by the ring system; and still more difficult for II, where they are tied back more tightly by the smaller ring.

Imagine- or, better, *make* -a model of I or II. You could squash the top of the molecule flat, but only by distorting the angles of the other bonds away from their normal tetrahedral angle, and thus introducing *angle strain* (Sec. 9.7).

Now, why is there this need to be flat? Partly, to permit formation of the strongest possible σ bonds through sp^2 hybridization. But there is a second ad-

vantage of flatness, one which is related to the major factor determining carbonium ion stability, *accommodation of charge.*

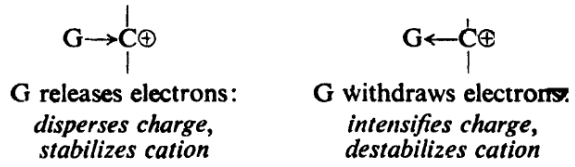
5.17 Stability of carbonium ions. Accommodation of charge

The characteristic feature of a carbonium ion is, by definition, the electron-deficient carbon and the attendant positive charge. The relative stability of a carbonium ion is determined chiefly by how well it *accommodates* that charge.

According to the laws of electrostatics, **the stability of a charged system is increased by dispersal of the charge.** Any factor, therefore, that tends to spread out the positive charge of the electron-deficient carbon and distribute it over the rest of the ion must stabilize a carbonium ion.

Consider a substituent, G, attached to an electron-deficient carbon in place of a hydrogen atom. Compared with hydrogen, G may either release electrons or withdraw electrons (Sec. 1.23).

Carbonium Ion Stability



An electron-releasing substituent tends to reduce the positive charge at the electron-deficient carbon; in doing this, the substituent itself becomes somewhat positive. This dispersal of the charge stabilizes the carbonium ion.

An electron-withdrawing substituent tends to intensify the positive charge on the electron-deficient carbon, and hence makes the carbonium ion less stable.

We consider (Sec. 1.23) electronic effects to be of two kinds: *inductive effects*, related to the electronegativity of substituents; and *resonance effects*. In the case of carbonium ions, we shall see (Sec. 8.21), a resonance effect involves overlap of the "empty" p orbital of the electron-deficient carbon with orbitals on other, nearby atoms; the result is, of course, that the p orbital is no longer empty, and the electron-deficient carbon no longer so positive. Maximum overlap depends on coplanarity in this part of the molecule, and it is here that we find the second advantage of flatness in a carbonium ion.

So far, we have discussed only factors operating *within* a carbonium ion to make it more or less stable than another carbonium ion. But what is *outside* the carbonium ion proper—its environment—can be even more important in determining how fast a carbonium ion is formed, how long it lasts, and what happens to it. There are *anions*, one of which may stay close by to form an ion pair. There is the *solvent*: a cluster of solvent molecules, each with the positive end of its dipole turned toward the cation; possibly one solvent molecule—or two—playing a special role through overlap of one or both lobes of the p orbital. There may be a *neighboring group effect* (Chap. 28), in which a substituent on a neighboring carbon approaches closely enough to share its electrons and form a covalent bond: an internal factor, actually, but in its operation much like an external factor.

In all this we see the characteristic of carbonium ions that underlies their whole pattern of behavior: a *need for electrons to complete the octet of carbon.*

5.21 Ease of formation of carbonium ions

The ease with which alcohols undergo dehydration follows the sequence $3° > 2° > 1°$. There is evidence that a controlling factor in dehydration is the formation of the carbonium ion, and that one alcohol is dehydrated more easily than another chiefly because it forms a carbonium ion more easily.

Carbonium ions can be formed from compounds other than alcohols, and in reactions other than elimination. In all these cases the evidence indicates that the ease of formation of carbonium ions follows the same sequence:

Ease of formation of carbonium ions $3° > 2° > 1° > CH_3^+$

In listing carbonium ions in order of their ease of formation, we find that we have at the same time listed them in order of their stability. **The more stable the carbonium ion, the more easily it is formed.**

Is it reasonable that the more stable carbonium ion should be formed more easily? To answer this question, we must look at a reaction in which a carbonium ion is formed, and consider the nature of the transition state.

In the dehydration of an alcohol, the carbonium ion is formed by loss of water from the protonated alcohol, ROH_2^+, that is, by breaking of the carbon–oxygen bond. In the reactant the positive charge is mostly on oxygen, and in the product it is on carbon. In the transition state the C—O bond must be partly broken, oxygen having partly pulled the electron pair away from carbon. The positive charge originally on oxygen is now divided between carbon and oxygen. Carbon has partly gained the positive charge it is to carry in the final carbonium ion.

$$\underset{\substack{\text{Reactant}\\ \textit{Oxygen has full positive charge}}}{R{:}OH_2^+} \longrightarrow \underset{\substack{\text{Transition state}\\ \textit{Carbon and oxygen have partial positive charges}}}{\left[R\cdots{:}\overset{\delta_+}{O}H_2\right]^{\delta_+}} \longrightarrow \underset{\substack{\text{Products}\\ \textit{Carbon has full positive charge}}}{R^+ + {:}OH_2}$$

Electron-releasing groups tend to disperse the partial positive charge (δ_+) developing on carbon, and in this way stabilize the transition state. Stabilization of the transition state lowers E_{act} and permits a faster reaction (see Fig. 5.10).

Thus the same factor, electron release, that stabilizes the carbonium ion also stabilizes the *incipient* carbonium ion in the transition state. The more stable carbonium ion is formed faster.

We shall return again and again to the relationship between electronic effects and dispersal of charge, and between dispersal of charge and stability. We shall find that these relationships will help us to understand carbonium ion reactions of many kinds, and, in fact, all reactions in which a charge—positive or negative—develops or disappears. These will include reactions as seemingly different from dehydra-

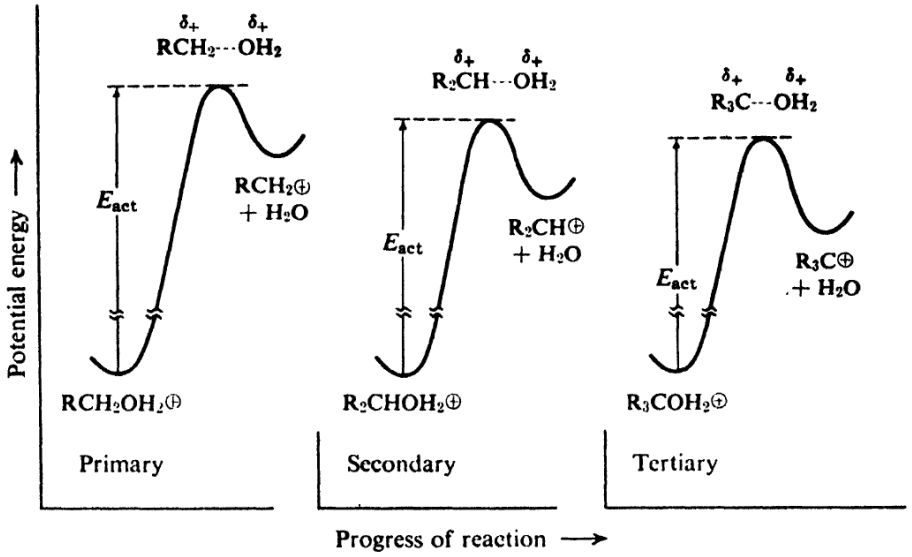


Figure 5.10. Molecular structure and rate of reaction. Stability of transition state parallels stability of carbonium ion: more stable carbonium ion formed faster. (Plots aligned with each other for easy comparison.)

tion of alcohols as: addition to alkenes, aromatic and aliphatic substitution, rearrangements, acidity and basicity.

5.22 Rearrangement of carbonium ions

Very often, dehydration gives alkenes that do not fit the mechanism as we have so far seen it. The double bond appears in unexpected places; sometimes the carbon skeleton is even changed. For example:

$CH_3CH_2CH_2CH_2OH \xrightarrow{H^+} CH_3CH{=}CHCH_3$
n-Butyl alcohol — 2-Butene (*Chief product*)

$CH_3CH_2\underset{\displaystyle CH_3}{\overset{|}{C}}HCH_2OH \xrightarrow{H^+} CH_3CH{=}\underset{\displaystyle CH_3}{\overset{|}{C}}CH_3$
2-Methyl-1-butanol — 2-Methyl-2-butene (*Chief product*)

$CH_3\underset{\displaystyle CH_3}{\overset{|}{C}}CHOHCH_3 \xrightarrow{H^+} CH_3\underset{\displaystyle CH_3}{\overset{|}{C}}{=}CCH_3$ and $CH_3\underset{\displaystyle CH_3}{\overset{|}{C}}HC{=}CH_2$
3,3-Dimethyl-2-butanol — 2,3-Dimethyl-2-butene (*Chief product*); 2,3-Dimethyl-1-butene

Take the formation of 2-butene from *n*-butyl alcohol. Loss of water from the protonated alcohol gives the *n*-butyl carbonium ion. Loss of the proton from the

carbon adjacent to the positive carbon could give 1-butene but *not* the 2-butene that is the major product.

$$CH_3CH_2CH_2CH_2\overset{\oplus}{O}H_2 \longrightarrow H_2O + CH_3CH_2CH_2CH_2^{\oplus} \longrightarrow CH_3CH_2CH{=}CH_2$$

The other examples are similar. In each case we conclude that if, indeed, the alkene is formed from a carbonium ion, *it is not the same carbonium ion that is initially formed from the alcohol.*

A similar situation exists for many reactions besides dehydration. The idea of intermediate carbonium ions accounts for the facts *only* if we add this to the theory: *a carbonium ion can rearrange to form a more stable carbonium ion.*

n-Butyl alcohol, for example, yields the *n*-butyl cation; this rearranges to the *sec*-butyl cation, which loses a hydrogen ion to give (predominantly) 2-butene:

$$CH_3CH_2CH_2CH_2\overset{\oplus}{O}H_2 \longrightarrow CH_3CH_2CH_2CH_2^{\oplus} + H_2O$$

$$\underset{(1°)}{CH_3CH_2CH_2CH_2^{\oplus}} \longrightarrow \underset{(2°)}{CH_3CH_2\overset{\oplus}{C}HCH_3} \qquad \textit{Rearrangement}$$

$$CH_3CH_2\overset{\oplus}{C}HCH_3 \longrightarrow \underset{\substack{\text{2-Butene}\\ \textit{Chief product}}}{CH_3CH{=}CHCH_3} + H^+$$

In a similar way, the 2-methyl-1-butyl cation rearranges to the 2-methyl-2-butyl cation,

$$\underset{(1°)}{CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2^{\oplus}} \longrightarrow \underset{(3°)}{CH_3CH_2\overset{CH_3}{\overset{|}{C}}CH_3} \qquad \textit{Rearrangement}$$

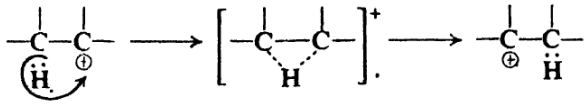
and the 3,3-dimethyl-2-butyl cation rearranges to the 2,3-dimethyl-2-butyl cation.

$$\underset{(2°)}{CH_3C(CH_3)_2CHCH_3} \longrightarrow \underset{(3°)}{CH_3C(CH_3)_2CCH_3} \qquad \textit{Rearrangement}$$

We notice that in each case rearrangement occurs in the way that yields the more stable carbonium ion: primary to a secondary, primary to a tertiary, or secondary to a tertiary.

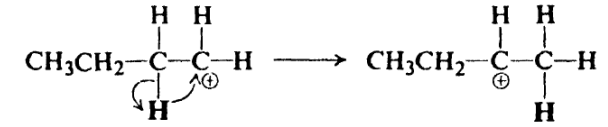
Just how does this rearrangement occur? Frank Whitmore (of The Pennsylvania State University) pictured rearrangement as taking place in this way: a hydrogen atom or alkyl group migrates *with a pair of electrons* from an adjacent carbon to the carbon bearing the positive charge. The carbon that loses the migrating group acquires the positive charge. A migration of hydrogen with a pair of electrons is known as a **hydride shift**; a similar migration of an alkyl group is known as an **alkyl shift**. These are just two examples of the most common kind

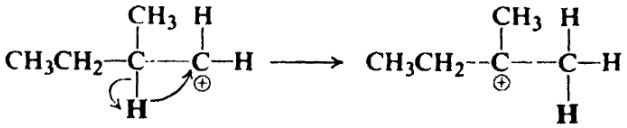
of rearrangement, the **1,2-shifts**: *rearrangements in which the migrating group moves from one atom to the very next atom.*

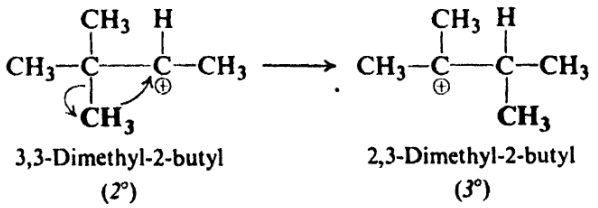


We can account for rearrangements in dehydration in the following way. A carbonium ion is formed by the loss of water from the protonated alcohol. **If a 1,2-shift of hydrogen or alkyl can form a more stable carbonium ion, then such a rearrangement takes place.** The new carbonium ion now loses a proton to yield an alkene.

In the case of the *n*-butyl cation, a shift of hydrogen yields the more stable *sec*-butyl cation; migration of an ethyl group would simply form a different *n*-butyl cation. In the case of the 2-methyl-1-butyl cation, a hydride shift yields a tertiary cation, and hence is preferred over a methyl shift, which would only yield a secondary cation. In the case of the 3,3-dimethyl-2-butyl cation, on the other hand, a methyl shift can yield a tertiary cation and is the rearrangement that takes place.



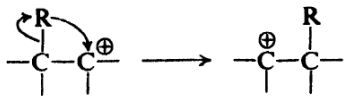




Historically, it was the occurrence of rearrangements that was chiefly responsible for the development of the carbonium ion theory. Reactions of seemingly

28.1 Rearrangements and neighboring group effects: intramolecular nucleophilic attack

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

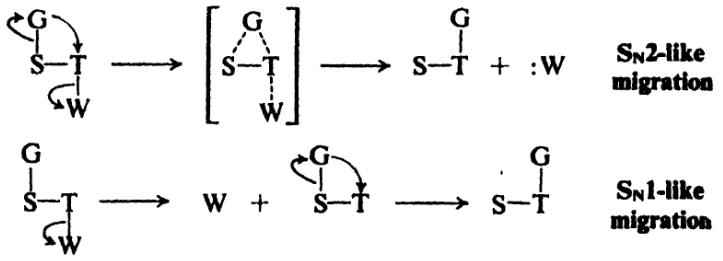


carbon. Indeed, when carbonium ions were first postulated as reactive intermediates (p. 160), it was to account for rearrangements of a particular kind. Such rearrangements still provide the best single clue that we are dealing with a carbonium ion reaction.

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

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

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



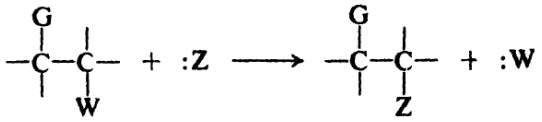
G = migrating group
S = migration source
T = migration terminus

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

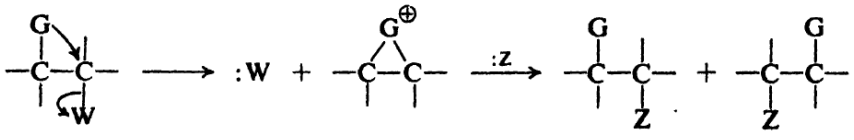
The term *anchimeric assistance* (Gr., *anchi* + *meros*, adjacent parts) is often used to describe the help given by a migrating group in the expelling of a leaving group.

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

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



But what is actually happening may be this:



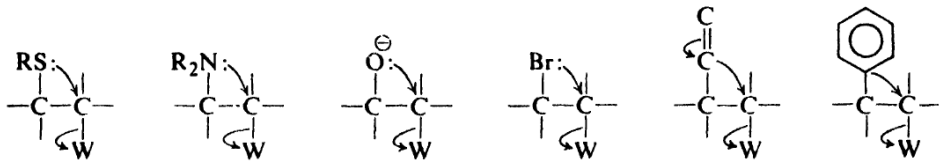
I

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

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

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

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



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

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

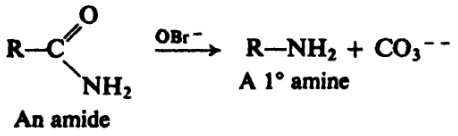
Enzymes function by accelerating, very specifically, rates of the organic reactions involved in life processes. They evidently do this by bringing reactants together into exactly the right positions for reaction to occur. Underlying much enzyme activity, it appears, are what amount to neighboring group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

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

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

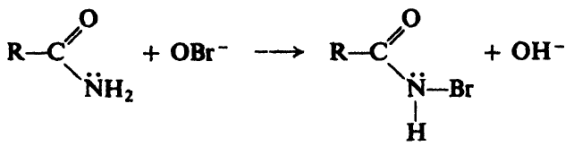
28.2 Hofmann rearrangement. Migration to electron-deficient nitrogen

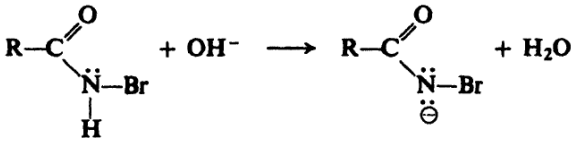
Let us begin with a reaction that we encountered earlier as a method of synthesis of amines: the Hofmann degradation of amides. Whatever the mechanism

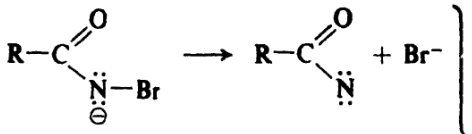


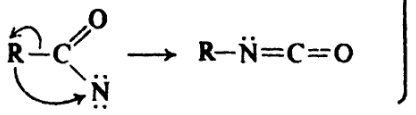
of the reaction, it is clear that rearrangement occurs, since the group joined to carbonyl carbon in the amide is found joined to nitrogen in the product.

The reaction is believed to proceed by the following steps:

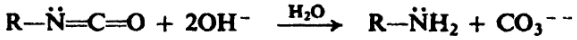
(1) 

(2) 

(3) 

(4) 

Simultaneous

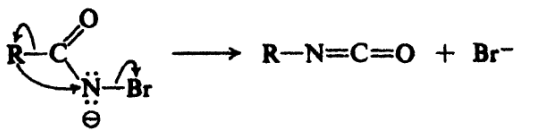
(5) 

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

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

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

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

(3,4) 

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

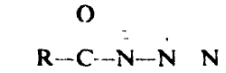
Step (5) is the hydrolysis of an isocyanate (R—N=C=O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

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

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

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

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



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

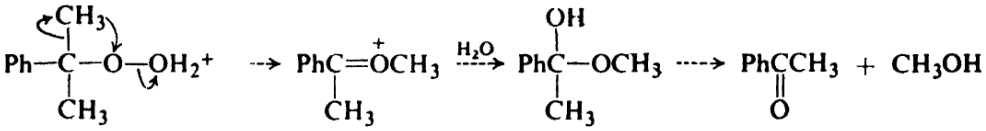
28.3 Hofmann rearrangement. Intramolecular or intermolecular?

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

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

28.7 Rearrangement of hydroperoxides. Migratory aptitude

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

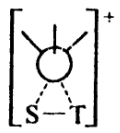


Acetophenone Methanol

Not obtained

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

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



IV

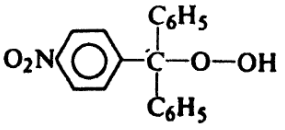
Alkyl migration. *pentavalent carbon*

V

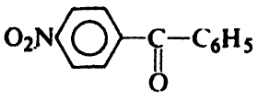
Aryl migration: *benzenonium ion*

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

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



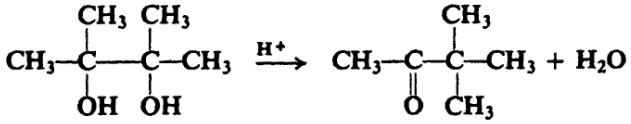
VI



VII

28.8 Pinacol rearrangement. Migration to electron-deficient carbon

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



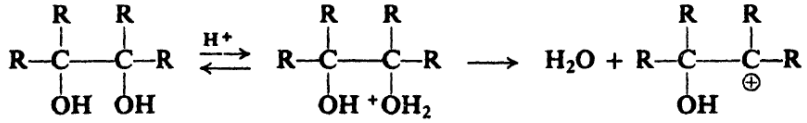
Pinacol
2,3-Dimethyl-2,3-butanediol

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

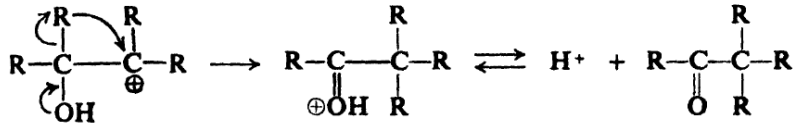
glycol undergoes dehydration, and in such a way that rearrangement of the carbon skeleton occurs. Other glycols undergo analogous reactions, which are known collectively as **pinacol rearrangements.**

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

(1)



(2)



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

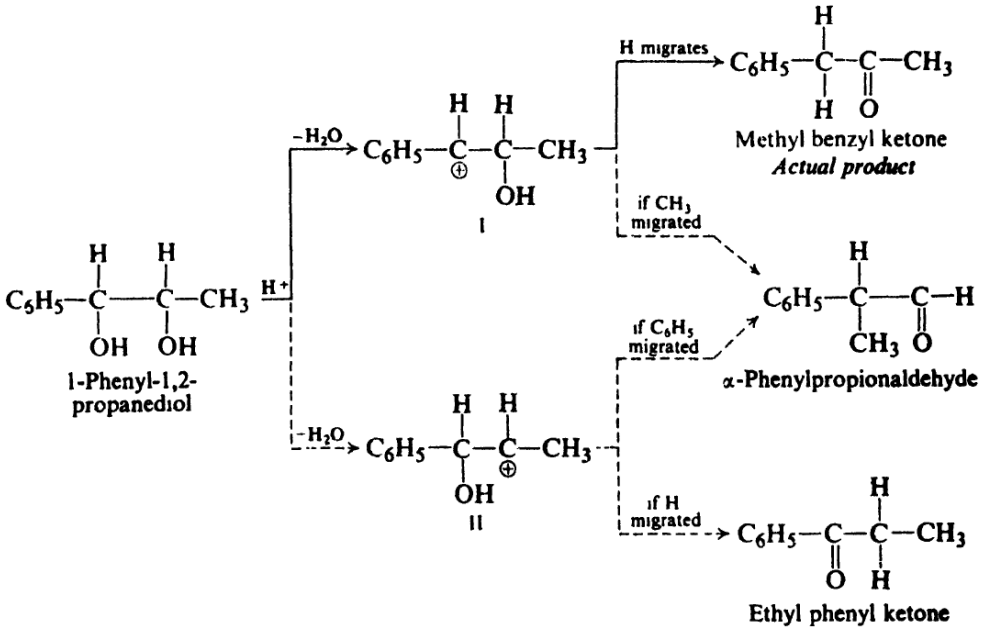
usual one behind carbonium ion reactions: the need to provide the electron-deficient carbon with electrons. The special feature of the pinacol rearrangement is the presence in the molecule of the second oxygen atom; it is this oxygen atom, with its unshared pairs, that ultimately provides the needed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

Problem 28.7 Account for the products of the following reactions:

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

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

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



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

Chapter 9 Alicyclic Hydrocarbons

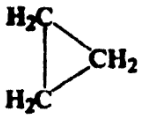
9.1 Open-chain and cyclic compounds

In the compounds that we have studied in previous chapters, the carbon atoms are attached to one another to form *chains*; these are called **open-chain** compounds. In many compounds, however, the carbon atoms are arranged to form *rings*; these are called **cyclic** compounds.

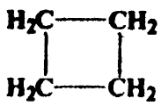
In this chapter we shall take up the *alicyclic* hydrocarbons (*aliphatic cyclic* hydrocarbons). Much of the chemistry of cycloalkanes and cycloalkenes we already know, since it is essentially the chemistry of open-chain alkanes and alkenes. But the cyclic nature of some of these compounds confers very special properties on them. It is because of these special properties that, during the past fifteen years, alicyclic chemistry has become what Professor Lloyd Ferguson, of the California State College at Los Angeles, has called "the playground for organic chemists." It is on some of these special properties that we shall focus our attention.

9.2 Nomenclature

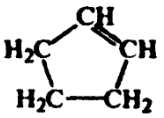
Cyclic aliphatic hydrocarbons are named by prefixing **cyclo-** to the name of the corresponding open-chain hydrocarbon having the same number of carbon atoms as the ring. For example:



Cyclopropane



Cyclobutane



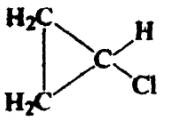
Cyclopentene

Substituents on the ring are named, and their positions are indicated by numbers,

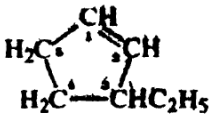
Table 9.1 CYCLIC ALIPHATIC HYDROCARBONS

Name	M.p., °C	B.p., °C	Density (at 20°C)
Cyclopropane	−127	− 33	
Cyclobutane	− 80	13	
Cyclopentane	− 94	49	0.746
Cyclohexane	6.5	81	.778
Cycloheptane	− 12	118	.810
Cyclooctane	14	149	.830
Methylcyclopentane	−142	72	.749
cis-1,2-Dimethylcyclopentane	− 62	99	.772
trans-1,2-Dimethylcyclopentane	−120	92	.750
Methylcyclohexane	−126	100	.769
Cyclopentene	− 93	46	.774
1,3-Cyclopentadiene	− 85	42	.798
Cyclohexene	−104	83	.810
1,3-Cyclohexadiene	− 98	80.5	.840
1,4-Cyclohexadiene	− 49	87	.847

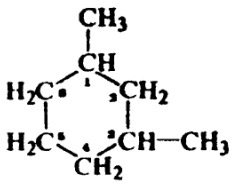
the lowest combination of numbers being used. In simple cycloalkenes and cycloalkynes the doubly- and triply-bonded carbons are considered to occupy positions 1 and 2. For example:



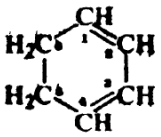
Chlorocyclopropane



3-Ethylcyclopentene



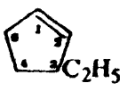
1,3-Dimethylcyclohexane



1,3-Cyclohexadiene

For convenience, aliphatic rings are often represented by simple geometric figures: a triangle for cyclopropane, a square for cyclobutane, a pentagon for cyclopentane, a hexagon for cyclohexane, and so on. It is understood that two hydrogens are located at each corner of the figure unless some other group is indicated. For example:

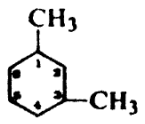
Cyclopentane



3-Ethylcyclopentene

1,3-Cyclopentadiene

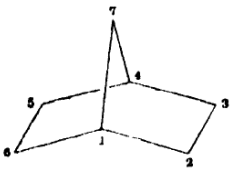
Cyclohexane



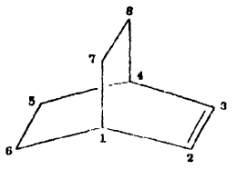
1,3-Dimethylcyclohexane

1,3-Cyclohexadiene

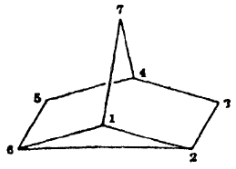
Polycyclic compounds contain two or more rings that share two or more carbon atoms. We can illustrate the naming system with *norbornane*, whose systematic name is bicyclo[2.2.1]heptane: (a) *heptane*, since it contains a total of *seven* carbon atoms; (b) *bicyclo*, since it contains *two* rings, that is, breaking two carbon–



Bicyclo[2.2.1]heptane
Norbornane



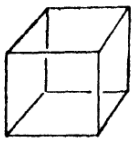
Bicyclo[2.2.2]octa-2-ene



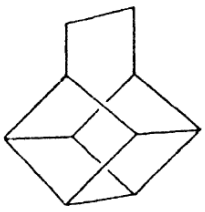
Tricyclo[2.2.1.$0^{2,6}$]heptane
Nortricyclene

carbon bonds converts it into an open-chain compound; (c) [2.2.1], since the number of carbons between bridgeheads (shared carbons) is *two* (C–2 and C–3), *two* (C–5 and C–6), and *one* (C–7).

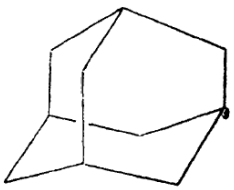
Polycyclic compounds in a variety of strange and wonderful shapes have been made, and their properties have revealed unexpected facets of organic chemistry. Underlying much of this research there has always been the challenge: ***can such a compound be made?***



Cubane

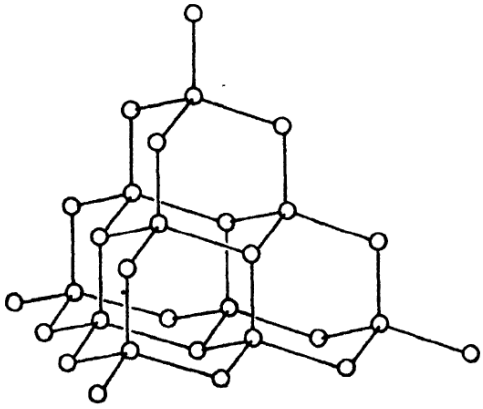


Basketane



Adamantane

The ultimate polycyclic aliphatic system is *diamond* which is, of course, not a hydrocarbon at all, but one of the allotropic forms of elemental carbon. In diamond each



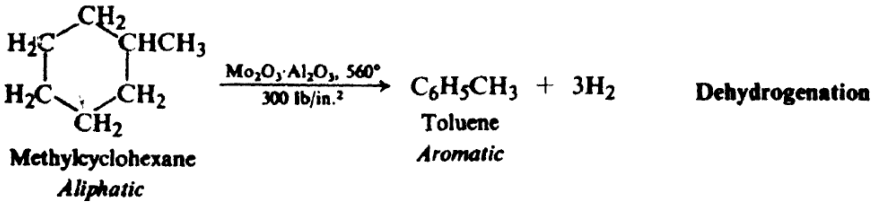
Diamond

carbon atom is attached to four others by tetrahedral bonds of the usual single bond length, 1.54 A. (Note the cyclohexane chairs, Sec. 9.11.)

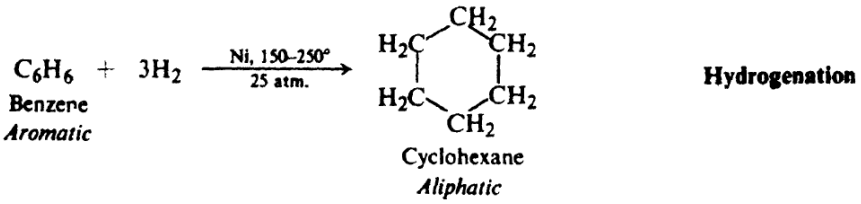
9.3 Industrial source

We have already mentioned (Sec. 3.13) that petroleum from certain areas (in particular California) is rich in cycloalkanes, known to the petroleum industry as *naphthenes*. Among these are cyclohexane, methylcyclohexane, methylcyclopentane, and 1,2-dimethylcyclopentane.

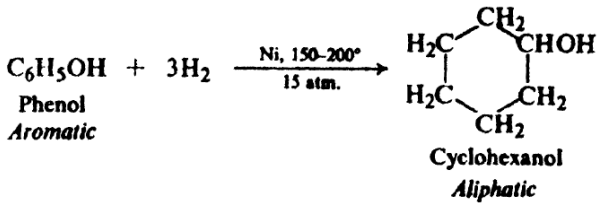
These cycloalkanes are converted by *catalytic reforming* into aromatic hydrocarbons, and thus provide one of the major sources of these important compounds (Sec. 12.4). For example:



Just as elimination of hydrogen from cyclic aliphatic compounds yields aromatic compounds, so addition of hydrogen to aromatic compounds yields cyclic aliphatic compounds, specifically cyclohexane derivatives. An important example of this is the hydrogenation of benzene to yield pure cyclohexane.



As we might expect, hydrogenation of substituted benzenes yields substituted cyclohexanes. For example:



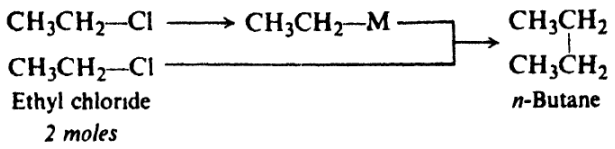
From cyclohexanol many other cyclic compounds containing a six-membered ring can be made.

9.4 Preparation

Preparation of alicyclic hydrocarbons from other aliphatic compounds generally involves two stages: (a) conversion of some open-chain compound or

compounds into a compound that contains a ring, a process called *cyclization*; (b) conversion of the cyclic compound thus obtained into the kind of compound that we want: for example, conversion of a cyclic alcohol into a cyclic alkene, or of a cyclic alkene into a cyclic alkane.

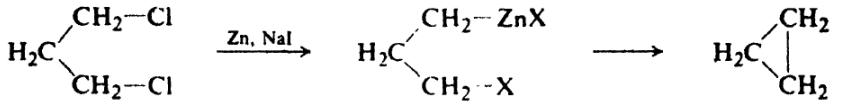
Very often, cyclic compounds are made by the *adapting* of a standard method of preparation to the job of closing a ring. For example, we have seen (Sec. 3.17) that the alkyl groups of two alkyl halides can be coupled together through conversion of one halide into an organometallic compound (a lithium dialkylcopper):



Ethyl chloride
2 moles

n-Butane

The same method applied to a *di*halide can bring about coupling between two alkyl groups *that are part of the same molecule*:



1,3-Dichloropropane

Cyclopropane

In this case zinc happens to do a good job. Although this particular method works well only for the preparation of cyclopropane, it illustrates an important principle: the carrying out of what is normally an *intermolecular* (between-molecules) reaction under such circumstances that it becomes an *intramolecular* (within-a-molecule) reaction. As we can see, it involves tying together the ends of a difunctional molecule.

Alicyclic hydrocarbons are prepared from other cyclic compounds (e.g., halides or alcohols) by exactly the same methods that are used for preparing open-chain hydrocarbons from other open-chain compounds.

Problem 9.1 Starting with cyclohexanol (Sec. 9.3), how would you prepare: (a) cyclohexene, (b) 3-bromocyclohexene, (c) 1,3-cyclohexadiene?

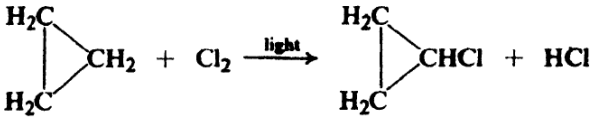
Problem 9.2 Bromocyclobutane can be obtained from open-chain compounds. How would you prepare cyclobutane from it?

The most important route to rings of many different sizes is through the important class of reactions called **cycloadditions**: *reactions in which molecules are added together to form rings*. We shall see one example of cycloaddition in Secs. 9.15–9.16, and others later on.

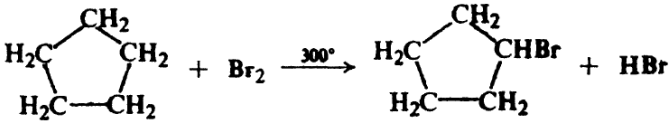
9.5 Reactions

With certain very important and interesting exceptions, alicyclic hydrocarbons undergo the same reactions as their open-chain analogs.

Cycloalkanes undergo chiefly free-radical substitution (compare Sec. 3.19). For example:

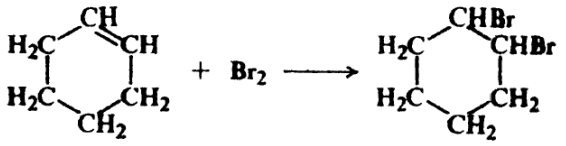


Cyclopropane Chlorocyclopropane

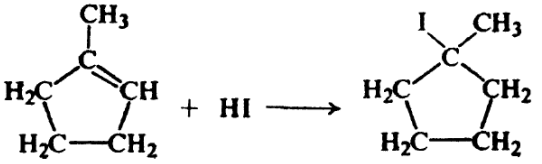


Cyclopentane Bromocyclopentane

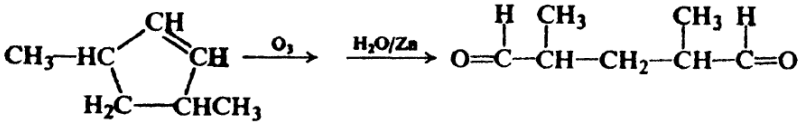
Cycloalkenes undergo chiefly addition reactions, both electrophilic and free radical (compare Sec. 6.2); like other alkenes, they can also undergo cleavage and allylic substitution. For example:



Cyclohexene 1,2-Dibromocyclohexane



1-Methylcyclopentene 1-Iodo-1-methylcyclopentane



3,5-Dimethylcyclopentene A dialdehyde

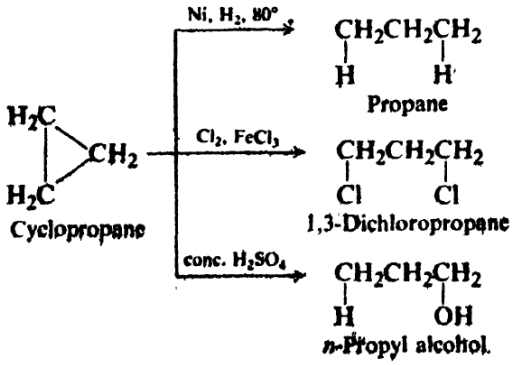
The two smallest cycloalkanes, cyclopropane and cyclobutane, show certain chemical properties that are entirely different from those of the other members of their family. Some of these exceptional properties fit into a pattern and, as we shall see, can be understood in a general way.

The chemistry of bicyclic compounds is even more remarkable, and is right now one of the most intensively studied areas of organic chemistry (Sec. 28.13).

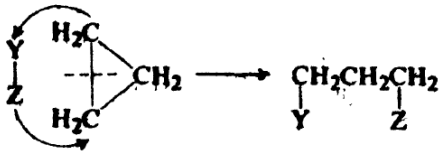
9.6 Reactions of small-ring compounds. Cyclopropane and cyclobutane

Besides the free-radical substitution reactions that are characteristic of cycloalkanes and of alkanes in general, cyclopropane and cyclobutane undergo certain

addition reactions. These addition reactions destroy the cyclopropane and cyclobutane ring systems, and yield open-chain products. For example:



In each of these reactions a carbon–carbon bond is broken, and the two atoms of the reagent appear at the ends of the propane chain:



In general, cyclopropane undergoes addition less readily than propylene: chlorination, for example, requires a Lewis acid catalyst to polarize the chlorine molecule (compare Sec. 11.11). Yet the reaction with sulfuric acid and other aqueous protic acids takes place considerably faster for cyclopropane than for propylene. (Odder still, treatment with bromine and $FeBr_3$ yields a grand mixture of bromopropanes.)

Cyclobutane does not undergo most of the ring-opening reactions of cyclopropane; it is hydrogenated, but only under more vigorous conditions than those required for cyclopropane. Thus cyclobutane undergoes addition less readily than cyclopropane and, with some exceptions, cyclopropane less readily than an alkene. The remarkable thing is that these cycloalkanes undergo addition at all.

9.7 Baeyer strain theory

In 1885 Adolf von Baeyer (of the University of Munich) proposed a theory to account for certain aspects of the chemistry of cyclic compounds. The part of his theory dealing with the ring-opening tendencies of cyclopropane and cyclobutane is generally accepted today, although it is dressed in more modern language. Other parts of his theory have been shown to be based on false assumptions, and have been discarded.

Baeyer's argument was essentially the following. In general, when carbon is bonded to four other atoms, the angle between any pair of bonds is the tetrahedral angle 109.5°. But the ring of cyclopropane is a triangle with three angles of 60°, and the ring of cyclobutane is a square with four angles of 90°. In cyclopropane or cyclobutane, therefore, one pair of bonds to each carbon cannot assume the tetrahedral angle, but must be compressed to 60° or 90° to fit the geometry of the ring.