

# General Principles for Writing Reaction Mechanisms

In writing a reaction mechanism, we give a step-by-step account of the bond (electron) reorganizations that take place in the course of a reaction. These mechanisms do not have any objective existence; they are merely our attempt to represent what is going on in a reaction. Although experiments can suggest that some mechanisms are reasonable and others are not, for many reactions there is no evidence regarding the mechanism, and we are free to write whatever mechanism we choose, subject only to the constraint that we conform to generally accepted mechanistic patterns.

The purpose of this book is to help you figure out a number of pathways for a new reaction by showing you some of the steps that often take place under a particular set of reaction conditions. This chapter is devoted to some general principles, derived from the results of many experiments by organic chemists, that can be applied to writing organic mechanisms. Subsequent chapters will develop the ideas further under more specific reaction conditions.

It often is difficult to predict what will actually happen in the course of a reaction. If you were planning to run a reaction that had never been done before, you would plan the experiment on the basis of previously run reactions that look similar. You would assume that the steps of bond reorganization that take place in the new reaction are analogous to those in the reactions previously run. However, you might find that one or more steps in your reaction scheme give unanticipated results. In other words, although a number of general ideas about the course of reactions have been developed on the basis of experiments, it is sometimes difficult to choose which ideas apply to a particular reaction. Working through the problems in this book will help you develop the ability to make some of those choices. Nonetheless, often you will conclude that there is more than one possible pathway for a reaction.

## I. BALANCING EQUATIONS

### Hint 2.1

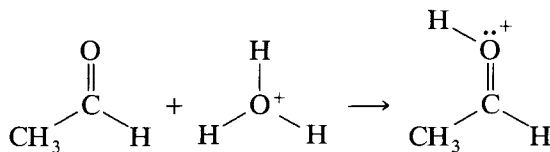
It can be assumed, unless otherwise stated, that when an organic reaction is written, the products shown have undergone any required aqueous workup, which may involve acid or base, to give a neutral organic molecule (unless salts are shown as the product). In other words, when an equation for a reaction is written in the literature or on an exam, an aqueous workup usually is assumed and intermediates, salts, etc. are not shown.

From the viewpoint of organic chemistry, an equation is usually considered to be balanced if it accounts for all the carbon atoms and is balanced with respect to charges and electrons. Ordinarily, no attempt is made to account for the changes in the inorganic species involved in the reaction.

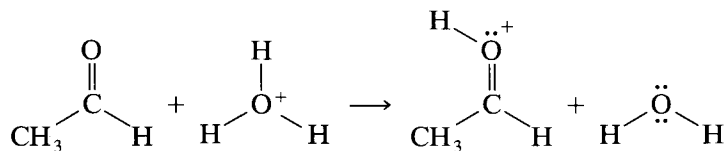
### Hint 2.2

Check that equations are balanced. First, balance all atoms on both sides of the equation, and then balance the charges. Be aware that when equations are written in the organic literature, they are frequently not balanced.

### Example 2.1. *Balancing atoms.*

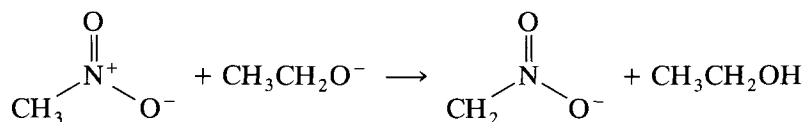


In this equation, the carbon atoms balance but the hydrogen and oxygen atoms do not. The equation is balanced by adding a molecule of water to the right-hand side.

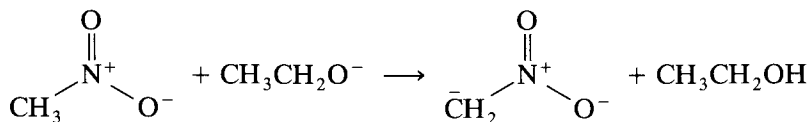


The equation is balanced with regard to charge: the positive charge on the left balances the positive charge on the right.

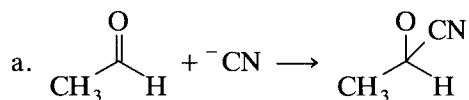
**Example 2.2. Balancing charges.**

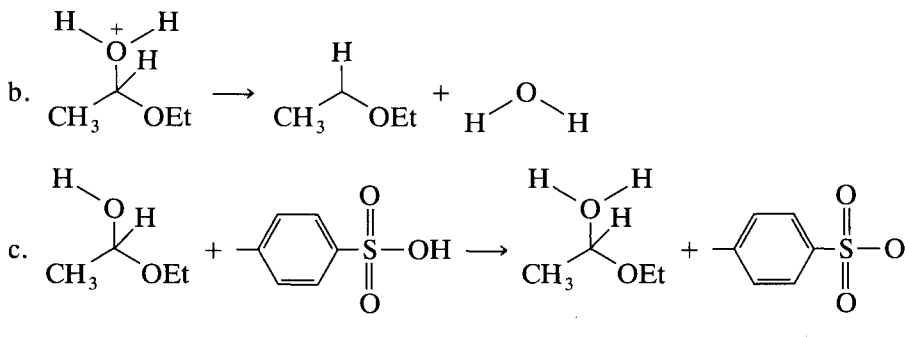


In this equation, the carbon, hydrogen, nitrogen, and oxygen atoms balance. At first glance, the charges also appear to balance because there is a single net negative charge on each side of the equation. However, the right-hand side of the equation contains an incorrect Lewis structure in which there is an electron-deficient carbon and the formal charge on nitrogen is omitted. The equation is balanced correctly by adding a negative charge on carbon and a positive charge on nitrogen.



**In the following steps, supply the missing charges and lone pairs. PROBLEM 2.1**  
**Assume that no molecules with unpaired electrons are produced.**



**PROBLEM 2.1***continued***2. USING ARROWS TO SHOW MOVING ELECTRONS**

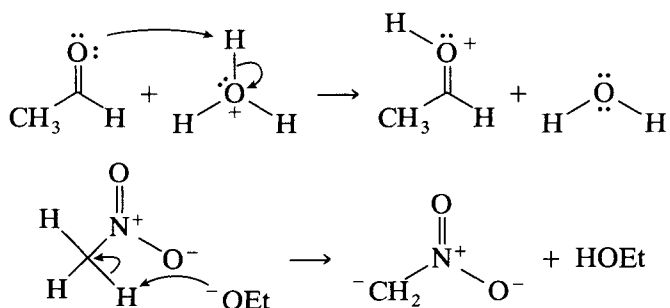
In writing mechanisms, bond-making and bond-breaking processes are shown by curved arrows. The arrows are a convenient tool for thinking about and illustrating what the actual electron redistribution for a reaction may be.

**Hint 2.3**

The arrows that are used to show the redistribution of electron density are drawn from a position of high electron density to a position that is electron-deficient. Thus, arrows are drawn leading away from negative charges or lone pairs and toward positive charges or the positive end of a dipole. In other words, they are drawn leading away from nucleophiles and toward electrophiles. Furthermore, it is only in *unusual* reaction mechanisms that two arrows will lead either away from or toward the same atom.

**Example 2.3. Using arrows to show redistribution of electron density.**

The following equations show the electron flow for the transformations in Examples 2.1 and 2.2.

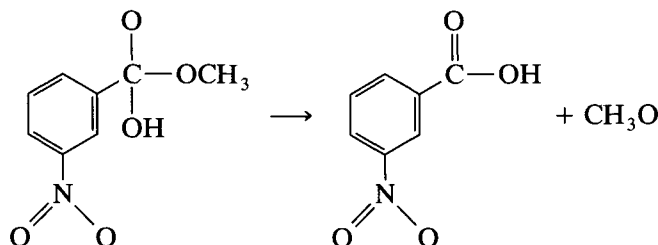
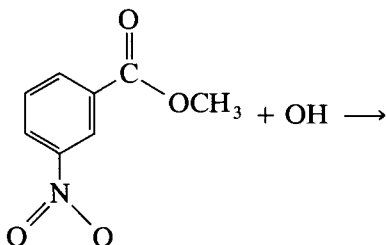
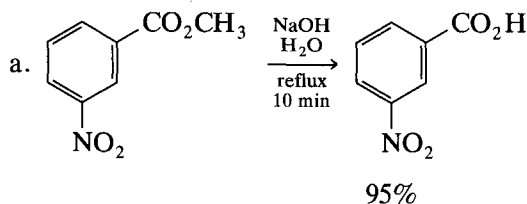


For an understanding of why the neutral oxygen in the first equation reacts with a proton of the hydronium ion rather than the positively charged oxygen, see Hint 2.9.

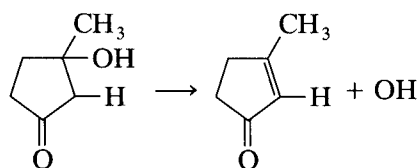
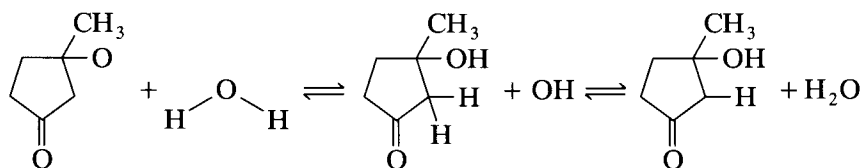
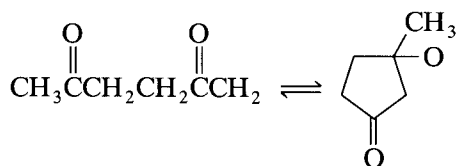
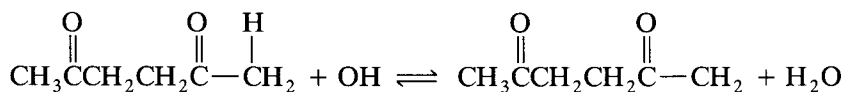
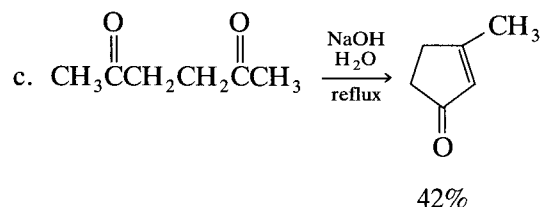
When you first start drawing reaction mechanisms, rewrite any intermediate structure before you try to manipulate it further. This avoids confusing the arrows associated with electron flow for one step with the arrows associated with electron flow for a subsequent step. As you gain experience, you will not need to do this. It will also be helpful to write the Lewis structure for at least the reacting atom and to write lone pairs on atoms such as nitrogen, oxygen, halogen, phosphorus, and sulfur.

**Hint 2.4**

For the following reactions, supply the missing charges and then use curved arrows to show the bond breaking and bond making for each step.

**PROBLEM 2.2**



**PROBLEM 2.2**  
continued**3. MECHANISMS IN ACIDIC AND BASIC MEDIA**

If a reaction is run in a strongly basic medium, any positively charged species must be weak acids. If a reaction is run in a strongly acidic medium, any negatively charged species must be weak bases. In a weak acid or base (like water), both strong acids and strong bases may be written as part of the mechanism.

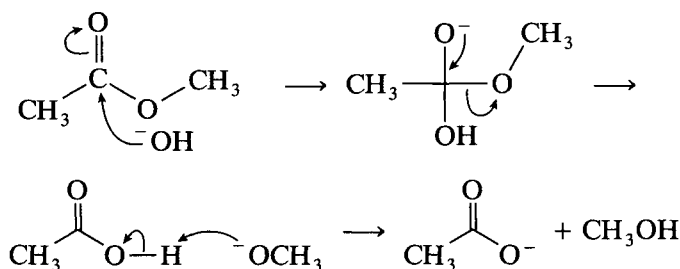
**Hint 2.5**

We can look at what this means in some specific situations. Using the  $pK_a$  values listed in Appendix C, we find that in a strongly basic solution like 5% aqueous sodium hydroxide ( $\text{pH} \sim 14$ ), the only protonated species would be those with a  $pK_a > 12$  (e.g., guanidine,  $pK_a$  13.4). In strongly acidic solutions like 5% aqueous hydrochloric acid ( $\text{pH} \sim 0$ ), the only anions present would

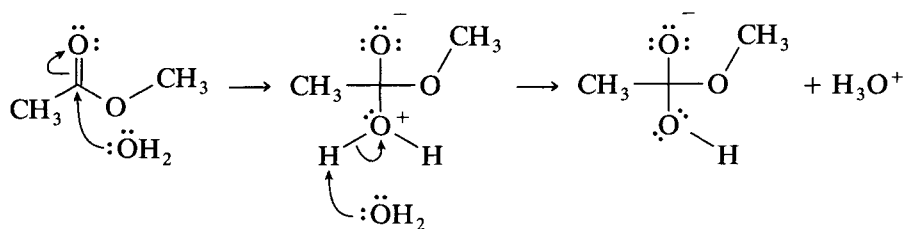
be those whose conjugate acid had a  $pK_a < -2$  (e.g.,  $\text{PhSO}_3\text{H}$ ,  $pK_a = 2.9$ ). In a solution closer to neutrality (e.g., 5%  $\text{NaHCO}_3$ ,  $\text{pH} = 8.5$ ), we would find positively charged guanidine and aliphatic amino groups ( $pK_a = 13.4$  and  $10.7$ , respectively), as well as neutral aromatic amines ( $pK_a \sim 4$ ), and anions such as acetate and 2,4-dinitrophenolate ( $pK_a = 4.7$  and  $4.1$ , respectively).

**Example 2.4. Writing a mechanism in a strong base.**

The following mechanism for the hydrolysis of methyl acetate in a strong base is consistent with the experimental data for the reaction.



As suggested in Hint 2.5, all of the charged species in this mechanism are negatively charged because the reaction occurs in strong base. Thus, the following steps would be incorrect for a reaction in base because they involve the formation of  $\text{ROH}_2^+$  (the intermediate) and  $\text{H}_3\text{O}^+$ , both of which are strong acids.

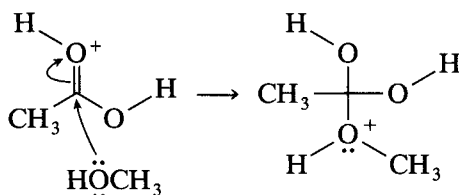


Another way of looking at this is to realize that, in aqueous base, hydroxide ion has a significant concentration. Because hydroxide is a much better nucleophile than water, it will act as the nucleophile in the first step of the reaction.

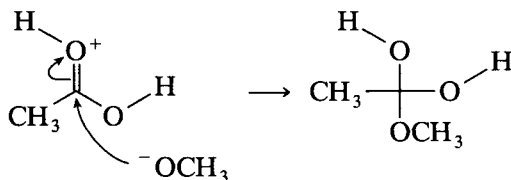


**Example 2.5. Writing a mechanism in strong acid.**

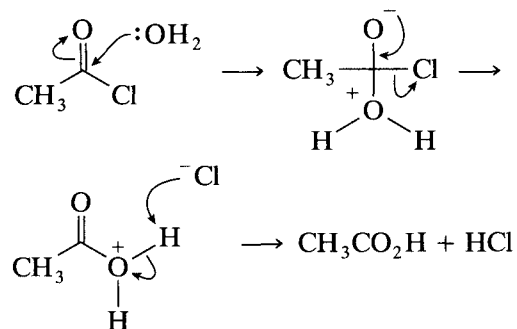
The following step is consistent with the facts known about the esterification of acetic acid with methanol in strong acid.



Because the fastest reaction for a strong base,  $\text{CH}_3\text{O}^-$ , in acid is protonation, the concentration of  $\text{CH}_3\text{O}^-$  would be negligible and the following mechanistic step would be highly improbable for esterification in acid:

**Example 2.6. Writing a mechanism in a weak base or weak acid.**

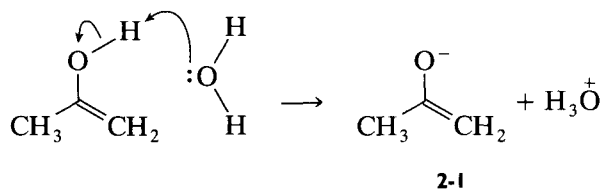
When a reaction occurs in the presence of a weak acid or weak base, the intermediates do not necessarily carry a net positive or negative charge. For example, the following mechanism often is written for the hydrolysis of acetyl chloride in water. (Most molecules of acetyl chloride probably are protonated on oxygen before reaction with a nucleophile, because acid is produced as the reaction proceeds.)



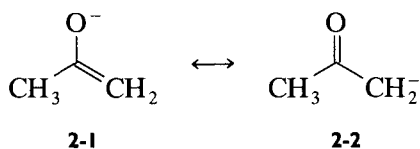
In the first step, the weak base water acts as a nucleophile. In the second step, the weak base chloride ion is shown removing a proton. This second step also could have been written with water acting as the base. Notice that in this example most of the lone pairs have been omitted from the Lewis structures. Reactions in the chemical literature often are written in this way.

**Example 2.7.** *Strong acids and bases as intermediates in the tautomerization of enols in water (neutral conditions).*

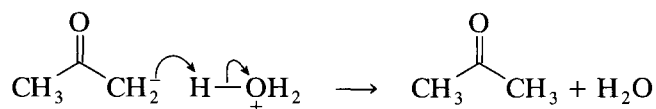
The first step is usually described as a proton transfer from the enol to a molecule of water. However, when arrows are used to show the flow of electrons, the arrow must proceed from the nucleophile to the electrophile.



This step produces a strong acid, hydronium ion, and a strong base, the enolate anion **2-1**. This anion is a resonance hybrid of structures **2-1** and **2-2**.



The hybrid can remove a proton from the hydronium ion to give the ketone form of the tautomers. Although not strictly correct (because resonance structures do not exist), such reactions commonly are depicted as arising from the resonance structure that bears the charge on the atom that is adding the proton.



2-2

Because enolization under neutral conditions produces both a strong acid and a strong base, the reaction is very slow. Addition of a very small amount of either a strong acid or a strong base dramatically increases the rate of enolization.

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Approach writing the mechanism in a logical fashion. For example, if the reagent is a strong base, look for acidic protons in the substrate, then look for a reasonable reaction for the anion produced. If the anion formed by deprotonation has a suitable leaving group, its loss would lead to overall elimination. If the anion formed is a good nucleophile, look for a suitable electrophilic center at which the nucleophile can react. (For further detail, see Chapter 3.)

**Hint 2.6**

For mechanisms in acid, follow a similar approach and look for basic atoms in the substrate. Protonate a basic atom and consider what reactions would be expected from the resulting cation.

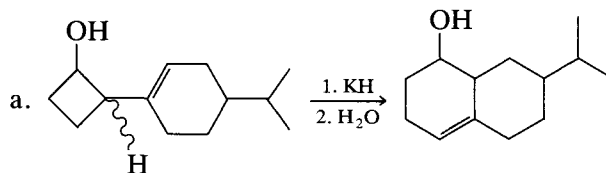
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When writing mechanisms in acid and base, keep in mind that protons are removed by bases. Even very weak bases like  $\text{HSO}_4^-$ , the conjugate base of sulfuric acid, can remove protons. Protons do not just leave a substrate as  $\text{H}^+$  because the bare proton is very unstable! Nonetheless the designation  $-\text{H}^+$  is often used when a proton is removed from a molecule. (Whether this designation

**Hint 2.7**

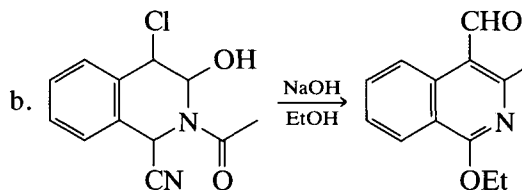
is acceptable is up to individual taste. If you are using this book in a course, you will have to find out what is acceptable to your instructor.) A corollary is that when protons are added to a substrate, they originate from an acid, that is, protons are not added to substrates as freely floating (unsolvated) protons.

**PROBLEM 2.3** In each of the following reactions, the first step in the mechanism is removal of a proton. In each case, put the proton most likely to be removed in a box. The  $pK_a$  values listed in Appendix C may help you decide which proton is most acidic.

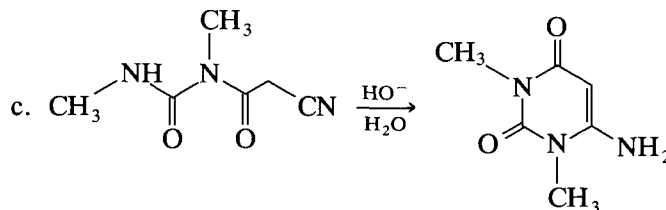


The wavy bond line means that the stereochemistry is unspecified.

Cohen, T.; Bhupathy, M. *J. Am. Chem. Soc.* **1983**, *105*, 520–525.



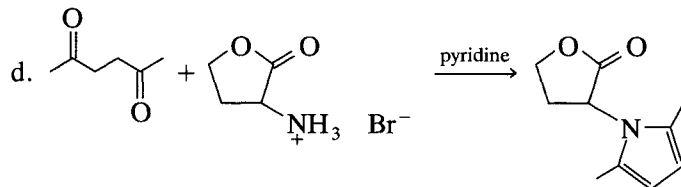
Kirby, G. W.; McGuigan, H.; Mackinnon, J. W. M.; Mallinson, R. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 405–408; Kirby, G. W.; Mackinnon, J. W. M.; Elliott, S.; Uff, B. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1298–1302.



Bernier, J. L.; Henichart, J. P.; Warin, V.; Trentesaux, C.; Jardillier, J. C. *J. Med. Chem.* **1985**, *28*, 497–502.

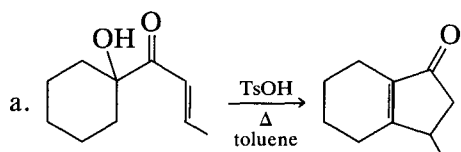
**PROBLEM 2.3**  
*continued*

In this example, removal of the most acidic proton does not lead to the product. Which is the most acidic proton and which is the one that must be removed in order to give the product? (Hint 2.14 may be helpful in relating the atoms of the starting material and the product.)



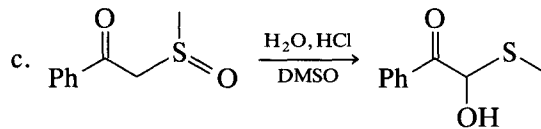
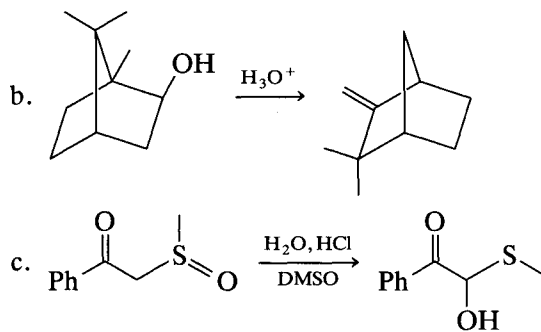
Jaffe, K.; Cornwell, M.; Walker, S.; Lynn, D. G. *Abstracts of Papers*, 190th National Meeting of American Chemical Society, Chicago; American Chemical Society: Washington DC, 1985; ORGN 267.

**For each of the following reactions, the first step in the mechanism is protonation. In each case, put the atom most likely to be protonated in a box.**

**PROBLEM 2.4**

TsOH = *p*-toluenesulfonic acid

Jacobson, R. M.; Lahm, G. P. *J. Org. Chem.* **1979**, *44*, 462-464.



76-81%

House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; p. 726.

**Hint 2.8**

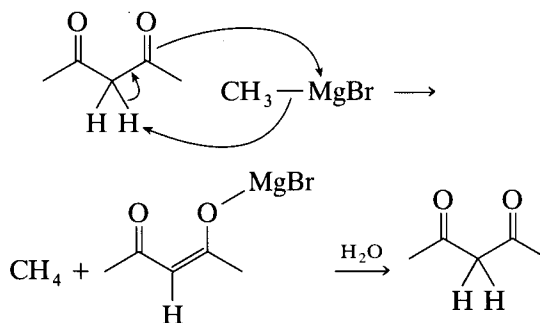
When a mechanism involves the removal of a proton, removal of the most acidic proton does not always lead to the product. An example is Problem 2.3.c, in which removal of the most acidic proton by base does not lead to the product. (A mechanism for this reaction is proposed in the answer to Problem 2.3.c.) Similarly, when a mechanism involves protonation, it is not always protonation of the most basic atom that leads to product. Such reactions are called unproductive steps. When equilibria are involved, they are called unproductive equilibria.

**4. ELECTRON-RICH SPECIES: BASES OR NUCLEOPHILES?****Hint 2.9**

A Lewis base, that is, a species with a lone pair of electrons, can function either as a base, abstracting a proton, or as a nucleophile, reacting with a positively charged atom (usually carbon). Which of these processes occurs depends on a number of factors, including the structure of the Lewis base, the structure of the substrate, the specific combination of base and substrate, and the solvent.

**Example 2.8. Abstraction of an acidic proton in preference to nucleophilic addition.**

Consider the reaction of methylmagnesium bromide with 2,4-pentanedione. This substrate contains carbonyl groups that might undergo nucleophilic reaction with the Grignard reagent. However, it also contains very acidic protons (see Appendix C), one of which reacts considerably faster with the Grignard reagent than the carbonyl groups. Thus, the reaction of methylmagnesium bromide with 2,4-pentanedione leads to methane and, after aqueous workup, starting ketone.





In the reaction of isopropyl bromide with sodium ethoxide in ethanol, the dual reactivity of sodium ethoxide is apparent. Ethoxide ion can act as a nucleophile, displacing bromide ion from carbon to produce isopropyl ethyl ether, or it can remove a proton, with simultaneous loss of bromide ion, to produce propene.

If you know the product of a reaction, usually it is not too difficult to determine whether an electron-rich reagent is acting as a base or as a nucleophile. Predicting the course of a reaction can be a more difficult task. However, as you work through a number of examples and problems, you will start to develop a feel for this as well.

## 5. TRIMOLECULAR STEPS

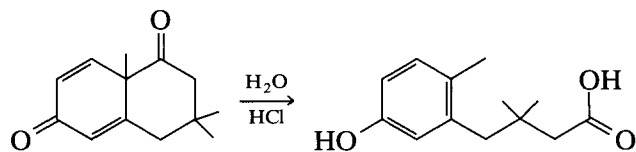
Trimolecular steps are rare because of the large decrease in entropy associated with three molecules simultaneously assuming the proper orientation for reaction.

### Hint 2.10

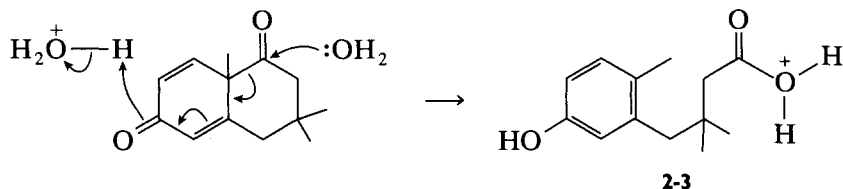
Avoid formulating mechanisms involving trimolecular steps. Instead, try to break a trimolecular step into two or more bimolecular steps.

### Example 2.11. *Breaking a trimolecular step into several bimolecular steps.*

When mechanisms for the following reaction are considered,

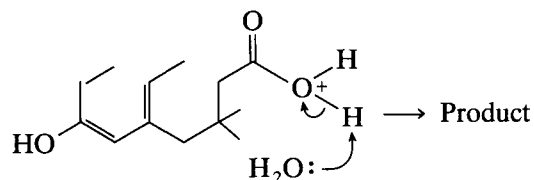


one of the steps could be written as a trimolecular reaction:

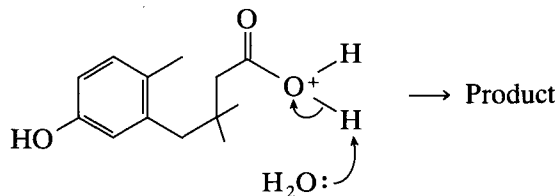
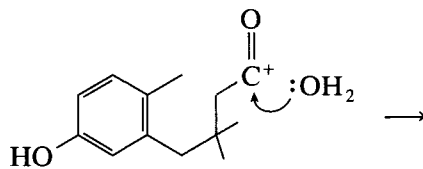
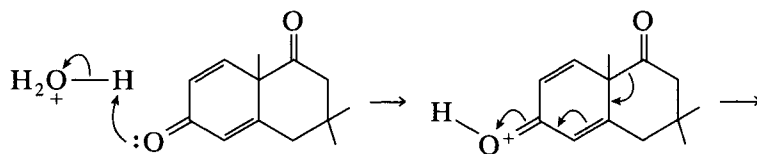




Note that, in the reaction that produces intermediate 2-3, only one lone pair is shown on the water molecules. This follows the common practice of selectively omitting lone pairs from Lewis structures and showing only the lone pairs actually taking part in the reaction. Intermediate 2-3 can lose a proton to water to give the product.



However, we can also write another mechanism, which avoids the trimolecular step:



See Problem 4.11.a for an alternative mechanism for this reaction.

## 6. STABILITY OF INTERMEDIATES

Any intermediates written for a reaction mechanism must have reasonable stability. For example, second row elements (e.g., carbon, nitrogen, and oxygen) should not be written with more than eight valence electrons,

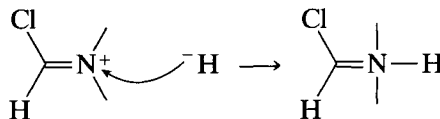
although third row elements like sulfur and phosphorus can, and do, expand their valence shells to accommodate 10 (occasionally more) electrons. In addition, positively charged carbon, nitrogen, and oxygen species with only six valence electrons are generally formed with difficulty. Although carbocations (six electrons) are high-energy intermediates that are encountered in many reactions, the corresponding positively charged nitrogen and oxygen species with six electrons are rare, especially for oxygen. (For an example of an electron-deficient nitrogen species, the nitrenium ion, see Chapter 4.)

**Hint 2.11**

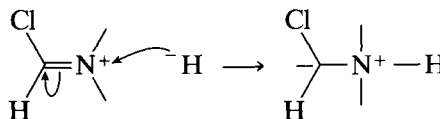
Nucleophilic reaction cannot occur at a positively charged oxygen or nitrogen that has a filled valence shell. Only eight electrons can be accommodated by elements in the second period of the periodic table. However, third period elements, like sulfur and phosphorus, can (and do) expand their valence shells to accommodate 10 (occasionally more) electrons.

**Example 2.12.** *Nitrogen cannot accommodate more than eight electrons in the valence shell.*

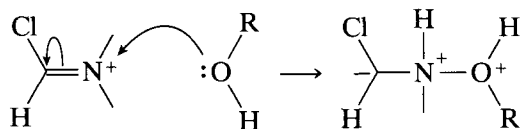
The following step is inappropriate because, in the product, nitrogen has expanded its valence shell to 10 electrons.



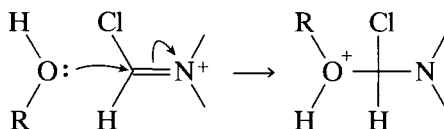
To avoid this situation, the  $\pi$  electrons in the double bond could move to the adjacent carbon, giving an internal salt called an ylide. Although they are rather unstable, ylides are intermediates in some well-known reactions.



If a neutral nucleophile reacted with nitrogen in a similar manner, there would be three charges on the product. The two positive charges on adjacent atoms would make this a very unstable intermediate.



With the preceding reagents, a more appropriate reaction would be

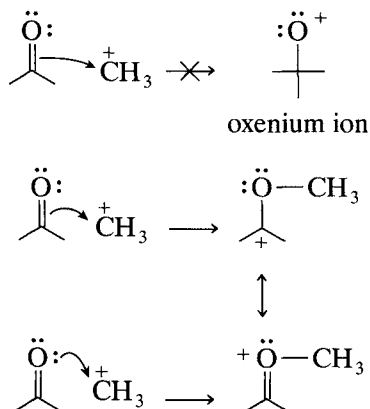


In writing a mechanism, avoid intermediates containing positively charged nitrogen or oxygen ions with less than eight electrons. These species are rare and have high energy because of the high electronegativities of oxygen and nitrogen.

### Hint 2.12

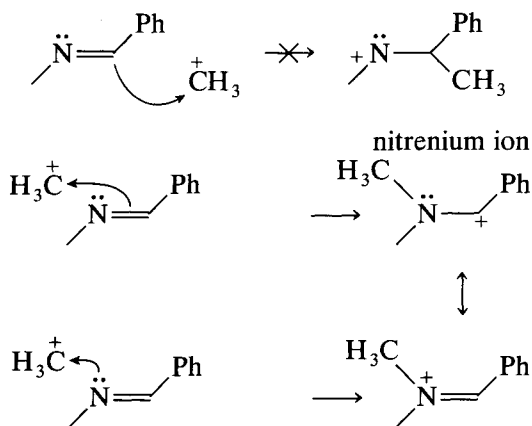
**Example 2.13.** *How to avoid writing mechanisms with electron-deficient, positively charged oxygen and nitrogen species.*

Take a look at the following mechanistic steps:



If the electrophile bonds to the carbon, the process generates an oxenium ion, a highly unstable species. If the electrophile bonds to the oxygen, the process generates a resonance-stabilized carbocation. Note that if we depict the bond being formed by the bonding electron pair between carbon and oxygen, we obtain the product with the electrophile bonded either to carbon or to oxygen. If we use the lone pair of electrons on oxygen, we obtain the product in which the electrophile is bonded to oxygen. It does not matter which pair of electrons we use as long as we draw correct Lewis structures and obtain intermediates that have reasonable stability. (For another example of this, see the answer to Problem 2.5.b.) Our choice of mechanism is based not on which electrons we choose to “push,” but on the stability of the intermediate formed.

The situation with nitrogen is analogous. The nitrenium ion is highly unstable, and the carbonium ion is resonance-stabilized.



The preceding reaction steps present another difficulty, namely, attack by the methyl cation. Primary carbocations that lack stabilizing groups are highly unstable, and the methyl cation is the least stable of the carbocations. In fact, even in “superacid” ( $\text{FSO}_3\text{H}-\text{SbF}_5$ ), no primary carbocation is stable enough to be detected. Consequently, a mechanism that invokes such a species should be looked upon with suspicion.

## 7. DRIVING FORCES FOR REACTIONS

### Hint 2.13

A viable reaction should have some energetic driving force. Examples include formation of a stable inorganic compound, formation of a stable double bond or aromatic system, formation of a stable carbocation, anion, or radical from a less stable one, and formation of a stable small molecule (see Hint 2.14).

A reaction may be driven by a decrease in enthalpy, an increase in entropy, or a combination of the two. Reactions driven by entropy often involve forming more product molecules from fewer starting molecules. Reactions that form more stable bonds are primarily enthalpy-driven. When writing a mechanism, constantly ask the following questions: Why would this reaction go this way? What is favorable about this particular step?

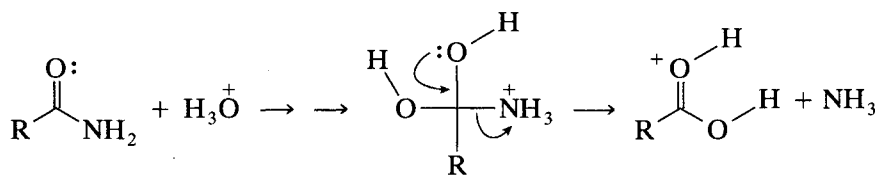
### A. Leaving Groups

When a reaction step involves a nucleophilic substitution, the nature of the leaving group often is a key factor in determining whether the reaction will occur. In general, *leaving group ability is inversely related to base strength*. Thus,  $\text{H}_2\text{O}$  is a much better leaving group than  $\text{OH}^-$ , and  $\text{I}^-$  is a better leaving group than  $\text{F}^-$ . A list of common leaving groups appears in Table 3.1.

If the reaction involves a poor leaving group, then a very good nucleophile will be necessary to induce the reaction to occur, as the next example illustrates.

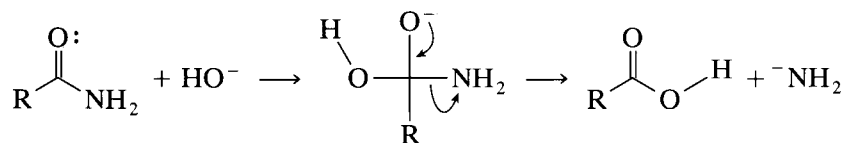
**Example 2.14.** *A rationale for the involvement of different leaving groups in the acid- and base-promoted hydrolysis of amides.*

Ammonia is the leaving group in the acid-promoted hydrolysis of amides. Amide ion,  $\text{NH}_2^-$ , is the leaving group in the base-promoted hydrolysis. The difference can be explained by the driving force of the intramolecular nucleophile relative to the ability of amide ion or ammonia to act as a leaving group. In acid, the intramolecular nucleophile is the oxygen of one of the hydroxyl groups of the tetrahedral intermediate.



In base, the intramolecular nucleophile is the oxyanion of the tetrahedral

intermediate:



The hydroxyl group is not a strong enough nucleophile, even intramolecularly, to drive the loss of an amide ion, so that under acidic conditions, the nitrogen must be protonated in order to form a sufficiently good leaving group. The leaving group then becomes ammonia, a better leaving group than amide anion. In base, the oxyanion formed by reaction of the original amide with a hydroxyl ion is a strong enough nucleophile to drive the loss of an amide ion.

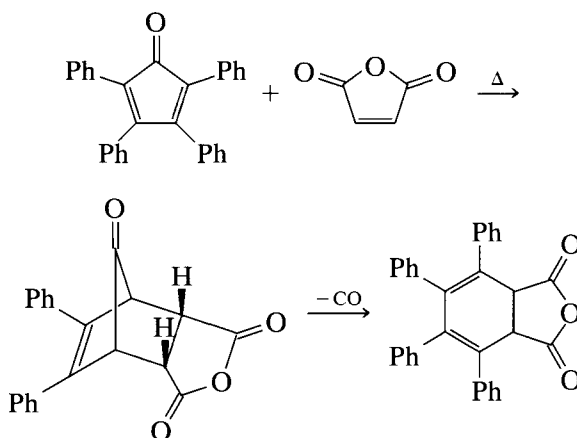
## B. Formation of a Small Stable Molecule

Formation of a small stable molecule can be a significant driving force for a reaction because this involves a decrease in enthalpy and an increase in entropy.

### Hint 2.14

A frequent driving force for a reaction is formation of the following small stable molecules: nitrogen, carbon monoxide, carbon dioxide, water, and sulfur dioxide.

**Example 2.15.** *Loss of carbon monoxide in the thermal reaction of tetraphenylcyclopentadienone with maleic anhydride.*



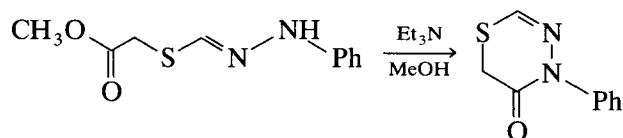
## 8. STRUCTURAL RELATIONSHIPS BETWEEN STARTING MATERIALS AND PRODUCTS

Numbering of the atoms in the starting material and the product can help you determine the relationship between the atoms in the starting material and those in the product.

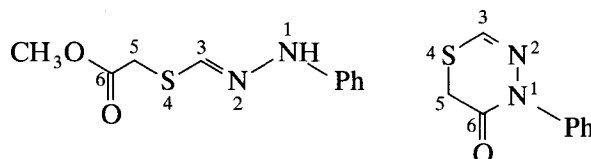
Number the atoms of the starting material in any logical order. Next, by looking for common sequences of atoms and bonding patterns, identify atoms of the product that correspond with atoms of the starting material and assign to the atoms of the product the corresponding number of the atoms from the starting material. Then, using the smallest possible number of bond changes, fill in the rest of the numbers.

**Hint 2.15**

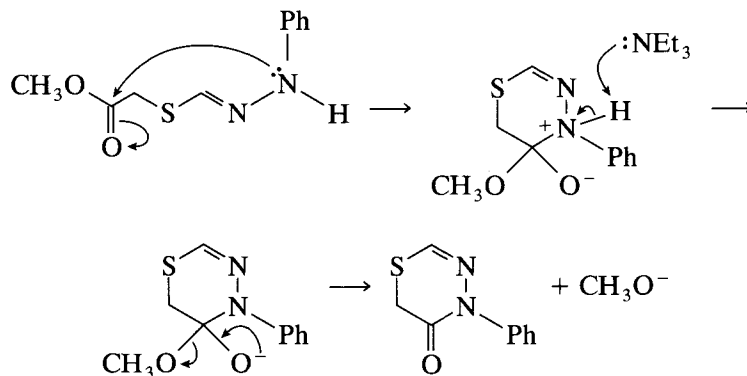
**Example 2.16.** Using a numbering scheme when writing a mechanism.



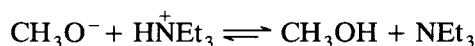
Numbering of the atoms in the starting material and product makes it clear that nitrogen-1 becomes attached to carbon-6.



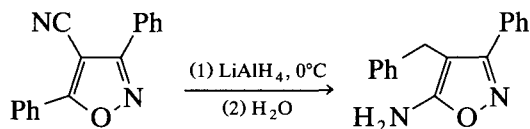
With this connection established, we can write the mechanism as follows:



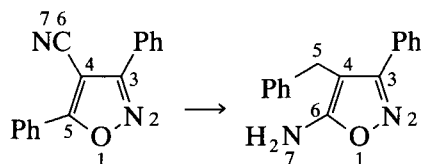
The other products, methoxide ion and triethylammonium ion, would equilibrate to give the weakest acid and weakest base (see Appendix C).



**Example 2.17.** *Using a numbering scheme to decide which bonds have been formed and which broken.*



First, consecutively number the atoms in the starting material. In this example, the atoms in the product can be numbered by paying close attention to the location of the phenyl groups and nitrogens:



Without having to write any mechanistic steps, the numbering scheme allows us to decide that the bond between C-5 and O-1 breaks and that a new bond forms between O-1 and C-6. This numbering scheme gives the least possible rearrangement of the atoms when going from starting material to product. This information is invaluable when writing a mechanism for this reaction.

This example is derived from Alberola, A.; Gonzalez, A. M.; Laguna, M. A.; Pulido, F. J. *J. Org. Chem.* **1984**, *49*, 3423–3424; a mechanism is suggested in this paper.

## 9. SOLVENT EFFECTS

Usually, the primary function of a solvent is to provide a medium in which reactants and products can come into contact with one another and interact. Accordingly, solubility dictates the choice of solvent for many organic reactions. However, the nature of the solvent can influence the mechanism of a reaction, and sometimes the choice of solvent dictates the pathway by which a reaction proceeds. In terms of effect on the mechanism, interactions of polar



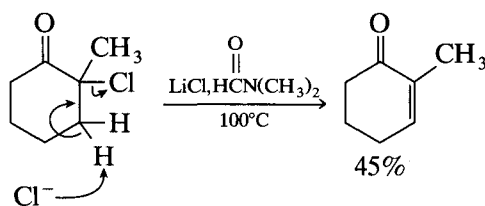
solvents with polar reagents are the most important. Accordingly, solvents can be divided into three groups:

1. Protic solvents, e.g., water, alcohols, and acids.
2. Polar aprotic solvents, e.g., dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile ( $\text{CH}_3\text{CN}$ ), acetone, sulfur dioxide, and hexamethylphosphoramide (HMPA).
3. Nonpolar solvents, e.g., chloroform, tetrahydrofuran (THF), ethyl ether, benzene, carbon tetrachloride.

Interactions between a polar solvent and a charged species are stabilizing. Protic solvents can stabilize both anionic and cationic species, whereas polar aprotic solvents stabilize only cationic species. Thus, protic solvents favor reactions in which charge separation occurs in the transition state, the high-energy point in the reaction pathway. In nucleophilic substitution reactions, the pathway where two charged species are formed (i.e.,  $\text{S}_{\text{N}}1$  reaction) is favored in protic solvents, whereas the pathway with a less polar transition state (i.e.,  $\text{S}_{\text{N}}2$  reaction) is favored in nonprotic solvents.

**Example 2.18.** *The influence of solvent on basicity.*

Chloride ion generally is a moderate nucleophile and a weak base. However, in the following dehydrohalogenation reaction, chloride ion functions as a base, removing a proton to bring about elimination of the elements of HCl.



Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth. Coll. Vol. 4*, 1963, 162.

In this reaction, chloride functions as a base because the reaction is carried out in the polar aprotic solvent DMF. In polar aprotic solvents, cations are stabilized by solvent interaction, but anions do not interact with the solvent. The “bare” chloride anion functions as a base because it is not stabilized by solvent interaction.

For another example of the effect of solvent on reaction mechanism, see Example 4.14.

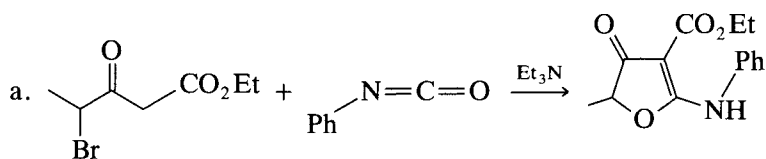
**Hint 2.16** Use the combination of reagents and solvents specified as a guide to the mechanism. Ionic reagents and polar solvents point to ionic mechanisms. The absence of ionic reagents and use of a nonpolar solvent may suggest a nonionic mechanism.

## 10. A LAST WORD

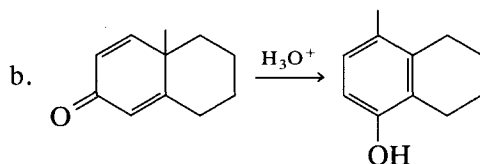
The fourteenth century English philosopher William of Occam introduced the principle known as Occam's razor. A paraphrase of this principle which can be applied to writing organic reaction mechanisms is expressed in Hint 2.17.

**Hint 2.17** When more than one mechanistic scheme is possible, the simplest is usually the best.

**PROBLEM 2.5** For each of the following transformations, number all relevant non-hydrogen atoms in the starting materials, and number the same atoms in the product.



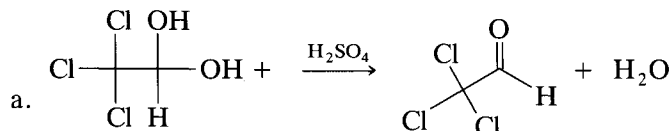
(See Problem 3.19.b for further exploration of this reaction.)



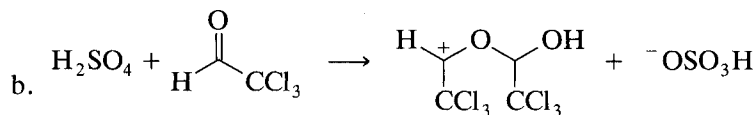
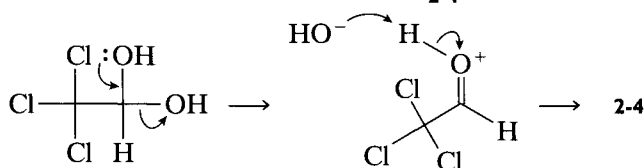
(See Example 4.10 for further exploration of this reaction.)

In each of the following problems, an overall reaction is given, followed by a mechanism. For each mechanism shown, identify inappropriate steps, give the number of any applicable hint, and explain its relationship to the problem. Then write a more reasonable mechanism for each reaction.

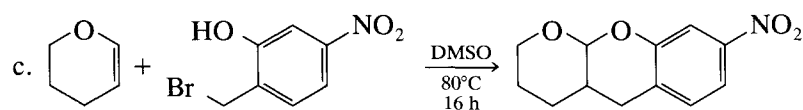
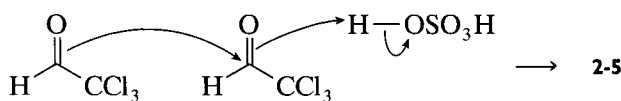
## PROBLEM 2.6



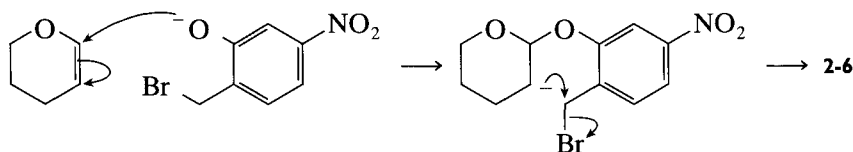
2-4



2-5



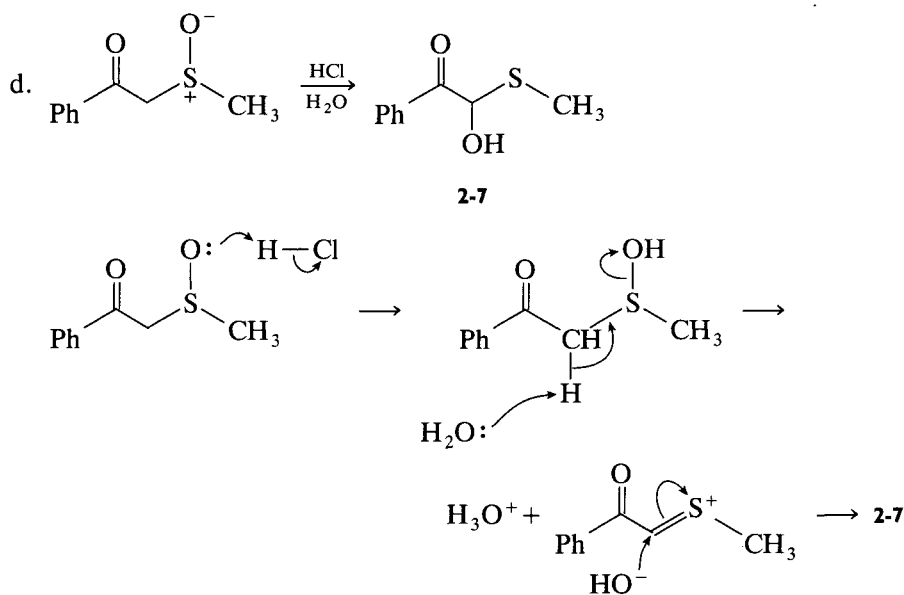
2-6



Kirby, A. J.; Martin, J. J. *J. Chem. Soc., Perkin Trans. II* **1983**, 1627-1632.

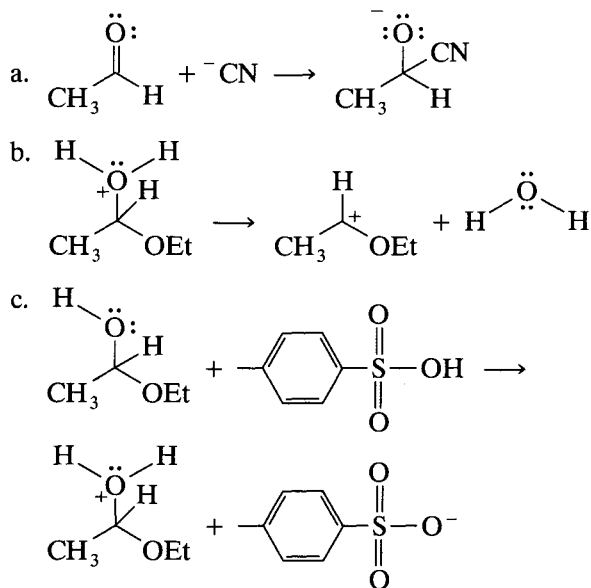
## PROBLEM 2.6

continued

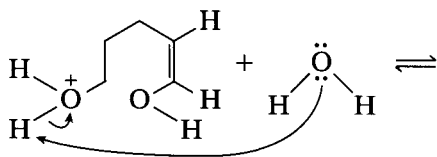
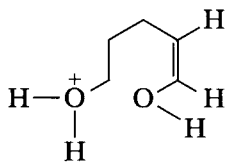
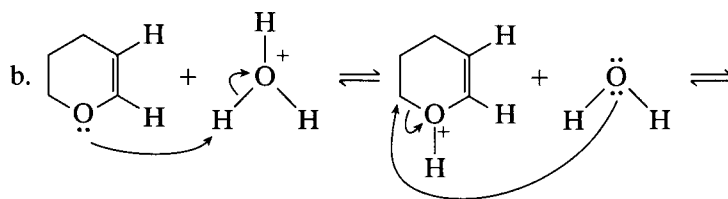
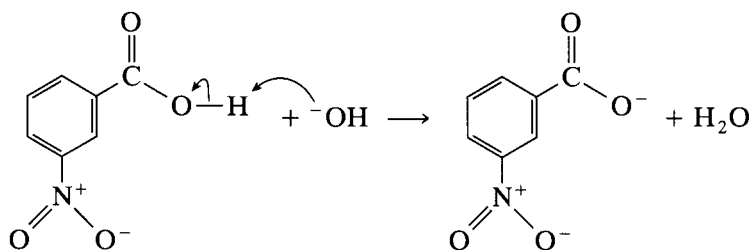
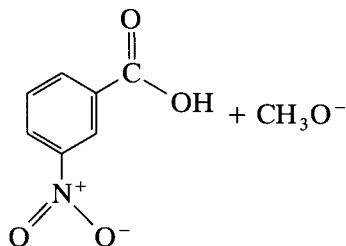
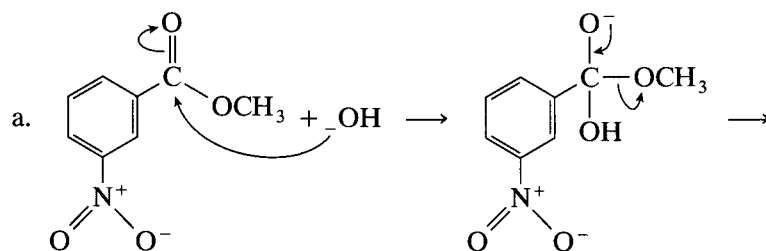
Kunieda, N.; Fujiwara, Y.; Suzuki, A.; Kinoshita, M. *Phosphorus Sulfur* **1983**, *16*, 223–232.

## ANSWERS TO PROBLEMS

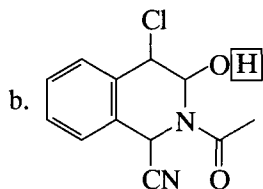
## Problem 2.1



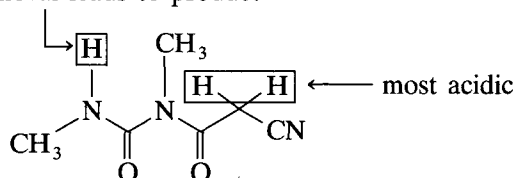
## Problem 2.2



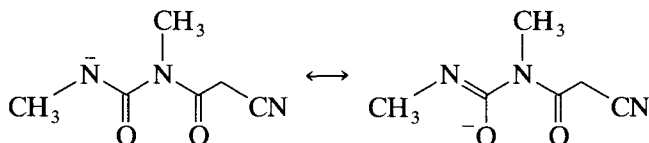


Problem 2.3  
continued

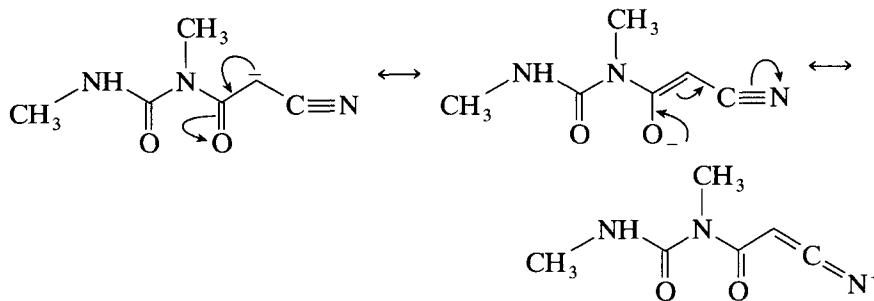
c. removal leads to product



On the basis of acidity, the protons in this molecule can be divided into three groups: the methyl hydrogens, the amide hydrogen, and the methylene hydrogens. Of these, the methyl hydrogens are the least acidic, and the methylene hydrogens are the most acidic. We can estimate the acidity of the protons by examining the stabilities of the anions that result when different hydrogens are removed from the molecule. Removal of a proton from either methyl group gives an anion stabilized only by the inductive effects of nitrogen; no resonance forms are possible. Removal of hydrogen from the amide nitrogen gives an anion stabilized by two resonance forms, one with negative character on nitrogen and one with negative character on oxygen:



Finally, removal of hydrogen from the methylene group gives an anion with three resonance forms in which the negative charge is on nitrogen, oxygen, or carbon:



Thus, the anion formed by loss of a proton from the methylene group should be more stable.

Problem 2.3  
continued

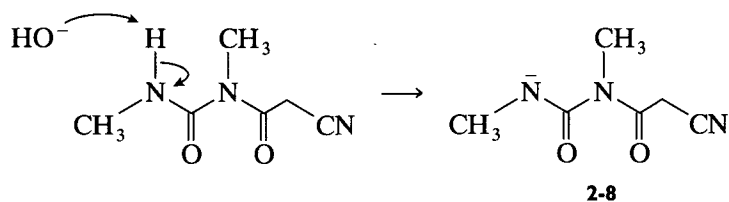
We also can compare the acidities of the various protons by using the  $pK_a$  values listed in Appendix C.

Acid	Conjugate base	$pK_a$
$\text{CH}_3\overset{\text{O}}{\parallel}\text{CNH}_2$	$\text{CH}_3\overset{\text{O}}{\parallel}\text{CNH}^-$	25.5
$\text{NCCH}_2\overset{\text{O}}{\parallel}\text{COCH}_3$	$\text{NC}\overset{\ominus}{\text{C}}\text{H}\overset{\text{O}}{\parallel}\text{COCH}_3$	12.8
$\text{CH}_3\overset{\text{O}}{\parallel}\text{COCH}_2\text{CH}_3$	$\overset{\ominus}{\text{C}}\text{H}_2\overset{\text{O}}{\parallel}\text{COCH}_2\text{CH}_3$	30
$\text{CH}_3\overset{\text{O}}{\parallel}\text{CN}(\text{CH}_2\text{CH}_3)_2$	$\overset{\ominus}{\text{C}}\text{H}_2\overset{\text{O}}{\parallel}\text{CN}(\text{CH}_2\text{CH}_3)_2$	34.5

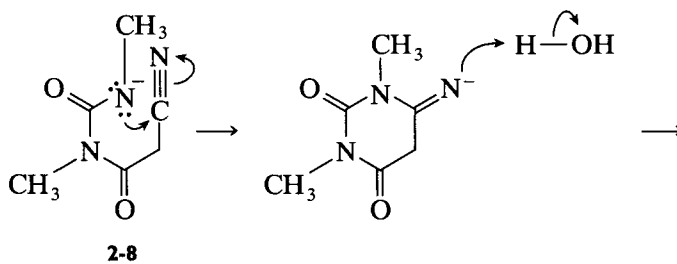
Using these values, there are several ways to compare the acidity of the protons in the boxes. The  $pK_a$  of the amide protons in acetamide is 25.5. The  $pK_a$  of the amide proton in this compound should be somewhat greater, because the second amido nitrogen will reduce the resonance stabilization of the anion formed when the amide proton is removed. The precedent for the other boxed protons is the  $pK_a$  of the methylene protons of methyl cyanoacetate, 12.8. Because the carbonyl group in the given compound is an amide rather than an ester, the  $pK_a$  of its protons will be somewhat higher, but not nearly as high as the value for the amide proton.

We can arrive at the same conclusion in a different way using an alternative analysis based on the  $pK_a$  values in Appendix C. The  $pK_a$  of the protons on the  $\alpha$  carbon of ethyl acetate is 30, whereas the  $pK_a$  of those of methyl cyanoacetate is 12.8. Therefore, a cyano group lowers the  $pK_a$  of the  $\alpha$  carbon protons by  $30 - 12.8 = 17$  units. The  $pK_a$  of the  $\alpha$  carbon protons of an  $N,N$ -disubstituted amide,  $N,N$ -diethylacetamide, is 34.5. If we assume that the cyano group enhances the acidity of the methylene protons in the given compound by the same amount, their  $pK_a$  would be  $34.5 - 17 = 16.5$ . Thus, the estimated  $pK_a$  of the methylene protons is at least 9  $pK$  units lower than that of the amide proton, a factor of one billion.

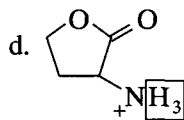
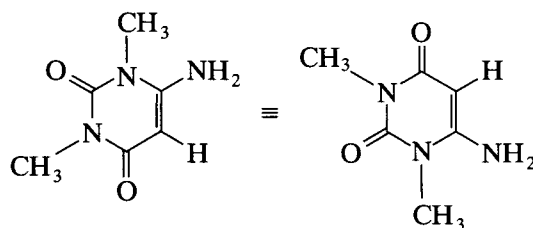
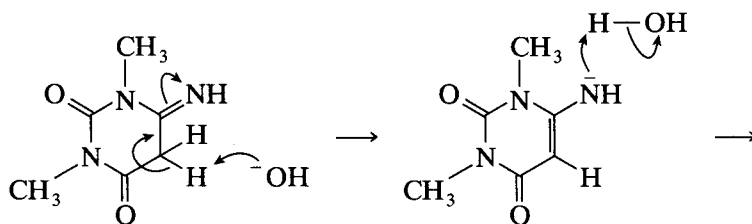
The mechanism for the reaction could be written as follows. First, the proton is removed by base:





Problem 2.3  
continued

The resulting anion, **2-8**, can be written in a conformation that makes it clear how the subsequent cyclization takes place.  
Now the intermediate tautomerizes to give the final product.



## Problem 2.4

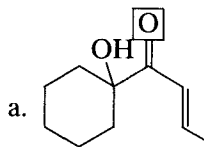
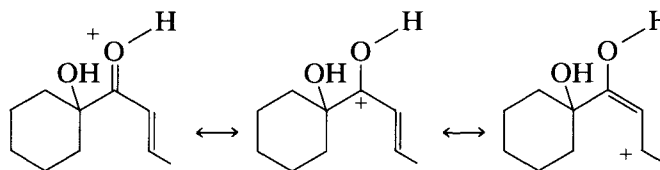
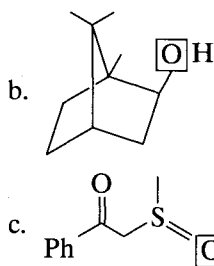


Table 1.3 and Appendix C indicate that carbonyl oxygens are more basic than the oxygen of an alcohol. The protonated carbonyl is stabilized by resonance, whereas the protonated alcohol is not. In this case, the protonated carbonyl is further stabilized by delocalizations of charge onto the C=C double bond.



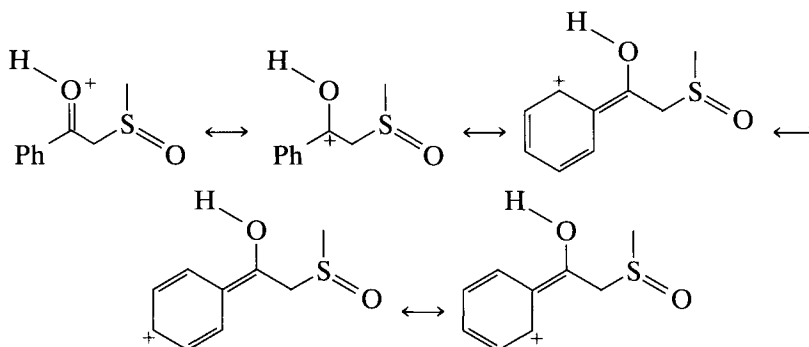
In the paper cited (Jacobsen and Lahm, 1979), the mechanism proposed suggests that the starting material is dehydrated before cyclization occurs. This means that protonation of the less basic group leads to the product. Satisfy yourself that this is reasonable by writing possible reaction mechanisms that would result from protonation of the hydroxyl and carbonyl hydrogens.



Appendix C is of help here. The  $pK_a$  of protonated acetophenone is  $-4.3$ , whereas the  $pK_a$  of protonated dimethyl sulfoxide is  $-1.5$ . Thus, dimethyl sulfoxide is almost  $10^3$  times more basic than acetophenone. These compounds are excellent models for the two functional groups in the compound given.

If hard data like those in Appendix C are unavailable, it is very difficult to decide which oxygen is more basic, by simply considering the functional groups and the structure of the molecule. On one hand, because sulfur is slightly more electronegative than carbon (see Table 1.2), one might predict that the carbonyl oxygen is more basic than the sulfoxide oxygen. Furthermore, protonation of the carbonyl group leads to a cation that is

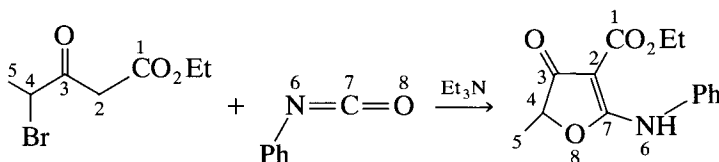
stabilized by resonance delocalization onto the aromatic ring:



On the other hand, the  $\pi$  bond between C and O should be stronger than the  $\pi$  overlap between S and O because C and O both use  $2p$  orbitals to form  $\pi$  bonds, whereas a  $\pi$  bond between S and O utilizes the less effective  $3p-2p$  overlap. This should make the oxygen of the sulfoxide functional group more negative. Additionally, sulfur stabilizes charges more effectively than do carbon and oxygen because of its higher polarizability.

In the absence of hard data, qualitative arguments suggest that both oxygens are fairly basic. In a situation like this, it is usually best to adopt a trial-and-error approach, first writing mechanisms that start with the protonation of one functional group and then writing mechanisms that start with the protonation of the other functional group. Remember, a mechanism does not always proceed through protonation of the most basic atom.

- a. Start numbering the product at the carboethoxy group, which has not been altered by the reaction. Once you notice that the keto group of the ketoester reactant is also unchanged, the remaining atoms easily fall into place. For the isocyanate, N-6 is obvious, and C-7 and O-8 follow.



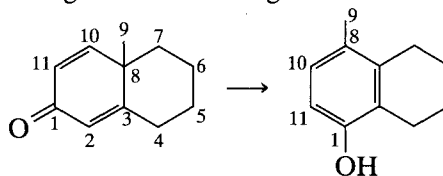
- b. The first thing to notice is that the position of the C—O bond, relative to the methyl group, has not changed. Thus, an initial attempt to number the product would leave those atoms in the same relative positions as in the

Problem 2.4  
continued

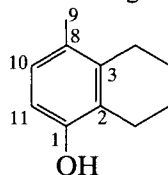
Problem 2.5

**Problem 2.5**  
*continued*

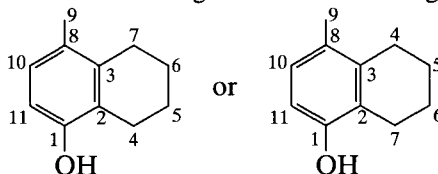
starting material. This gives the following numbers:



A strong possibility is that the left-hand ring of the product contains the same carbons that this ring contained in the starting material. By minimizing the changes in bonding, the following results:



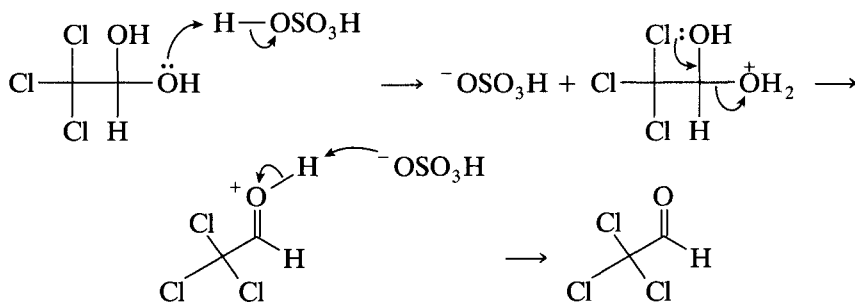
This leaves two possible numbering schemes for the right-hand ring:



The structure on the right involves less rearrangement; however, if we examine the symmetrical intermediate involved in this reaction (see Example 4.10), we see that, in fact, the two numbering schemes are equivalent in terms of bond reorganization.

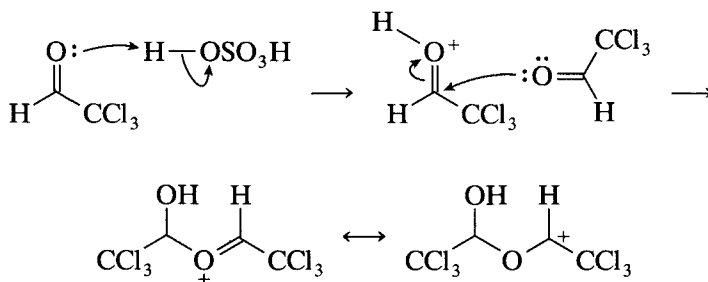
**Problem 2.6**

- a. Hint 2.5. This reaction is taking place in a strongly acidic medium. Therefore, strong bases like  $\text{OH}^-$  will be in such low concentration that they cannot be effective reagents in the reaction. A better mechanism would be to protonate the oxygen of one of the hydroxyl groups to convert it into a better (and neutral) leaving group, the water molecule.

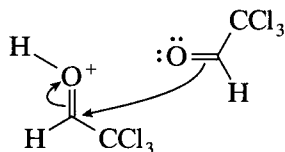


Problem 2.6  
*continued*

- b. Hint 2.8. Break up the trimolecular step. First, protonate the carbonyl group, converting it to a better electrophile. Follow this with nucleophilic reaction with the carbonyl group by the oxygen of another molecule of starting material.

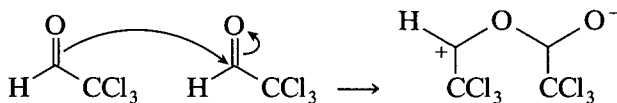


The nucleophilic addition of the carbonyl compound to another protonated molecule can be written either as shown or by using the  $\pi$  bond as the nucleophile instead of a lone pair on oxygen. This second kind of addition leads to the second resonance form shown instead of the first:



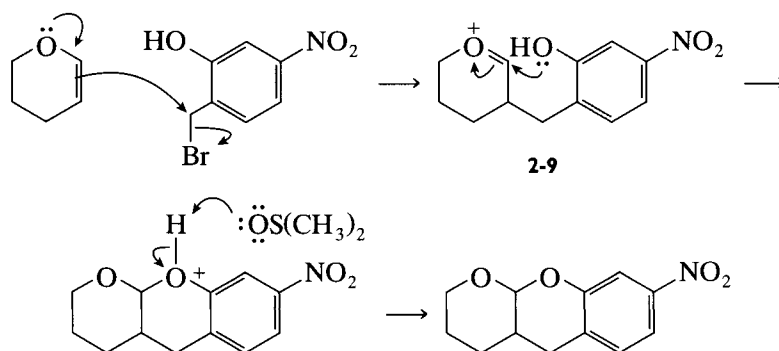
The two representations for this step are equivalent.

The oxygen of one starting aldehyde molecule must be protonated before nucleophilic addition of the carbonyl oxygen of the second. Otherwise, a very basic anion is formed in a very acidic medium (the same problem discussed in part a).

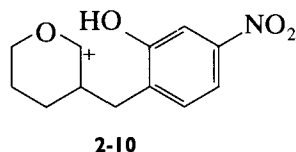


Problem 2.6  
continued

- c. There are two major problems with the mechanism shown. Data from Appendix C indicate that the substituted phenol would not be ionized significantly in DMSO. Protonated dimethyl sulfoxide has a  $pK_a$  of  $-1.5$ , whereas *m*-nitrophenol has a  $pK_a$  of  $8.3$ . Also, the intermediate carbanion, resulting from the addition, is very unstable; it is not stabilized by resonance in any way. The following mechanism avoids these problems by forming an intermediate cation, **2-9**, which is stabilized by resonance, and by leaving removal of the proton to the last step.



Intermediate **2-9** could also be written as the other resonance form, **2-10**, which contributes to the stabilization of the positive charge:



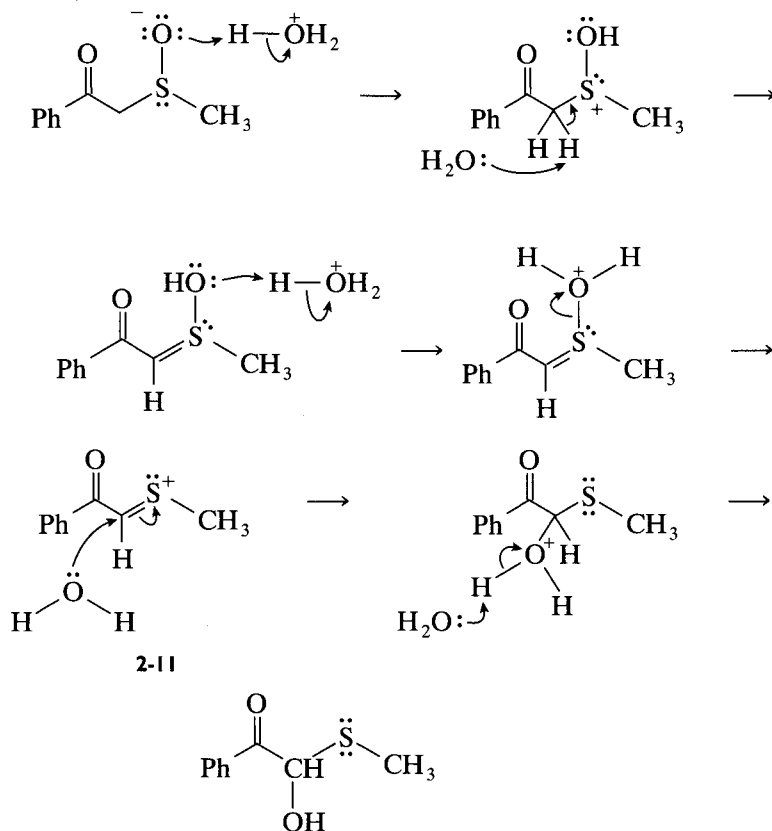
Often it is useful to draw resonance forms for proposed intermediates because their existence is an indication of stability, which represents a driving force for the reaction. Removal of a proton from the OH group of the resonance hybrid of **2-9** and **2-10** is unlikely because bromide ion is an even weaker base than DMSO (the  $pK_a$  of HBr is  $-9$ ). Therefore, it is expected that ring closure, by nucleophilic reaction with the cation, takes place before removal of the proton.

- d. Hint 2.5. The given mechanism has two steps that are unlikely in strong acid: loss of hydroxide ion and its subsequent nucleophilic reaction. Water is a much better leaving group than hydroxide, so that in acidic solution, where protonation of the oxygen can occur, water acts as the leaving

Problem 2.6  
*continued*

group. Notice that because hydrochloric acid is completely dissociated in aqueous solution, hydronium ion, not hydrochloric acid, acts as the protonating agent. In acidic solution, the concentration of hydroxide ion is so low that, although hydroxide ion is a better nucleophile than water, it cannot compete with water for the nucleophilic site.

It is always a good idea to keep track of lone pairs of electrons on heteroatoms, such as oxygen and sulfur, by drawing them in. As the mechanism proceeds, it is also a good idea to keep track of formal charges on the atoms of interest, in this case oxygen and sulfur.



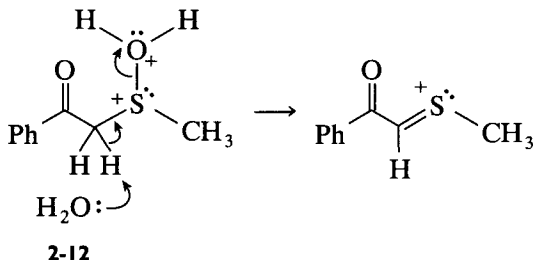
Note that the first two steps of the mechanism represent a tautomerization, in which the overall result is movement of a proton from carbon to oxygen and movement of a double bond. Notice, also, that there are several intermediates in which sulfur has an expanded octet.

Take a look at some alternative mechanistic steps:

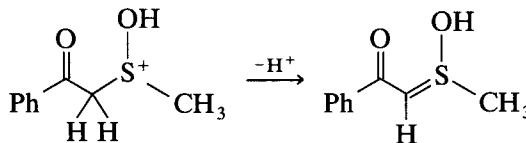
(i) One possibility is formation of **2-12** (by doubly protonating the sulfoxide oxygen of starting material), from which simultaneous elimina-

Problem 2.6  
continued

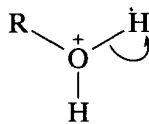
tion of water and loss of a proton from the methylene group might be written. This would not be as good a step as those shown previously because the development of two adjacent positive centers is destabilizing.



(ii) Removal of a proton always requires reaction with a base, which in this step could be water. Thus, the following representation is not strictly correct because no base is indicated to remove the proton; however, as stated previously, this would be considered acceptable by a number of instructors.



(iii) Showing 2-13 for removal of a proton is not accurate for two reasons. First, the arrow indicates electron movement in the wrong direction; this would produce  $\text{H}^-$  instead of  $\text{H}^+$ . (See Chapter 3 for further discussion of hydride loss.) Second, proton removal always requires reaction with a base, even if it is a weak base.

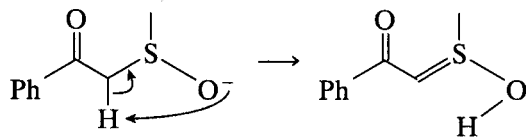


2-13



(iv) The following equation is an example of a [1,3] sigmatropic intramolecular shift of hydrogen. Chapter 6 discusses why this type of tautomeric reaction is unlikely to occur.

Problem 2.6  
*continued*



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