# 23 Substitution Reactions of Carbonyl Compounds at the α Carbon




**Tamoxifen** is a potent anticancer drug used widely in the treatment of breast cancer. Tamoxifen binds to estrogen receptors, and in this way inhibits the growth of breast cancers that are estrogen dependent. One method to synthesize tamoxifen forms a new carbon–carbon bond on the α carbon to a carbonyl group using an intermediate enolate. In Chapter 23 we learn about these and other carbon–carbon bond-forming reactions that occur at the α carbon.

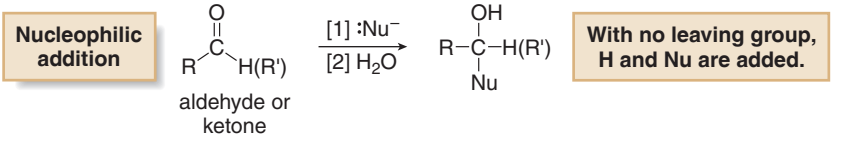
**Chapters 23 and 24 focus on reactions** that occur at the α carbon to a carbonyl group. These reactions are different from the reactions of Chapters 20–22, all of which involved nucleophilic attack at the electrophilic carbonyl carbon. In reactions at the α carbon, the carbonyl compound serves as a *nucleophile* that reacts with a carbon or halogen electrophile to form a new bond to the α carbon.

Chapter 23 concentrates on **substitution reactions at the α carbon,** whereas Chapter 24 concentrates on reactions between two carbonyl compounds, one of which serves as the nucleophile and one of which is the electrophile. Many of the reactions in Chapter 23 form new carbon–carbon bonds, thus adding to your repertoire of reactions that can be used to synthesize more complex organic molecules from simple precursors. As you will see, the reactions introduced in Chapter 23 have been used to prepare a wide variety of interesting and useful compounds.

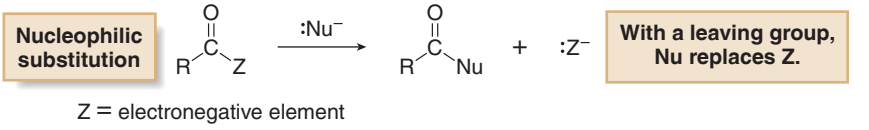
## 23.1 Introduction

Up to now, the discussion of carbonyl compounds has centered on their reactions with nucleophiles at the electrophilic carbonyl carbon. **Two general reactions are observed,** depending on the structure of the carbonyl starting material.

- *Nucleophilic addition* occurs when there is no electronegative atom Z on the carbonyl carbon (as with aldehydes and ketones).

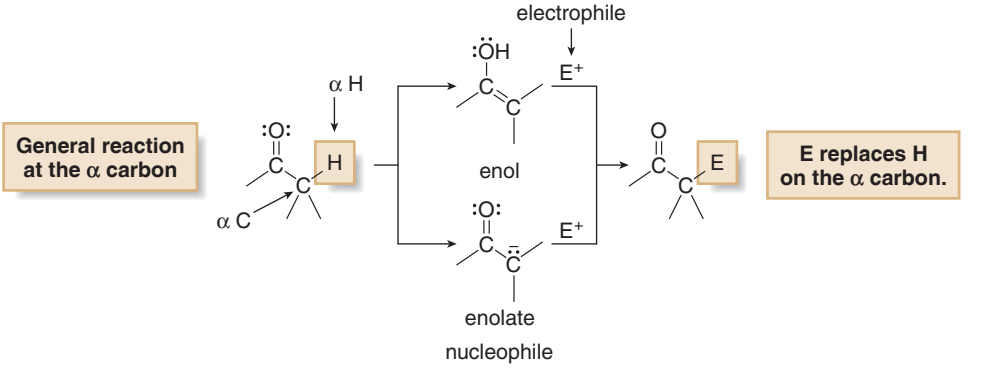



- *Nucleophilic acyl substitution* occurs when there is an electronegative atom Z on the carbonyl carbon (as with carboxylic acids and their derivatives).



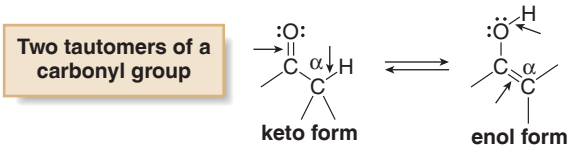

Reactions can also occur at the α carbon to the carbonyl group. These reactions proceed by way of **enols** or **enolates,** two electron-rich intermediates that react with electrophiles, forming a new bond on the α carbon. This reaction results in the **substitution of the electrophile E for hydrogen.**

Hydrogen atoms on the α carbon are called **α hydrogens.**



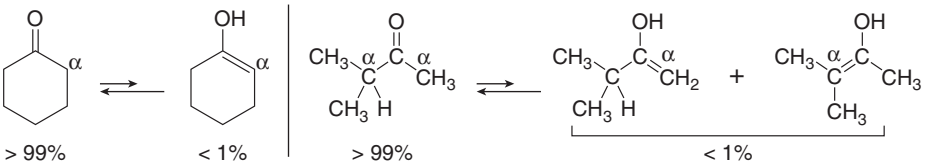

## 23.2 Enols

Recall from Chapter 11 that **enol and keto forms are tautomers of the carbonyl group that differ in the position of a double bond and a proton.** These constitutional isomers are in equilibrium with each other.

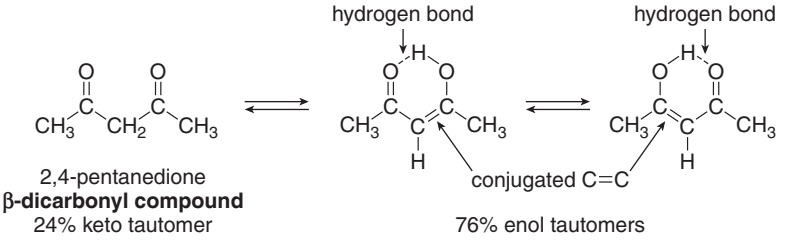



- A keto tautomer has a C = O and an additional C – H bond.
- An enol tautomer has an O – H group bonded to a C = C.

Equilibrium favors the keto form for most carbonyl compounds largely because a C=O is much stronger than a C=C. For simple carbonyl compounds, < 1% of the enol is present at equilibrium. With unsymmetrical ketones, moreover, two different enols are possible, yet they still total < 1%.



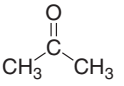

With compounds containing two carbonyl groups separated by a single carbon (called β-dicarbonyl compounds or 1,3-dicarbonyl compounds), however, the concentration of the enol form sometimes exceeds the concentration of the keto form.

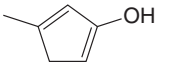



Two factors stabilize the enol of β-dicarbonyl compounds: **conjugation** and **intramolecular hydrogen bonding.** The C=C of the enol is conjugated with the carbonyl group, allowing delocalization of the electron density in the π bonds. Moreover, the OH of the enol can hydrogen bond to the oxygen of the nearby carbonyl group. Such intramolecular hydrogen bonds are especially stabilizing when they form a six-membered ring, as in this case.

## Sample Problem 23.1

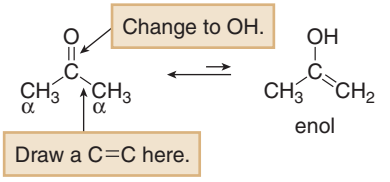
Convert each compound to its enol or keto tautomer.

a. 

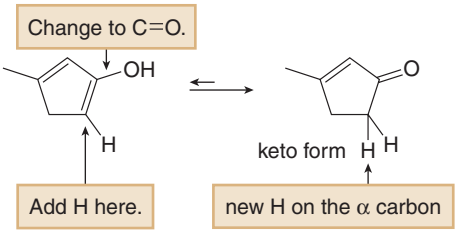
b. 

### Solution

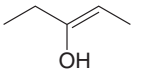
a. To convert a carbonyl compound to its enol tautomer, draw a double bond between the carbonyl carbon and the α carbon, and change the C=O to C–OH. In this case, both α carbons are identical, so only one enol is possible.

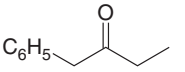



b. To convert an enol to its keto tautomer, change the C–OH to C=O and add a proton to the other end of the C=C.



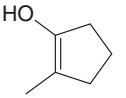
**Problem 23.1** Draw the enol or keto tautomer(s) of each compound.

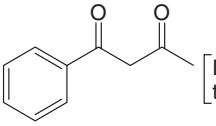
a. 

c. 

e. $C_6H_5CH_2CH_2CO_2CH_2CH_3$

b. $C_6H_5CH_2CHO$

d. 

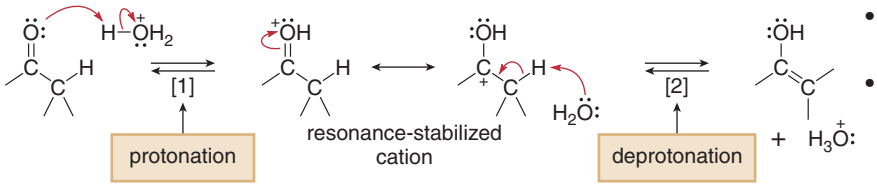
f. 


**Problem 23.2** Ignoring stereoisomers, draw the two possible enols for 2-butanone ($CH_3COCH_2CH_3$), and predict which one is more stable.

## 23.2A The Mechanism of Tautomerization

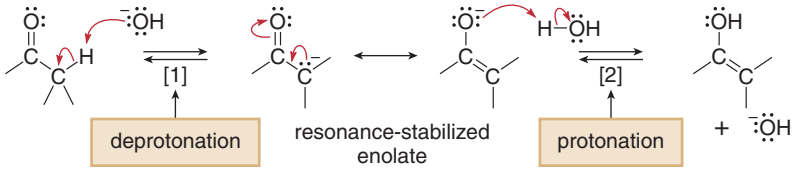
**Tautomerization,** the process of converting one tautomer into another, is catalyzed by both acid and base. Tautomerization always requires two steps (**protonation** and **deprotonation**), but the order of these steps depends on whether the reaction takes place in acid or base. In Mechanisms 23.1 and 23.2 for tautomerization, the keto form is converted to the enol form. All of the steps are reversible, though, so they equally apply to the conversion of the enol form to the keto form.

### Mechanism 23.1 Tautomerization in Acid



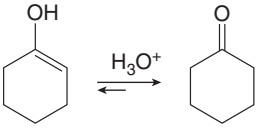

- With acid, **protonation *precedes* deprotonation.**
- **Protonation** of the carbonyl oxygen forms a resonance-stabilized cation in Step [1], and deprotonation in Step [2] forms the enol. The net result of these two steps is the movement of a double bond and a proton.

### Mechanism 23.2 Tautomerization in Base




- With base, **deprotonation *precedes* protonation.**
- **Removal of a proton from the α carbon** forms a resonance-stabilized enolate in Step [1].
- **Protonation** of the enolate with $H_2O$ forms the enol in Step [2].

**Problem 23.3** Draw a stepwise mechanism for the following reaction.




## 23.2B How Enols React

Like other compounds with carbon–carbon double bonds, **enols are electron rich, so they react as nucleophiles.** Enols are even more electron rich than alkenes, though, because the OH group has a powerful electron-donating resonance effect. A second resonance structure can be drawn