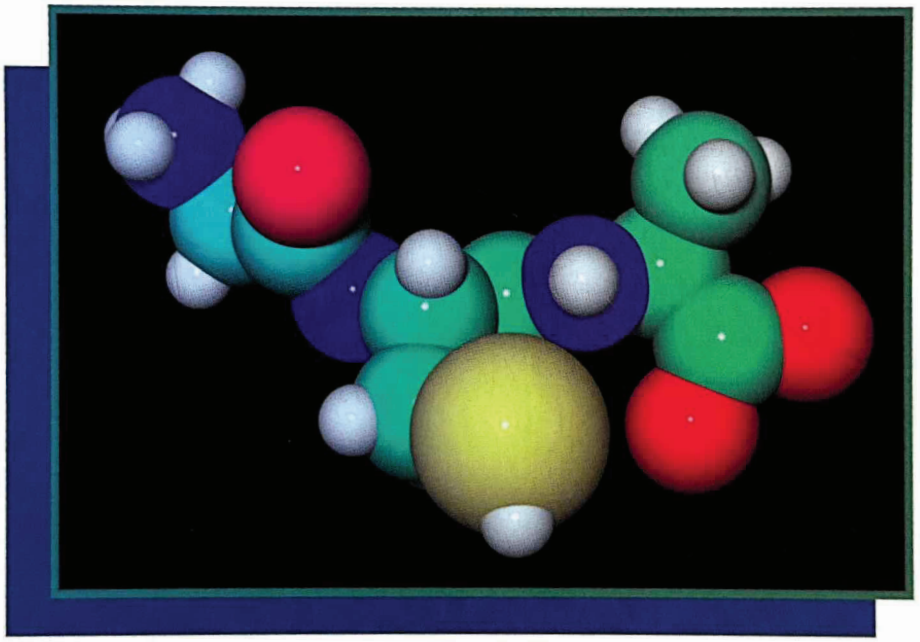
Organic Chemistry



Third Edition

L. G. WADE, JR.

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Organic Chemistry

L. G. Wade, Jr.
Whitman College



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A computer-generated representation of a tripeptide, glycylcysteylalanine. In this representation, carbon is green, hydrogen is white, nitrogen is blue, oxygen is red, and sulfur is yellow.

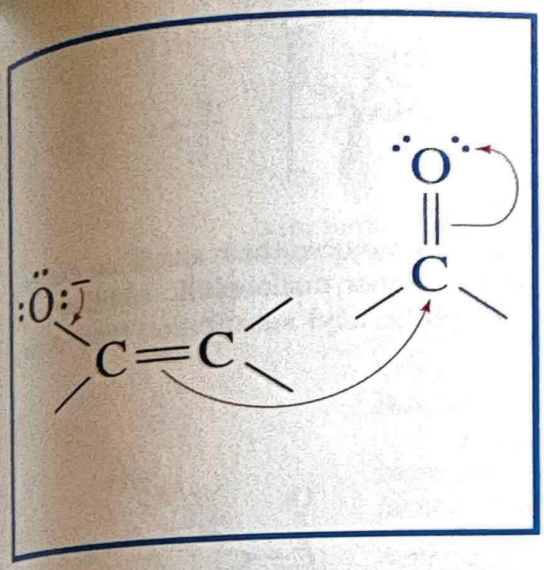
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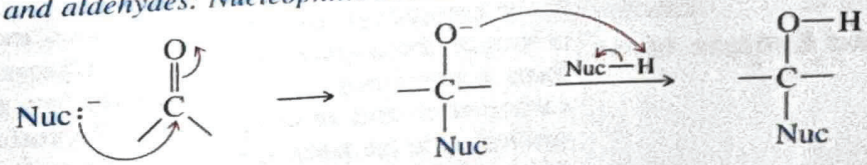
Additions and Condensations of Enols and Enolate Ions

22-1 Introduction

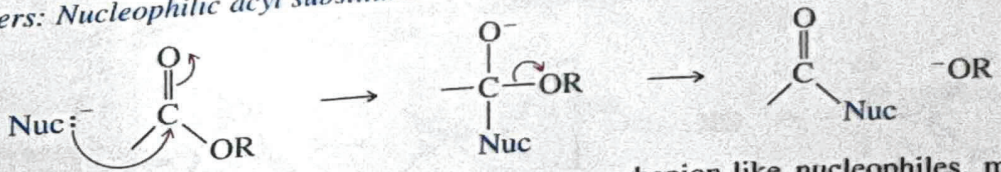
We have seen many electrophilic reactions of carbonyl compounds, with nucleophiles adding to carbonyl groups or substituting for leaving groups. In this chapter we consider how carbonyl compounds can become nucleophilic and attack other carbonyl groups or other types of electrophiles. First, let's review the most common electrophilic reactions of carbonyl compounds, then consider how to convert them to strong nucleophiles.

Ketones and aldehydes usually undergo nucleophilic addition to the carbonyl: A nucleophile attacks the electrophilic carbon atom, and the oxygen becomes protonated. Nucleophilic acyl substitution is the most common reaction of esters and other acid derivatives: Attack by a nucleophile is followed by elimination of an alkoxide or other leaving group.

Ketones and aldehydes: Nucleophilic addition

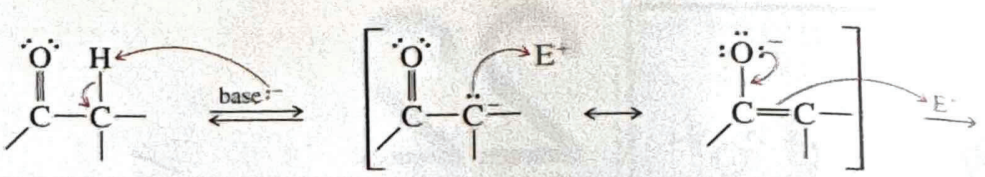


Esters: Nucleophilic acyl substitution



Carbonyl compounds can also serve as carbanion-like nucleophiles, most commonly at the carbon atom next to the carbonyl group: the **alpha carbon atom.** A proton can be removed from the alpha carbon to give a resonance-stabilized **enolate ion,** which is a strong nucleophile and can form a bond to an electrophile. Note that either resonance structure of the enolate ion can be shown attacking the electrophile; for illustration, both are shown on the following page.

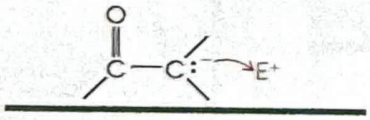
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enolate ion

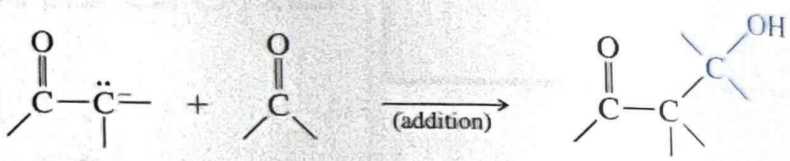
PROBLEM-SOLVING HINT

In drawing mechanisms, you can show either resonance structure of an enolate attacking the electrophile. It is often more intuitive to show the carbanion form attacking.

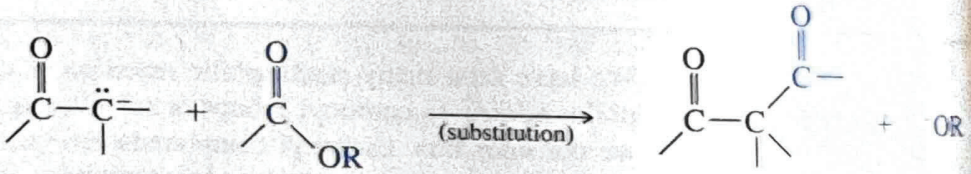


The most useful reactions of enolate ions involve their attack on carbonyl groups. Once again, these reactions may give either nucleophilic addition to the carbonyl (ketones and aldehydes) or nucleophilic acyl substitution (acid derivatives, especially esters).

Addition to ketones and aldehydes



Substitution with esters



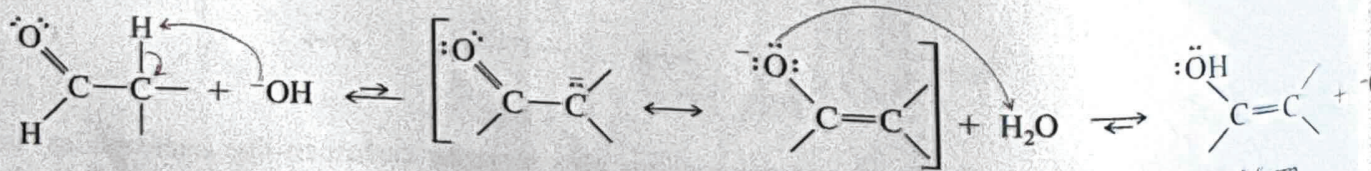
Nucleophilic reactions of carbonyl compounds are some of the most common methods for forming carbon–carbon bonds. A wide variety of compounds can participate as nucleophiles or electrophiles (or both) in these reactions, and many useful products can be synthesized. We begin our study of these reactions by considering the structure and formation of enols and enolate ions.

22-2 Enols and Enolate Ions

22-2A Keto–Enol Tautomerism

In the presence of strong bases, ketones and aldehydes act as weak proton acids. A proton on the α carbon (the carbon adjacent to the carbonyl group) is abstracted to form a resonance-stabilized **enolate ion** with the negative charge spread over a carbon atom and an oxygen atom. Reprotonation can occur either on the α carbon (returning to the **keto** form) or on the oxygen atom, giving a vinyl alcohol, the **enol** form.

Base-catalyzed keto–enol tautomerism



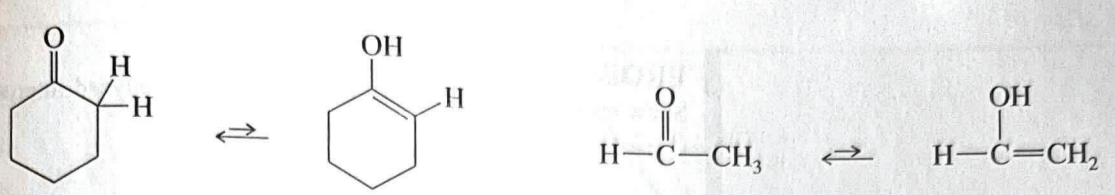
keto form

enolate ion

enol form (vinyl alcohol)

In this way, base catalyzes an equilibrium between isomeric keto and enol forms of a carbonyl compound. For simple ketones and aldehydes, the keto form predominates. Therefore, a vinyl alcohol (an enol) is best described as an alternative isomeric form of a ketone or aldehyde.

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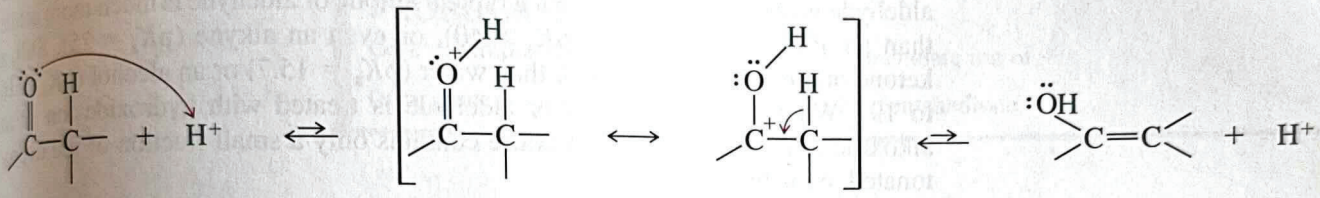


keto form (99.98%) | enol form (0.02%) | keto form (99.90%) | enol form (0.10%)

This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called **tautomerism,** and the isomers that interconvert are called **tautomers.** Tautomers are true isomers, and (under the right circumstances, with no catalyst present) either individual tautomeric form may be isolated.

Keto–enol tautomerism is also catalyzed by acid. In acid, a proton is moved from the α carbon to oxygen by first protonating oxygen and then removing a proton from carbon.

Acid-catalyzed keto–enol tautomerism



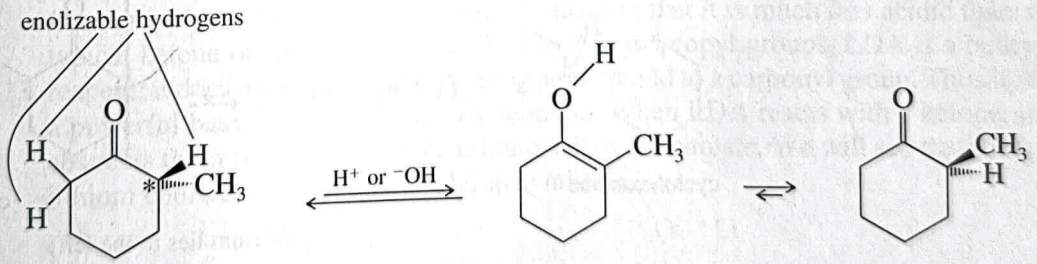
keto form | protonated carbonyl | enol form

PROBLEM-SOLVING HINT

In acid, proton transfers usually occur by adding a proton in the new position, then deprotonating the old position; in base, by deprotonating the old position, then reprotonating at the new position.

Compare the base-catalyzed and acid-catalyzed mechanisms shown above for keto–enol tautomerism. In base, the proton is removed from carbon, then replaced on oxygen. In acid, oxygen is protonated first, then carbon is deprotonated. Most proton-transfer mechanisms work this way. In base, the proton is removed from the old location, then replaced at the new location. In acid, protonation occurs at the new location, followed by deprotonation at the old location.

In addition to its mechanistic importance, keto–enol tautomerism affects the stereochemistry of ketones and aldehydes. A hydrogen atom on an α carbon (adjacent to a carbonyl group) may be lost and regained through keto–enol tautomerism; such a hydrogen is said to be **enolizable.** If a chiral carbon has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. A racemic mixture (or an equilibrium mixture of diastereomers) is the result.



(*R*) configuration | achiral | (*S*) configuration

PROBLEM 22-1

Phenylacetone can form two different enols.

(a) Show the structures of these enols.
(b) Predict which enol will be present in the larger concentration at equilibrium.
(c) Give mechanisms for the formation of the two enols in acid and in base.

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PROBLEM 22-2

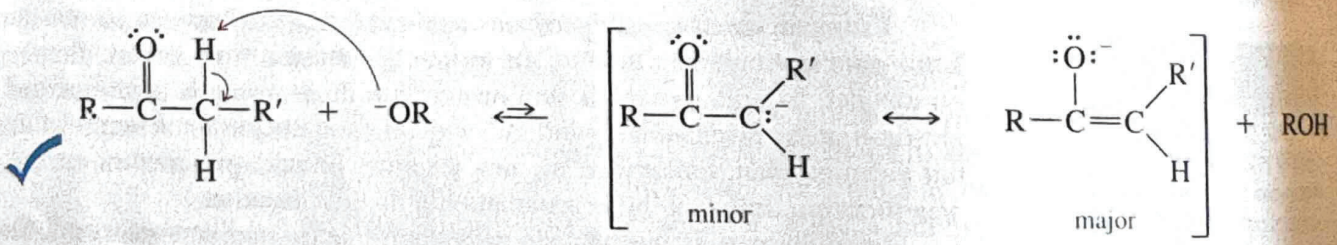
Show each step in the mechanism of the base-catalyzed interconversion of *(R)*- and *(S)*-2-methylcyclohexanone.

PROBLEM 22-3

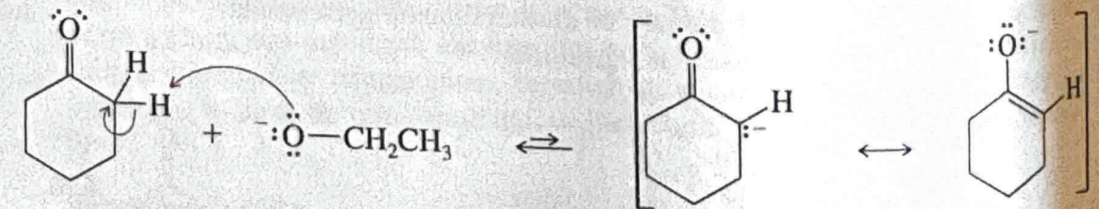
When *cis*-2,4-dimethylcyclohexanone is dissolved in aqueous ethanol containing a trace of NaOH, a mixture of cis and trans isomers results. Give a mechanism for this isomerization.

22-2B Formation and Stability of Enolate Ions

A carbonyl group dramatically increases the acidity of the protons on the α-carbon atom, because most of the enolate ion's negative charge resides on the electronegative oxygen atom. The pK_a for removal of an α proton from a typical ketone or aldehyde is about 20, showing that a typical ketone or aldehyde is much more acidic than an alkane or an alkene ($pK_a > 40$), or even an alkyne ($pK_a = 25$). Still, a ketone or aldehyde is less acidic than water ($pK_a = 15.7$) or an alcohol ($pK_a = 16$ to 19). When a simple ketone or aldehyde is treated with hydroxide ion or an alkoxide ion, the equilibrium mixture contains only a small fraction of the deprotonated, enolate form.



Example



Even though the equilibrium concentration of the enolate ion may be small, it serves as a useful, reactive nucleophile. When an enolate reacts with an electrophile (other than a proton), the enolate concentration decreases, and the equilibrium shifts to the right (Fig. 22-1). Eventually, all the carbonyl compound reacts via a low concentration of the enolate ion.

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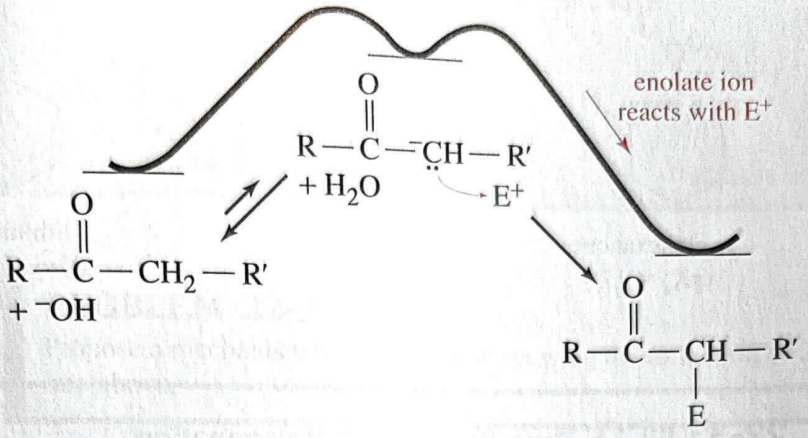


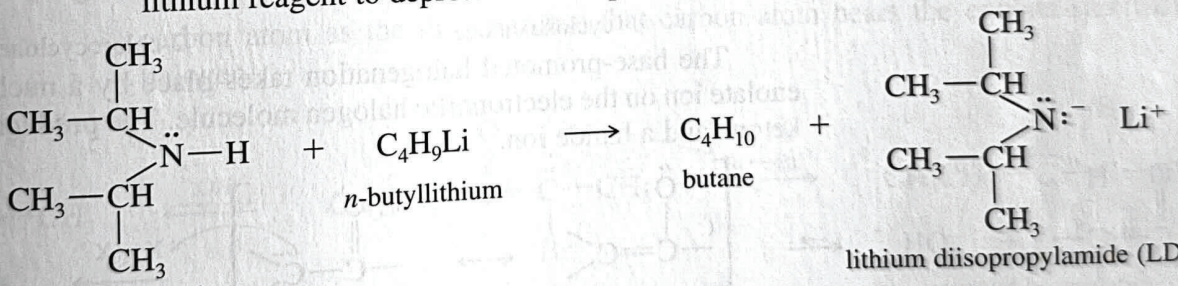
FIGURE 22-1 Reaction of the enolate ion with an electrophile removes it from equilibrium.

PROBLEM 22-4

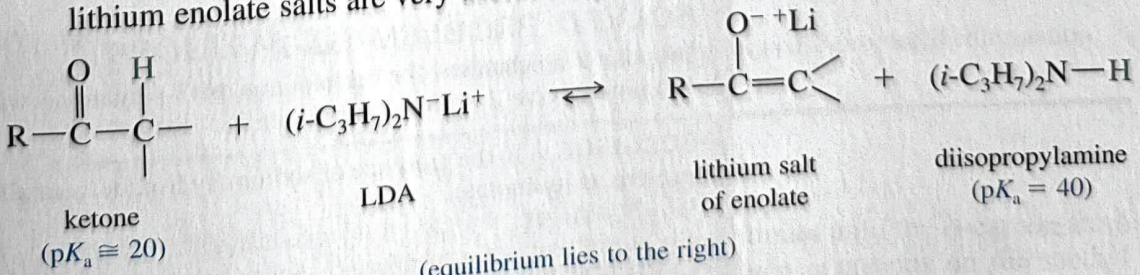
Give the important resonance structures for the enolate ion of

(a) acetone (b) cyclopentanone (c) 2,4-pentanedione

For some reactions, *all* the carbonyl compound must be converted to its deprotonated enolate form. Although sodium hydroxide and alkoxides are not sufficiently basic, powerful bases are available to convert a ketone completely to its enolate. The most effective and useful base for this purpose is lithium diisopropylamide (LDA), the lithium salt of diisopropylamine. LDA is made by using an alkyllithium reagent to deprotonate diisopropylamine.



Diisopropylamine has a pK_a of about 40, showing that it is much *less* acidic than a typical ketone or aldehyde. By virtue of its two isopropyl groups, LDA is a bulky reagent; it does not easily attack a carbon atom or add to a carbonyl group. Thus it is a powerful base, but not a strong nucleophile. When LDA reacts with a ketone, it abstracts the α proton to form the lithium salt of the enolate. We will see that these lithium enolate salts are very useful in synthesis.



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