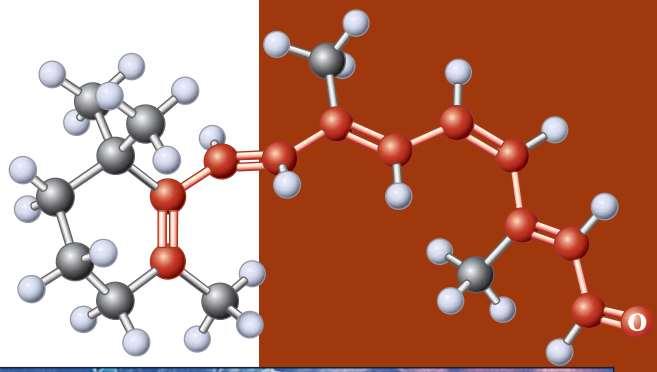
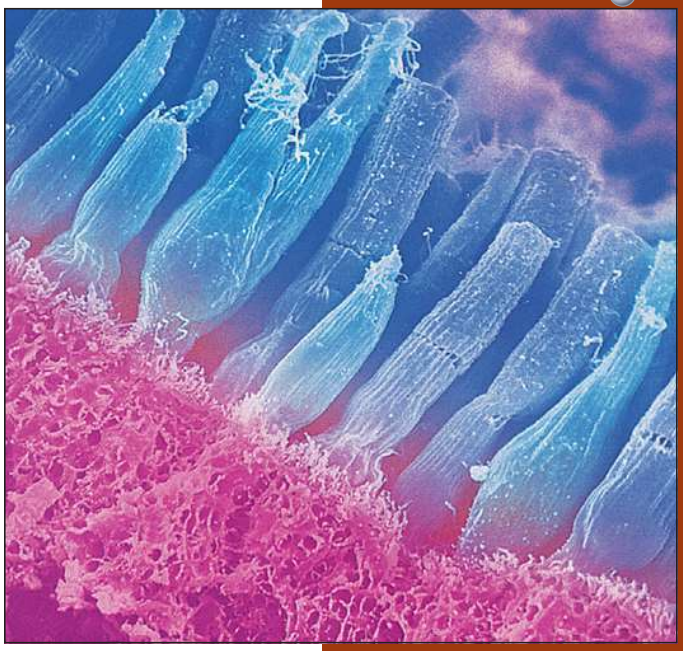
Enols, Enolates, and the Aldol Condensation

α,β-Unsaturated Aldehydes and Ketones

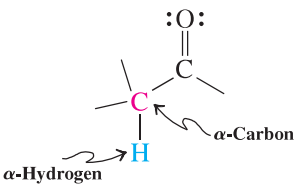


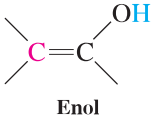


Photomicrograph of rod and cone cells in the retina. All known image-resolving eyes and, indeed, all known visual systems in nature use a single molecule, *cis*-retinal, for light detection. Absorption of a photon isomerizes the cis double bond to trans. The accompanying massive change in overall molecular geometry is responsible for triggering the nerve impulse that is perceived as vision.

Have another look at the Chapter Opening above. The very fact that you can see it is made possible by the chemistry alluded to in the caption: Photons impinge on the π system (Section 14-11) of *cis*-retinal bound to a protein to cause cis-trans isomerization. The associated conformational changes result, within picoseconds, in a nerve impulse that is translated by your brain into "vision" (Chemical Highlight 18-3). The crucial chemical feature of retinal that makes this process possible is the (in this case extended) conjugative communication between the carbonyl group and the adjacent π system. This chapter will show you that the carbonyl group (much like an ordinary carbon–carbon double bond; Section 14-1) activates adjacent C–H and C=C bonds even in much simpler systems, because of resonance. After you have absorbed the material that follows, you will be able to "look" at this page with quite a different perspective!

In the last chapter, we saw how the structure of the carbonyl group—a multiple bond that is also *highly polar*—gives rise to a characteristic combination of functional behaviors: addition reactions mediated by electrophilic attack (usually by protons) on the Lewis basic oxygen and attack by nucleophiles on the carbon. We turn now to a third site of reactivity in aldehydes and ketones, the carbon *next to* the carbonyl group, known as the **α-carbon.** The carbonyl group induces enhanced acidity of hydrogens on the α-carbon. Moving these **α-hydrogens** may lead to either of two electron-rich species: unsaturated alcohols called enols or their corresponding conjugate bases, known as enolate ions. Both enols and enolate ions are important nucleophiles, capable of attacking electrophiles such as protons, halogens, haloalkanes, and even other carbonyl compounds.



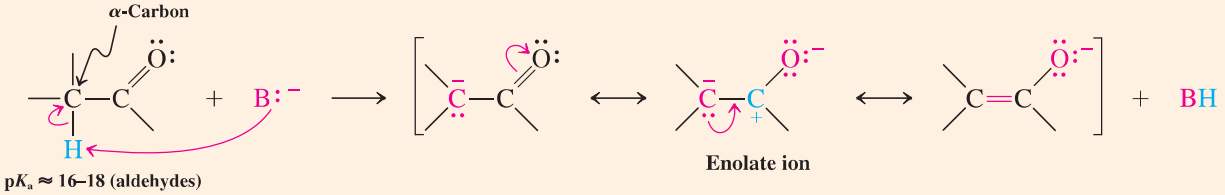


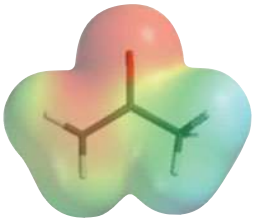
We begin by introducing the chemistry of enolates and enols. Especially important is a reaction between enolate ions and carbonyl compounds, called the aldol condensation. This process is widely used to form carbon–carbon bonds both in the laboratory and in nature. Among the possible products of aldol condensation are α,β-unsaturated aldehydes and ketones, which contain conjugated carbon–carbon and carbon–oxygen π bonds. As expected, electrophilic additions may take place at either π bond. However, more significantly, α,β-unsaturated carbonyl compounds are also subject to nucleophilic attack, a reaction that may involve the *entire* conjugated system.

18-1 Acidity of Aldehydes and Ketones: Enolate Ions

The pK_a values of aldehyde and ketone α-hydrogens range from 16 to 21, much lower than the pK_a values of ethene (44) or ethyne (25), but comparable with those of alcohols (15–18). Strong bases can therefore remove an α-hydrogen. The anions that result are known as **enolate ions** or simply **enolates.**

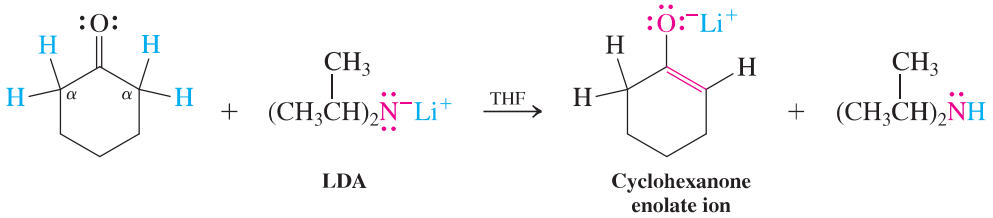
Deprotonation of a Carbonyl Compound at the α-Carbon




Acetone enolate

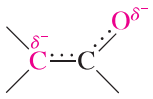
Why are aldehydes and ketones relatively acidic? We know that acid strength is enhanced by stabilization of the conjugate base (Section 2-2). In the enolate ion, the inductive effect of the positively polarized carbonyl carbon strongly stabilizes the negative charge at the α-position. Aldehydes are stronger acids than ketones because their carbonyl carbon bears a larger partial positive charge (Section 17-6). Further strong stabilization is provided by delocalization of charge onto the electronegative oxygen, as described by the resonance forms just pictured. The effect of delocalization is also reflected in the electrostatic potential map of the acetone enolate shown in the margin (on an attenuated scale), which exhibits negative charge (red) on the α-carbon as well as on the oxygen. An example of enolate formation is the deprotonation of cyclohexanone by lithium diisopropylamide (LDA; Section 7-8).

Enolate Preparation



Exercise 18-1

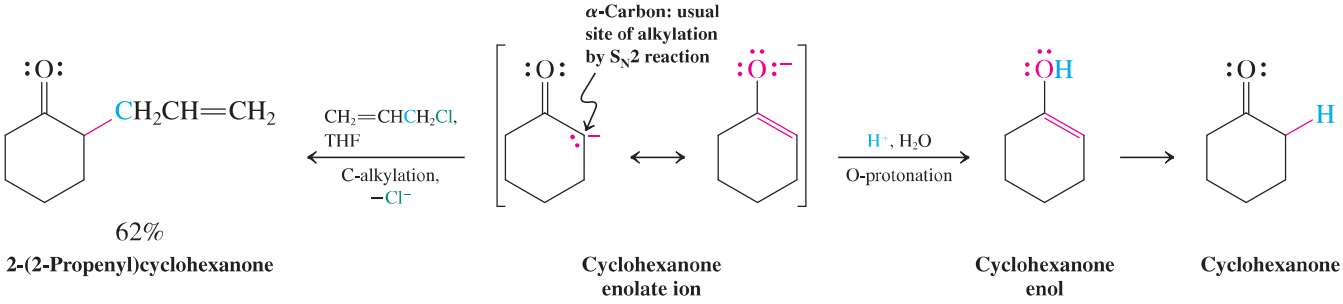
Identify the most acidic hydrogens in each of the following molecules. Give the structure of the enolate ion arising from deprotonation. **(a)** Acetaldehyde; **(b)** propanal; **(c)** acetone; **(d)** 4-heptanone; **(e)** cyclopentanone.


Resonance hybrid

Each resonance form contributes to the characteristics of the enolate ion and thus to the chemistry of carbonyl compounds. The resonance hybrid possesses partial negative charges on both carbon and oxygen; as a result, it is nucleophilic and may attack electrophiles at

either position. A species that can react at two different sites to give two different products is called **ambident** ("two fanged": from *ambi,* Latin, both; *dens,* Latin, tooth). The enolate ion is thus an ambident anion. Its carbon atom is normally the site of reaction, undergoing nucleophilic substitution with S_N2 substrates such as suitable haloalkanes. Because this reaction attaches an alkyl group to the reactive carbon, it is called **alkylation** (more specifically, C-alkylation). As we shall see in Section 18-4, alkylation is a powerful method for carbon–carbon bond formation of ketones. For example, alkylation of cyclohexanone enolate with 3-chloropropene takes place at carbon. Alkylation at oxygen (O-alkylation) is uncommon, although oxygen is typically the site of *protonation.* The product of protonation is an unsaturated alcohol, called an **alkenol** (or **enol** for short). Enols are unstable and rapidly isomerize back to the original ketones (recall Section 13-7).

Ambident Behavior of Cyclohexanone Enolate Ion



Exercise 18-2

Give the products of reaction of cyclohexanone enolate with **(a)** iodoethane (reacts by C-alkylation) and **(b)** chlorotrimethylsilane, $(CH_3)_3Si–Cl$ (reacts by O-silylation).

In Summary The hydrogens on the carbon next to the carbonyl group in aldehydes and ketones are acidic, with pK_a values ranging from 16 to 21. Deprotonation leads to the corresponding enolate ions, which may attack electrophilic reagents at either oxygen or carbon. Protonation at oxygen gives enols.

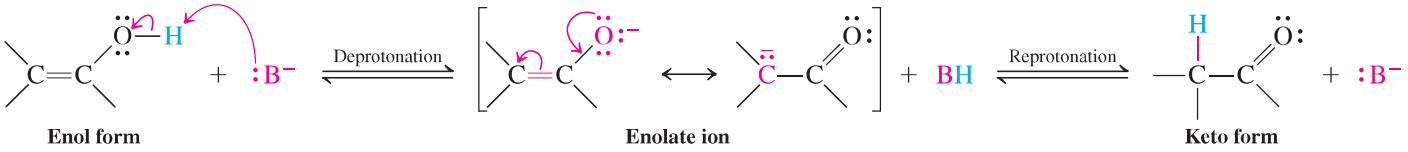
18-2 Keto–Enol Equilibria

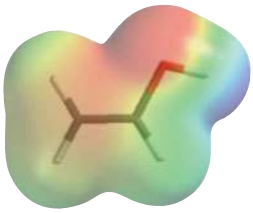
We have seen that protonation of an enolate at oxygen leads to an enol. The enol, an unstable isomer of an aldehyde or ketone, rapidly converts into the carbonyl system: It **tautomerizes** (Section 13-7). These isomers are called **enol** and **keto tautomers.** We begin by discussing factors affecting their equilibria, in which the keto form usually predominates. We then describe the mechanism of tautomerism and its chemical consequences.

An enol equilibrates with its keto form in acidic or basic solution

Enol–keto tautomerism proceeds by either acid or base catalysis. Base simply removes the proton from the enol oxygen, reversing the initial protonation. Subsequent (and slower) C-protonation furnishes the thermodynamically more stable keto form.

Base-Catalyzed Enol–Keto Equilibration

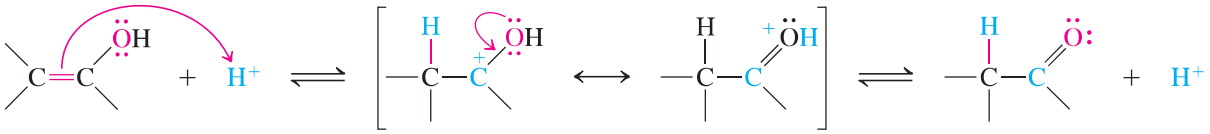




Ethenol

In the acid-catalyzed process, the enol form is protonated at the double-bonded carbon away from the hydroxy-bearing neighbor. The electrostatic potential map of ethenol (margin) shows that this carbon bears more negative charge (red). Moreover, the resulting cation is resonance-stabilized by the attached hydroxy group, and inspection of the corresponding resonance form reveals it to be simply the protonated carbonyl compound. Deprotonation then gives the product.

Acid-Catalyzed Enol–Keto Equilibration



Enol form — Protonated carbonyl system — Keto form

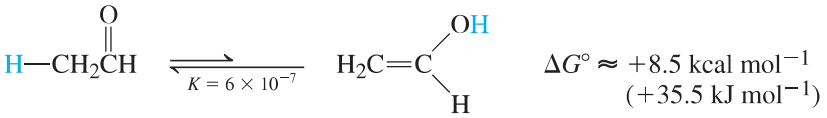
Both the acid- and base-catalyzed enol–keto interconversions occur rapidly in solution whenever there are traces of the required catalysts. Remember that although the keto form (usually) predominates, the enol-to-keto conversion is reversible and the mechanisms by which the keto form equilibrates with its enol counterpart are the exact reverse of the above two schemes.

Substituents can shift the keto–enol equilibrium

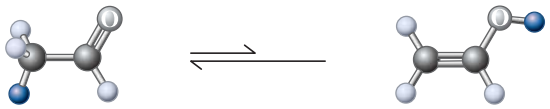
The equilibrium constants for the conversion of the keto into the enol forms are very small for ordinary aldehydes and ketones, only traces of enol (which is less stable by ca. 8–12 kcal mol^{-1}) being present. However, relative to its keto form, the enol of acetaldehyde is about a hundred times more stable than the enol of acetone, because the less substituted aldehyde carbonyl is less stable than the more substituted ketone carbonyl.

REACTION

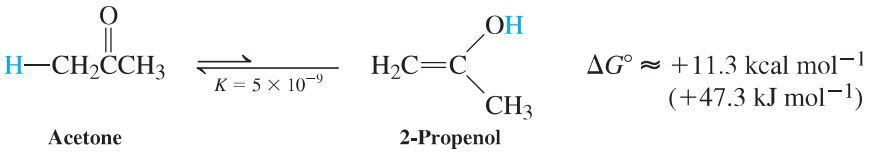
Keto–Enol Equilibria



$\Delta G^\circ \approx +8.5$ kcal mol^{-1} ($+35.5$ kJ mol^{-1})



Acetaldehyde — Ethenol (Vinyl alcohol)



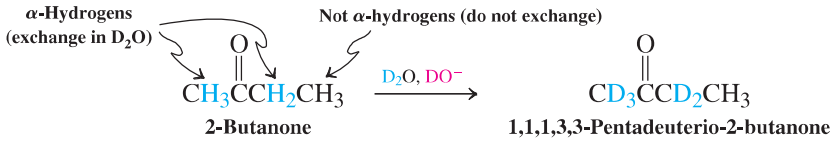
$\Delta G^\circ \approx +11.3$ kcal mol^{-1} ($+47.3$ kJ mol^{-1})

Acetone — 2-Propenol

Enol formation leads to deuterium exchange and stereoisomerization

What are some consequences of enol formation by tautomerism? One is that treatment of a ketone with traces of acid or base in D_2O solvent leads to the complete exchange of *all* the α-hydrogens.

Hydrogen–Deuterium Exchange of Enolizable Hydrogens



This reaction can be conveniently followed by ^{1}H NMR, because the signal for these hydrogens slowly disappears as each one is sequentially replaced by deuterium. In this way, the number of α-hydrogens present in a molecule can be readily determined.

Exercise 18-3

Formulate mechanisms for the base- and acid-catalyzed replacement of a single α-hydrogen in acetone by deuterium from D_2O.

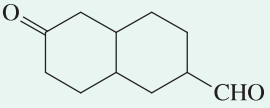
Exercise 18-4

Write the products (if any) of deuterium incorporation by the treatment of the following compounds with D_2O–NaOD.

(a) Cycloheptanone

(b) 2,2-Dimethylpropanal

(c) 3,3-Dimethyl-2-butanone

(d) 

Exercise 18-5

Working with the Concepts: Assigning NMR Signals of a Cyclic Ketone

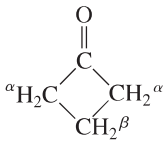
The ^{1}H NMR spectrum of cyclobutanone consists of a quintet at δ = 2.00 ppm and a triplet at δ = 3.13 ppm. Assign the signals in this spectrum to the appropriate hydrogens in the molecule.

Strategy

Using the information in Section 17-3 regarding chemical shifts of hydrogens in ketones, apply the tools of NMR analysis that you acquired in Chapter 10.

Solution

• The structure of cyclobutanone implies an ^{1}H NMR spectrum displaying two signals: One for the four α-hydrogens (on C2 and C4) and another for the two β-hydrogens (on C3).



• We learned in Section 17-3 that α-hydrogens in carbonyl compounds are more deshielded than β-hydrogens. Furthermore, in accordance with the (N + 1) rule for spin–spin splitting (Section 10-7), the signal for the α-hydrogens should appear as a triplet as a result of splitting by the two β-hydrogen neighbors; thus we may assign the triplet signal at δ = 3.13 ppm to the four α-hydrogens.

• Conversely, splitting by four neighboring α-hydrogens should cause the signal for the β-hydrogens to appear as a quintet, consistent with the signal at δ = 2.00 ppm.

Exercise 18-6

Try It Yourself

What would you expect to observe to change in the ^{1}H NMR spectrum of cyclobutanone upon treatment with D_2O–NaOD? (**Hint:** Deuterium atoms do not display signals in an ^{1}H NMR spectrum.)