CHAPTER

# 4

# Reactions Involving Acids and Other Electrophiles

Acids and electrophiles are electron-deficient species. According to the Lewis concept, all electrophiles (e.g., cations, carbenes, metal ions) are acids by definition. However, from long usage the term *acid* is frequently used to refer to a proton donor, whereas the term *Lewis acid* usually refers to charged electrophiles in general.

## 1. STABILITY OF CARBOCATIONS

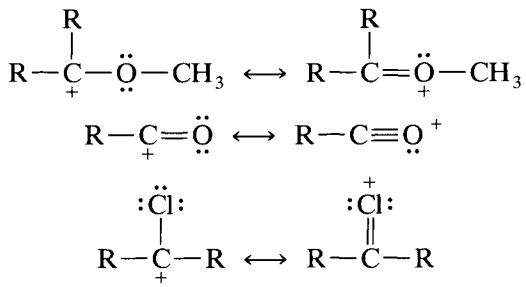
Reactions in acid often involve the formation of carbocations—trivalent, positively charged carbon atoms—as intermediates. The order of stability of carbocations containing only alkyl substituents is $3° > 2° > 1° > CH_3$. Cation stability is influenced by several factors:

1. *Hyperconjugation.* An increase in the number of alkyl substituents increases the stability of the carbocation due to orbital overlap between the

adjacent $\sigma$ bonds and the unoccupied $p$ orbital of the carbocation. The resulting delocalization of charge, which can be represented by resonance structures, stabilizes the cation.

2. *Inductive effects*. Neighboring alkyl groups stabilize a cation because electrons from an alkyl group, which is relatively large and polarizable compared to hydrogen, can shift toward a neighboring positive charge more easily than can electrons from an attached hydrogen.

3. *Resonance effects*. Conjugation with a double bond increases the stability of a carbocation. Thus, allylic and benzylic cations are more stable than their saturated counterparts. (For example, see Problem 1.4.c.) Heteroatoms with unshared electron pairs, e.g., oxygen, nitrogen, or halogen, can also provide resonance stabilization for cationic centers, as in the following examples:



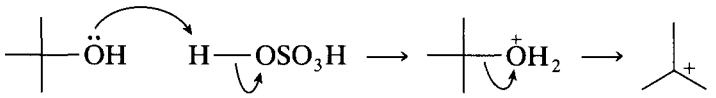
Cations at $sp^2$- or $sp$-hybridized carbons are especially unstable. In general, the more $s$ character in the orbitals, the less stable the cation. An approximate order of carbocation stability is $CH_3CO^+$ (acetyl cation) ~ $(CH_3)_3C^+ \gg PhCH_2^+ > (CH_3)_2CH^+ > H_2C{=}CH{-}CH_2^+ \gg CH_3CH_2^+ > H_2C{=}CH^+ > Ph^+ > CH_3^+$. The stabilities of various carbocations can be determined by reference to the order of stability for alkyl carbocations, $3° > 2° > 1° > CH_3$. The acetyl cation has a stability similar to that of the $t$-butyl cation. Secondary carbocations, primary benzylic cations, and primary allylic cations are all more stable than primary alkyl cations. Vinyl, phenyl, and methyl carbocations are less stable than primary alkyl cations.

## 2. FORMATION OF CARBOCATIONS

### A. Ionization

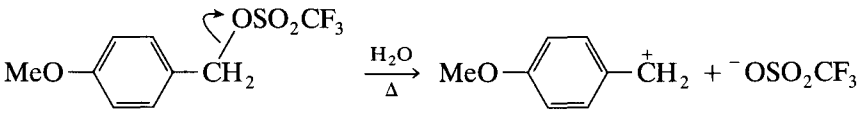
A compound can undergo unimolecular ionization to a carbocation and a leaving group. If the final product formed is due to substitution, the process is called $S_N1$. If it is due to elimination, the process is called E1. In both cases, the rate-determining step is the ionization, not the product-forming step.

**Example 4.1.** ***Acid-catalyzed loss of water from a protonated alcohol.***



In this process, protonation of the alcohol group is the first step. This occurs much faster than the rate-determining step, loss of water from the protonated alcohol.

**Example 4.2.** ***Spontaneous ionization of a triflate.***

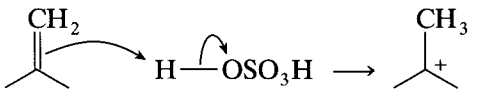


In this example, ionization is favored by several factors. First, the benzyl ion formed is resonance-stabilized and bears a methoxy group in the *para* position that can further stabilize the cation by resonance. In addition, the leaving group is triflate, an exceptionally good leaving group. Finally, the ionization takes place in water, a polar solvent that can stabilize the two charged species formed.

## B. Addition of an Electrophile to a $\pi$ Bond

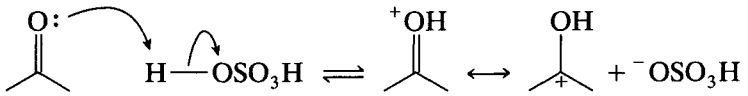
Intermediate cations are often produced by addition of a proton or a Lewis acid to a $\pi$ bond.

**Example 4.3.** ***Protonation of an olefin.***

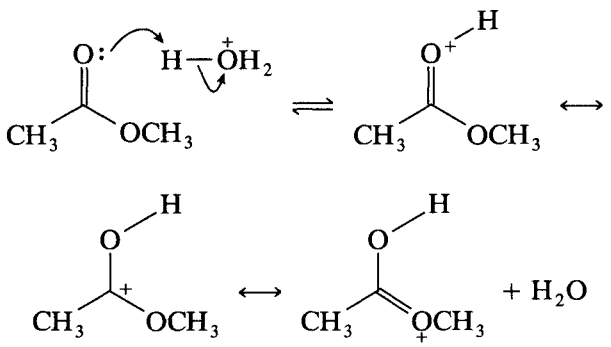


**Example 4.4.** ***Protonation of a carbonyl group.***

In acid, carbonyl compounds are in equilibrium with their protonated counterparts. Protonation is often the first step in nucleophilic addition or substitution of carbonyl groups. For aldehydes and ketones, the protonated carbonyl group is a resonance hybrid of two forms: one with positive charge on the carbonyl oxygen and one with positive charge on the carbonyl carbon.

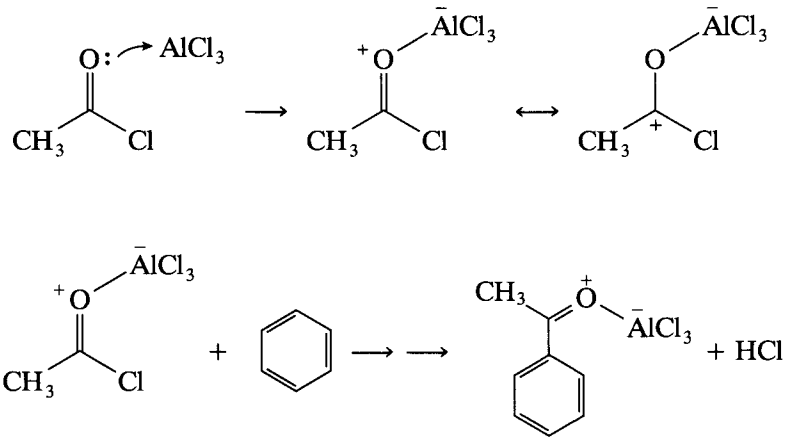


When esters are protonated at the carbonyl group, there are three resonance forms: two corresponding to the ones that form with aldehydes and ketones and a third with positive charge on the alkylated oxygen.



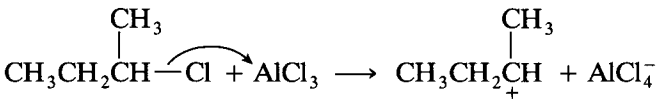
**Example 4.5.** ***Reaction of a carbonyl compound with a Lewis acid.***

Carbonyl groups form complexes or intermediates with Lewis acids like $AlCl_3$, $BF_3$, and $SnCl_4$. For example, in the Friedel–Crafts acylation reaction in nonpolar solvents, an aluminum chloride complex of an acid chloride is often the acylating agent. Because of the basicity of ketones, the products of the acylation reaction are also complexes. For more detail on electrophilic aromatic substitution, see Section 7.



## C. Reaction of an Alkyl Halide with a Lewis Acid

**Example 4.6.** ***Reaction of 2-chlorobutane and aluminum trichloride.***



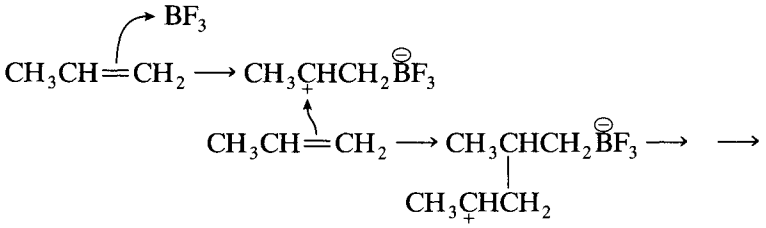
The Lewis acid removes the halide ion to give a carbocation.

## 3. THE FATE OF CARBOCATIONS

Once formed, carbocations have several options for further reaction. Among these are substitution, elimination, addition, and rearrangement.

1. Substitution ($S_N1$) occurs when the carbocation reacts with a nucleophile.
2. Elimination (E1) usually occurs with loss of a proton, as in the formation of 2-methyl-1-propene from the *t*-butyl cation.
3. The carbocation can react with an electron-rich reagent.

**Example 4.7.** ***Cationic olefinic polymerization.***



4. The carbocation can undergo rearrangement (see the following section).

(The negative sign on the boron indicates charge only; there is not an unshared pair of electrons on boron.)

## 4. REARRANGEMENT OF CARBOCATIONS

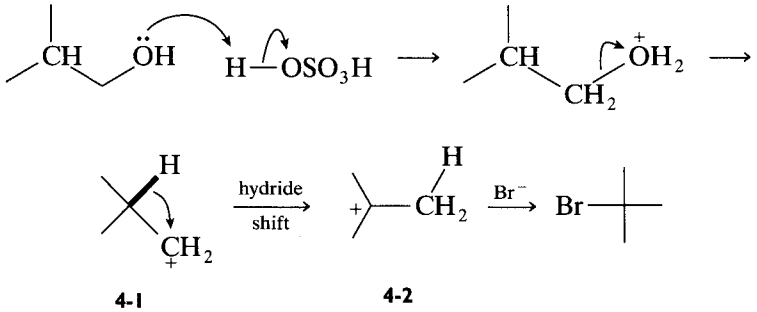
Carbocations tend to rearrange much more easily than carbanions. Under common reaction conditions, a carbocation rearranges to another carbocation of equal or greater stability. For example, a secondary carbocation will rearrange to a tertiary carbocation or a different secondary carbocation, but ordinarily it will not rearrange to a less stable primary carbocation. This generalization is not absolute, and because there is not a high energy barrier to the rearrangement of carbocations, rearrangement to a less stable cation can occur if it offers the chance to form a more stable product.

***Hint 4.1*** Rearrangement of a carbocation frequently involves an alkyl, phenyl, or hydride shift to the carbocation from an adjacent carbon (a 1,2-shift).

In many cases there are several different pathways by which rearrangement may take place. In these situations, the question of which group will migrate (migratory aptitude) is a complex one. In general, aryl and branched alkyl chains migrate in preference to unbranched chains, but the selectivity is not high. Similarly, the tendency of hydrogen to migrate is unpredictable: sometimes hydrogen moves in preference to an aryl group, at other times it migrates less readily than an alkyl. Very often, other factors such as stereochemistry, relief of strain, and reaction conditions are as important as the structure of the individual migrating group. *Frequently it is difficult to predict the product of a reaction in which a carbocation is formed; it is much easier to identify a reasonable pathway by which an experimentally obtained product is derived from starting material.*

**Example 4.8.** ***A hydride shift in the rearrangement of a carbocation.***

Treatment of isobutyl alcohol with HBr and $H_2SO_4$ at elevated temperatures leads to *t*-butyl bromide. In the first step, the hydroxyl group is protonated by the sulfuric acid to convert it into a better leaving group, the water molecule. Water then leaves, giving the primary isobutyl carbocation, **4-1**.




**4-1** **4-2**

The hydrogen and the electrons in its bond to carbon, highlighted in **4-1**, move to the adjacent carbon. Now the carbon from which the hydride left is deficient by one electron and is, thus, a carbocation. Because the new carbocation, **4-2**, is tertiary, the molecule has gone from a relatively unstable primary carbocation to the much more stable tertiary carbocation. In the final step, the nucleophilic bromide ion reacts with the positive electrophilic tertiary carbocation to give the alkyl halide product.

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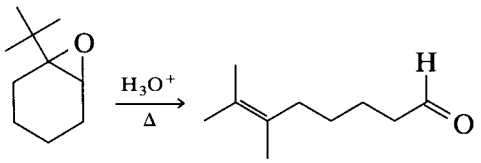
In rearrangement reactions, the method of numbering both the starting material and the product, introduced in Chapter 2, can be very helpful. ***Hint 4.2***

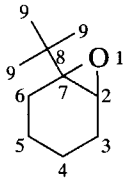
**Example 4.9.** ***An alkyl shift in the rearrangement of a carbocation.***

Consider the following reaction:

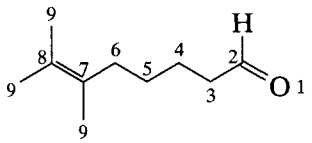



(This example is derived from Corona, T.; Crotti, P.; Ferretti, M.; Macchia, F. *J. Chem. Soc., Perkin Trans.* 1 **1985**, 1607–1616.)

Because the product has neither a *t*-butyl group nor a six-membered ring, a rearrangement must have taken place. Numbering of both the starting material and the product helps to visualize what takes place during the course of the reaction.



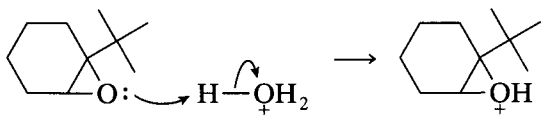
**4-3**



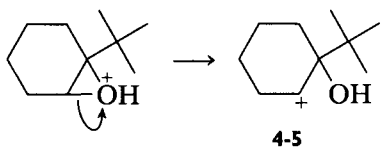
**4-4**

The three methyls in **4-3** are given the same number because they are chemically equivalent. The product **4-4** has been numbered so that the system conforms as closely as possible to that of the starting material, i.e., with the least possible rearrangement. Comparison of the numbering in **4-3** to that in **4-4** shows that one of the methyl groups shifts from carbon-8 to carbon-7 and that the bond between carbon-2 and carbon-7 is broken. Because a rearrangement to carbon-7 takes place, that carbon must have a positive charge during the course of the reaction.

The oxygen is the only basic atom in the molecule, so protonation of the oxygen must be the first step.

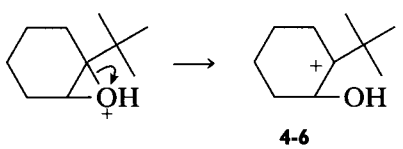


The protonated epoxide is unstable because of the high strain energy of the three-membered ring and opens readily. There are two possible modes of ring opening:



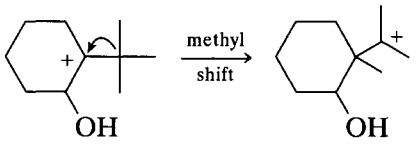
**4-5**

or



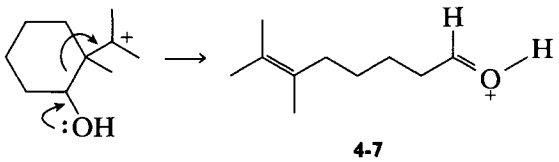
**4-6**

Because **4-6**, a tertiary carbocation, is more stable than **4-5**, a secondary cation, **4-6** would be expected to be formed preferentially. (However, if the tertiary carbocation did not lead to the product, we would go back to consider the secondary cation.) In addition, the formation of **4-6** appears to lead toward the product, because the carbon bearing the positive charge is number 7 in **4-3**. The tertiary carbocation can undergo rearrangement by a methyl shift to give another tertiary carbocation.



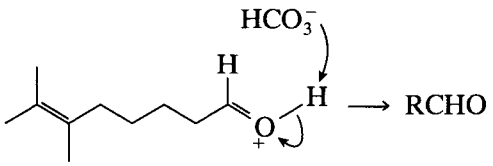

**4-6**

Now, one of the lone pairs of electrons on oxygen facilitates breaking the bond between C-2 and C-7. The formation of two new $\pi$ bonds compensates for the energy required to break the bond between C-2 and C-7.




**4-7**

The only remaining step is deprotonation of the protonated aldehyde, **4-7**, to give the neutral product. This would occur during the workup, probably in a mild base like sodium bicarbonate.

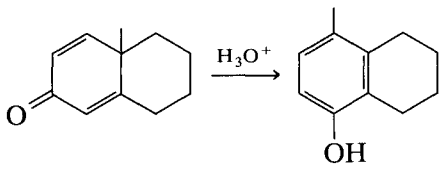


## A. The Dienone–Phenol Rearrangement

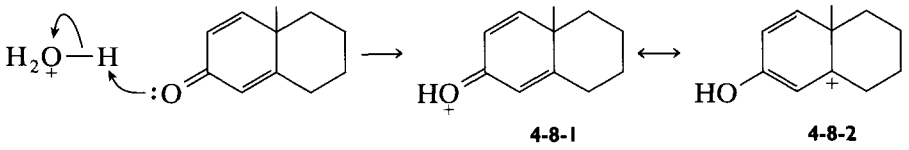
The dienone–phenol rearrangement is so named because the starting material is a dienone and the product is a phenol.

**Example 4.10.** ***Rearrangement of a bicyclic dienone to a tetrahydronaphthol system.***

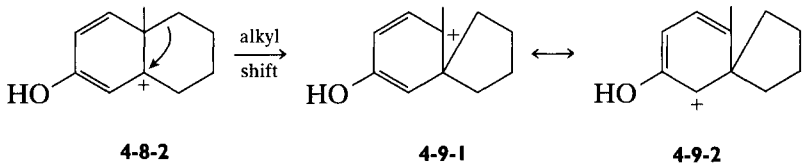
Inspection shows that a skeletal change occurs in the following transformation, that is, rearrangement occurs. (See the answer to Problem 2.4.b for an application of Hint 2.13 to analyzing the bonding changes involved.)



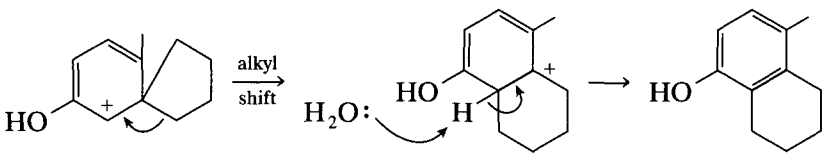

The first step in the mechanism for this reaction is protonation of the most basic atom in the molecule, the oxygen of the carbonyl.




The intermediate carbocation, **4-8**, undergoes an alkyl shift to give another resonance-stabilized carbocation, **4-9**.



Finally, **4-9** undergoes another alkyl shift, followed by loss of a proton, to give the product. Looking at the resonance structures that can be drawn for all the cations involved in the mechanism suggests that their energy should be comparable to that of the initial cation, **4-8-2**. The driving force for the reaction comes from the formation of the aromatic ring.

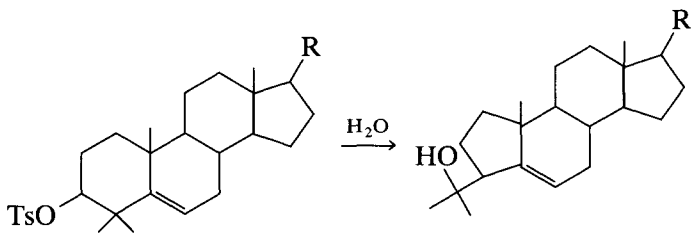



**4-9**

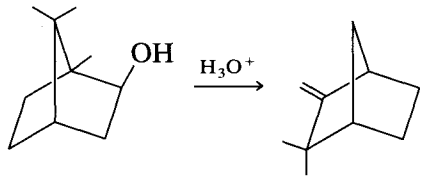
What initially appears to be a complicated reaction is the result of a series of simple steps. For other examples of this reaction, see Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245–256.

**Write step-by-step mechanisms for the following transformations.** **PROBLEM 4.1**

a.

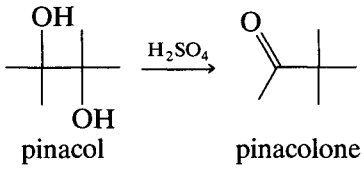



b.

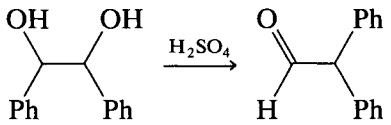


## B. The Pinacol Rearrangement

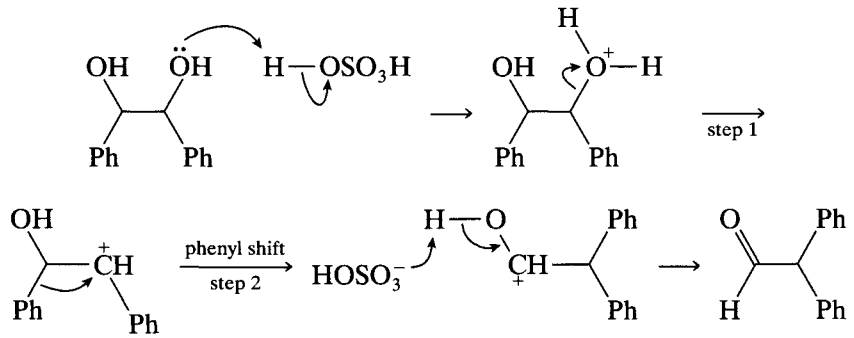
Many common rearrangement reactions are related to the rearrangement of 1,2-dihydroxy compounds to carbonyl compounds. Often these reactions are called pinacol rearrangements, because one of the first examples was the transformation of pinacol to pinacolone:




**Example 4.11.** ***The rearrangement of 1,2-diphenyl-1,2-ethanediol to 2,2-diphenylethanal.***



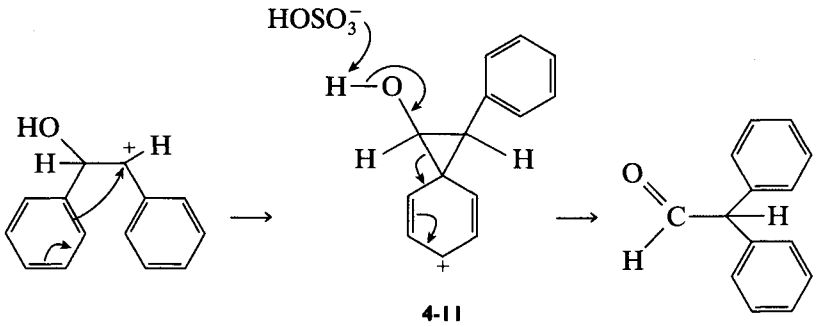

The mechanism of this reaction involves formation of an intermediate carbocation, a 1,2-phenyl shift, and loss of a proton to form the product:




4-10

In reactions of this type, it is possible to form more than one initial carbocation if the starting material is not symmetrical. In this situation, the more stable carbocation is usually formed in step 1. Once this initial carbocation has been formed, the course of step 2 is more difficult to predict because it depends on the propensity of one group to migrate in preference to another (*migratory aptitude*), which often depends on reaction conditions.

It has been suggested that in pinacols containing an aryl group, the initial carbocation formed by loss of hydroxyl can be stabilized by neighboring group participation of the phenyl group to give a bridged phenonium ion:

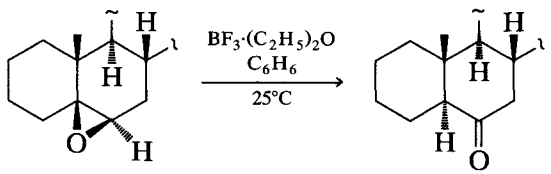



4-11

Although these types of bridged phenonium ions are accepted intermediates in a number of reactions, they do not appear to be involved in the pinacol rearrangement (see Schubert, W. M.; LeFevre, P. H. *J. Am. Chem. Soc.* **1972**, *94*, 1639). Stabilization of the carbocation **4-10** by resonance with the oxygen substituent may be a factor in determining the preference for phenyl migration over phenonium ion formation in the pinacol rearrangement.

**Write a step-by-step mechanism for the transformation of pinacol to pinacolone in the presence of sulfuric acid.** **PROBLEM 4.2**

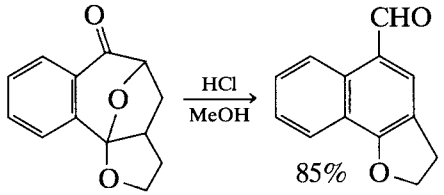
**For the following reaction write a step-by-step mechanism that accounts for the observed stereospecificity.** **PROBLEM 4.3**




99%

Heubest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 4596–4765.

**PROBLEM 4.4 Write a step-by-step mechanism for the following reaction.**




Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894–2900.

## 5. ELECTROPHILIC ADDITION

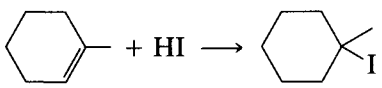
Addition of electrophiles is a reaction typical of aliphatic $\pi$ bonds (see Example 4.3). Such additions involve two major steps: (1) addition of the electrophile to the nucleophilic $\pi$ bond to give an intermediate carbocation, and (2) reaction of the carbocation with a nucleophile. Typical electrophiles are bromine, chlorine, a proton supplied by HCl, HBr, HI, $H_2SO_4$, or $H_3PO_4$, Lewis acids, and carbocations. The nucleophile in step 2 is often the anion associated with the electrophile, e.g., bromide, chloride, iodide, etc., or a nucleophilic solvent like water or acetic acid.

### A. Regiospecificity

Because the more stable of the two possible carbocations is formed predominantly as the intermediate in addition of the electrophile (step 1), electrophilic additions are often regiospecific.

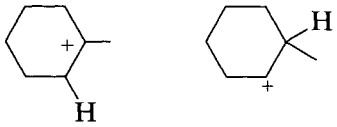
**Example 4.12.** ***Regiospecificity in electrophilic additions.***

When HI adds to a double bond, the proton acts as an electrophile, giving an intermediate carbocation that then reacts with the nucleophilic iodide ion to give the product. In the reaction of HI with 1-methylcyclohexene, there is only one product, 1-iodo-1-methylcyclohexane; no 1-iodo-2-methyl-cyclohexane is formed.




This reaction is said to be regiospecific because the iodide might occupy the ring position at either end of the original double bond, but only one of these

products is actually formed. The reaction is regiospecific because the proton adds to form the more stable tertiary carbocation, **4-12**, and not the secondary carbocation, **4-13**.



**4-12** **4-13**

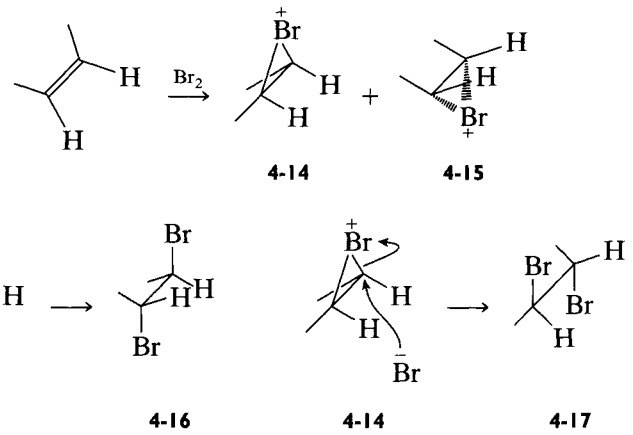
## B. Stereochemistry

### anti Addition

In some electrophilic additions an unusual three-membered-ring intermediate is formed. When this intermediate is stable under the reaction conditions, an *anti* addition of electrophile and nucleophile takes place.

**Example 4.13.** ***Stereospecific* anti *addition of bromine to* cis- *and* trans-*2-butene.***

The bromination of *cis*- and *trans*-2-butene occurs stereospecifically with each isomer.



**4-14** **4-15**

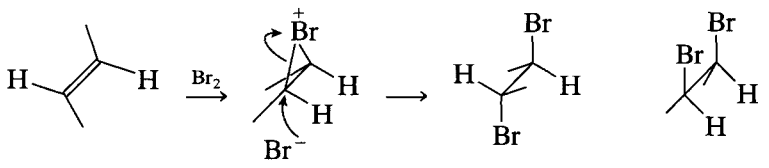
**4-14** **4-16** **4-14** **4-17**

From *cis*-2-butene, the products are the enantiomeric dibromides **4-16** and **4-17**, which are formed in equal amounts. The enantiomers are formed in equal amounts because bromine adds to the top and bottom faces of the alkene to give the intermediate bromonium ions, **4-14** and **4-15**, in equal amounts. Either carbon of each of these bromonium ions can then react with

the nucleophile on the side opposite the bromine to give the product dibromides.

Note that **4-16** and **4-17** are mirror images and nonsuperimposable. In like manner, the reaction of **4-15** with bromide ion also gives **4-16** and **4-17**.

From *trans*-2-butene, *anti* reaction of bromide at either carbon of the bromonium ion, **4-18**, gives only **4-19-1**, which is a *meso* compound because it has a mirror plane. This is most easily recognized in the eclipsed conformation, **4-19-2**, rather than the staggered conformation, **4-19-1**.




**4-18** **4-19-1** **4-19-2**

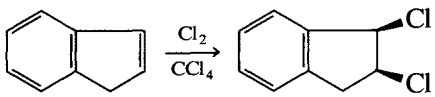
In the addition of bromine to *cis*- and *trans*-2-butene, the stereochemistry of each product occurs because the two bromines were introduced into the molecule on opposite faces of the original double bond.

Under some experimental conditions, electrophilic addition of either $Cl^+$ or a proton may form stable three-membered-ring intermediates. Thus, when a double bond undergoes stereospecific *anti* addition, formation of a three-membered-ring intermediate analogous to the bromonium ion is often part of the mechanism.

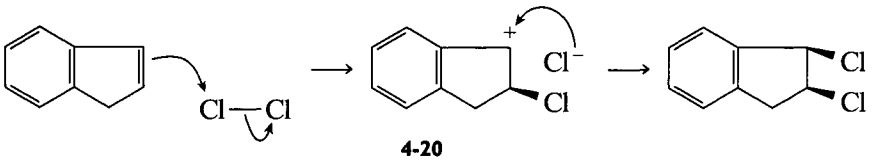
### *syn* Addition

Sometimes *syn* addition to a double bond may occur. These reactions usually occur in very nonpolar media.

**Example 4.14.** ***The chlorination of indene to give cis-1,2-dichloroindane.***




There are several factors that influence the course of this halogen addition: (1) the reaction takes place with chlorine rather than bromine; (2) the double bond of the starting material is conjugated with an aromatic ring; and (3) the reaction takes place in a nonpolar solvent.



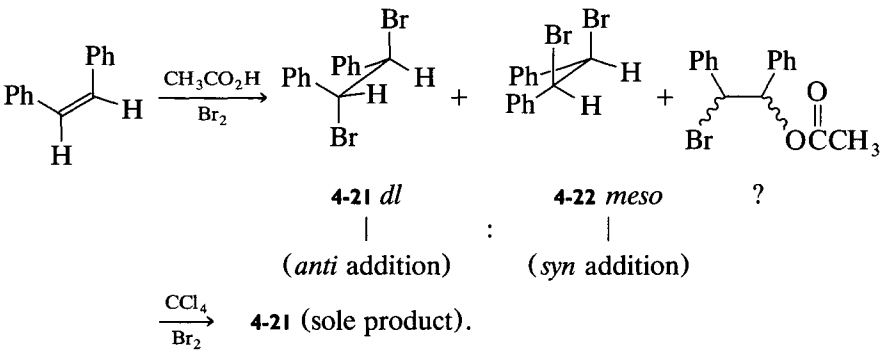
4-20

Chlorine is smaller and less polarizable than bromine and so has less of a tendency to form a bridged halonium ion than bromine. Also, the position of the double bond means that electrophilic addition of chlorine gives a stabilized benzylic cation, which is expected to be planar. In the nonpolar solvent, the planar cation is strongly attracted to the negative chloride ion to form the ion pair, **4-20**, because the carbocation and the chloride ion are not as strongly stabilized by solvation as they are in more polar solvents. Thus, the chloride ion remains in the position at which it was originally formed. Whereas a bridged chloronium ion would react most easily by backside reaction with the planar benzylic cation, the chloride ion can recombine without having to move to the other face of the cation. This step gives *syn* addition.

### Nonstereospecific addition

Electrophilic addition is not always stereospecific. Some substrates and reaction conditions lead to products from both *syn* and *anti* additions.

**Example 4.15.** ***The nonstereospecific bromination of* cis-*stilbene in acetic acid.***



**4-21** *dl* (*anti* addition) : **4-22** *meso* (*syn* addition) ?

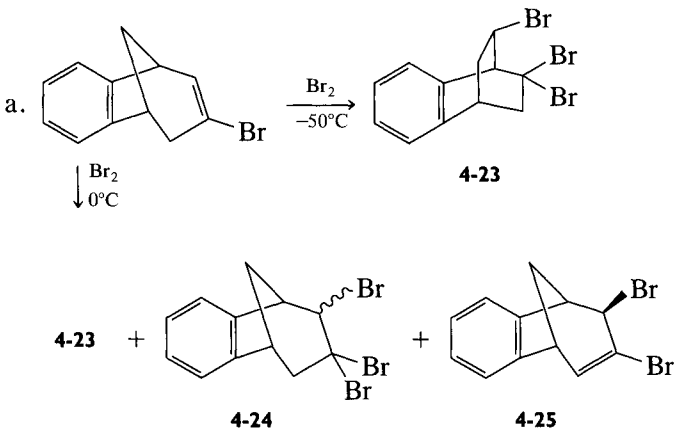
$\xrightarrow[Br_2]{CCl_4}$ **4-21** (sole product).

Buckles, R. E.; Bader, J. M.; Theimaier, R. J. *J. Org. Chem.* **1962**, *27*, 4523.

In the highly polar solvent, acetic acid, the reaction is completely nonstereospecific. The product distribution is consistent with reaction of *cis*-stilbene with bromine to form an intermediate carbocation, followed by reaction of bromide on either face of the planar intermediate to give **4-21** and **4-22**. In the nonpolar solvent, carbon tetrachloride, the product is exclusively the *dl* product **4-21** that would result from *anti* addition of bromide to a bridged bromonium ion. In the polar solvent, the localized charge on an intermediate planar carbocation would be more stabilized than the bromonium ion by solvent interactions, because the charge on the bridged bromonium ion is more dispersed.

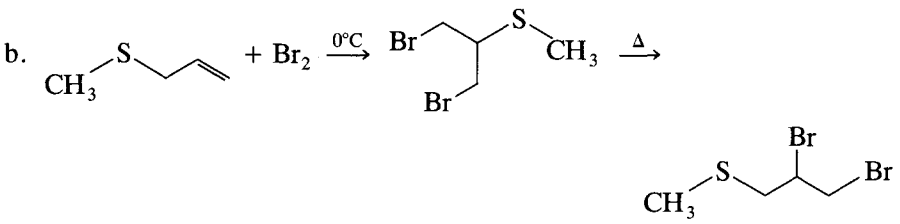
The side product of the reaction is most likely a mixture of bromoacetoxy compounds (unspecified stereochemistry is indicated by the wavy bond lines). Electrophilic additions in nucleophilic solvents often give a mixture of products because the nucleophile derived from the electrophilic reagent (e.g., $Br^-$) and the solvent compete for the intermediate carbocation.

**PROBLEM 4.5** **Write step-by-step mechanisms for the following transformations.**




At −50°C, **4-23** is the only product; at 0°C, **4-23** is still the major product, but **4-24** and **4-25** are also produced. Note that, as the wavy bond lines indicate, both the *exo* and *endo* isomers of the 2-bromo compound **4-24** are produced.

Harmandar, M.; Balci, M. *Tetrahedron Lett.* **1985**, *26*, 5465–5468.

b. 

Bland, J. M.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 4393–4394.

## 6. ACID-CATALYZED REACTIONS OF CARBONYL COMPOUNDS

Several examples of the importance of acid catalysis have already been given: Example 2.5 gives one of the steps in the acid-catalyzed formation of an ester, and Example 3.16 shows the acid-catalyzed mechanism for the formation of a hydrazone.

### A. Hydrolysis of Carboxylic Acid Derivatives

Acidic hydrolysis of all derivatives of carboxylic acids (e.g., esters, amides, acid anhydrides, acid chlorides) gives the corresponding carboxylic acid as the product. These hydrolyses can be broken down into the following steps.

(1) Protonation of the oxygen of the carbonyl group. This enhances the electrophilicity of the carbonyl carbon, increasing its reactivity with nucleophiles.

(2) The oxygen of water acts as a nucleophile and adds to the carbonyl carbon.

(3) The oxygen of the water, which has added and which is positively charged, loses a proton.

(4) A leaving group leaves. In the case of acid halides, the leaving group leaves directly; in the case of esters or amides, the leaving group leaves after prior protonation.

(5) A proton is lost from the protonated carboxylic acid.

**Example 4.16.** ***Hydrolysis of an amide.***

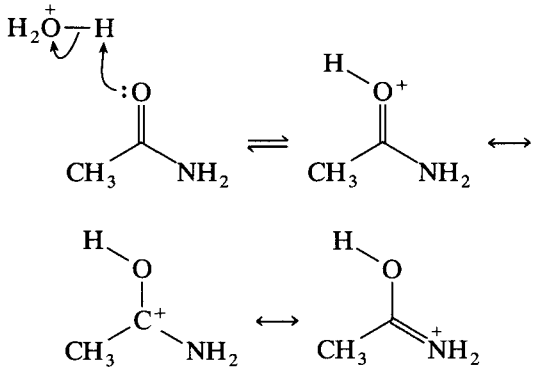
The overall reaction is as follows:

$$CH_3CONH_2 + H_3O^+ \longrightarrow CH_3CO_2H + {}^+NH_4$$

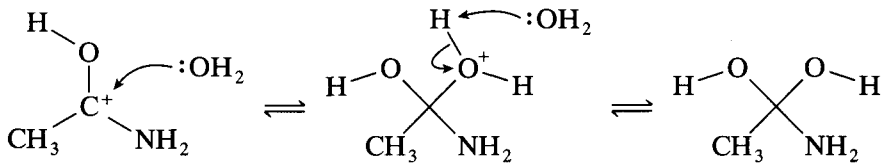
The mechanism of this reaction is as follows:

(1) The initial protonation of the carbonyl oxygen gives a cation that is a

resonance hybrid with positive character on carbon and nitrogen, as well as an oxygen.



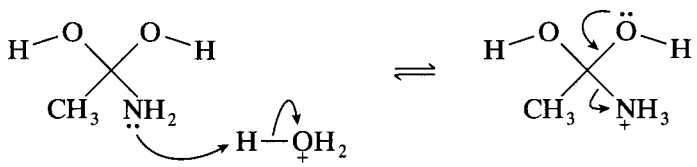
(2) The electrophilic cation reacts with the nucleophilic oxygen of water.



**4-26**

(3) Loss of a proton gives **4-26**:

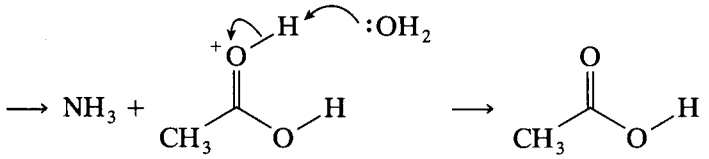
(4) The neutral intermediate, **4-26**, can be protonated on either oxygen or nitrogen, but only protonation on nitrogen leads to product formation. Notice that the $NH_2$ group is now an amine and is much more basic than the $NH_2$ group of the starting amide.



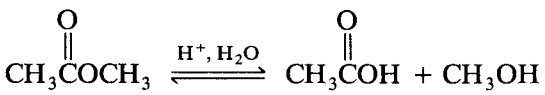
**4-26**

Note that the leaving group is ammonia rather than $^{-}NH_2$, which would be a very poor leaving group. Whereas the loss of ammonia is a potentially reversible process, the protonation of ammonia to give the ammonium ion occurs much more rapidly in the acidic medium. Thus, the loss of ammonia is irreversible, not because the addition of ammonia in the reverse process is energetically unfavorable, but because there is no ammonia present.

(5) Finally, a proton is removed from the protonated carboxylic acid to give the carboxylic acid product.

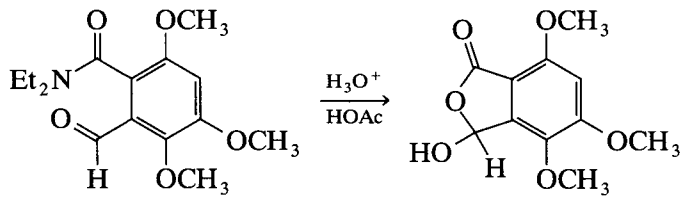


**Example 4.17.** ***Hydrolysis of an ester.***



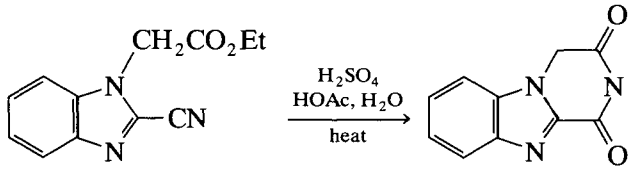
For esters, all of the steps of the hydrolysis reaction are reversible, and the mechanism of ester formation is the reverse of ester hydrolysis. The course of the reaction is controlled by adjusting the reaction conditions, chiefly the choice of solvent and the concentration of water, to drive the equilibrium in the desired direction. For hydrolysis, the reaction is carried out in an excess of water; for ester formation, the reaction is carried out with an excess of the alcohol component under anhydrous conditions. Frequently, an experimental set-up is designed to remove water as it is formed in order to favor ester formation.

**Write step-by-step mechanisms for the following transformations.** **PROBLEM 4.6**

a. 

Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 223–224.

**PROBLEM 4.6** *continued*

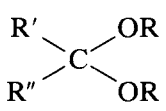
b. 


78%

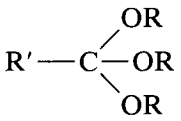
Serafin, B.; Konopski, L. *Pol. J. Chem.* **1978**, *52*, 51–62.

## B. Hydrolysis and Formation of Acetals and Orthoesters

Acetals, ketals, and orthoesters are polyethers, represented by the following structural formulas:



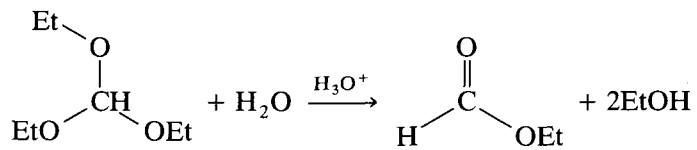

ketal
If R′ = H, the compound is an acetal.



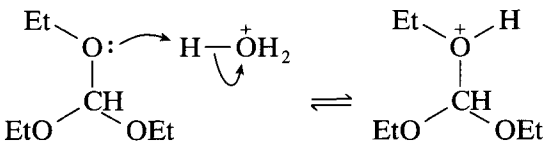

orthoester

The formation and hydrolysis of these groups are acid-catalyzed processes. Other derivatives of carbonyl groups, e.g., enamines, are also formed and hydrolyzed under acidic conditions by very similar mechanisms.

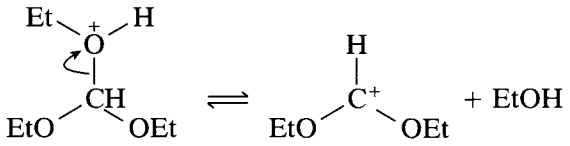
**Example 4.18.** ***Hydrolysis of ethyl orthoformate to ethyl formate.***




As in the case of other acid-catalyzed hydrolyses, the first step involves protonation of the most basic atom in the molecule. (In the case of ethyl orthoformate, all three oxygen atoms are equally basic.)

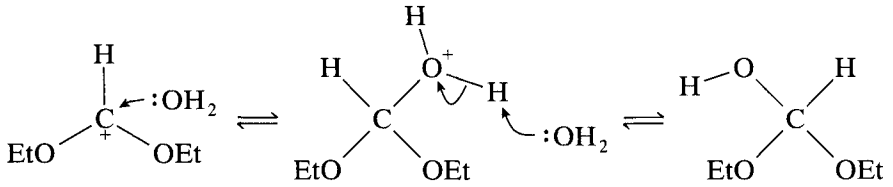


Protonation creates a better leaving group, that is, ethanol is a better leaving group than ethoxide ion.



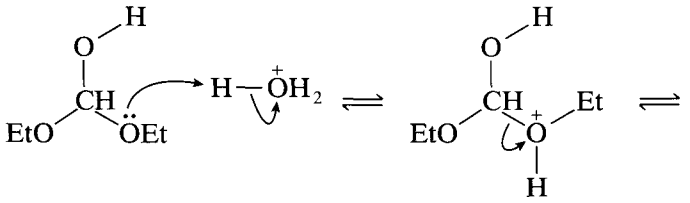
**4-27**

The electrophilic carbocation, **4-27**, reacts with nucleophilic water. Because water is present in large excess over ethanol, this reaction occurs preferentially and shifts the equilibrium toward the hydrolysis product. The protonated intermediate loses a proton to give **4-28**.

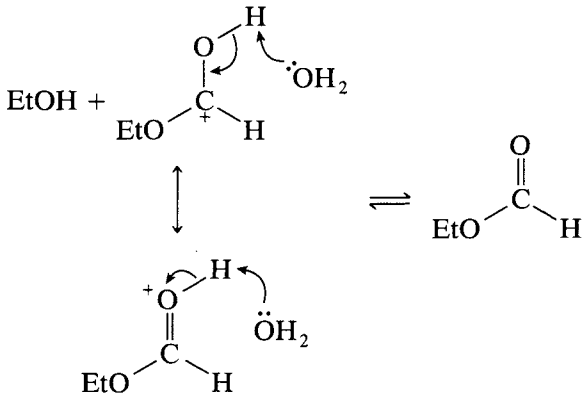


**4-27** **4-28**

The neutral intermediate, **4-28**, can be protonated on either a hydroxyl or ethoxy oxygen. Protonation on the hydroxyl oxygen is simply the reverse of the deprotonation step. Although this is a reasonable step, it leads to starting material. However, protonation on the oxygen of the ethoxy group leads to product.



Loss of ethanol, followed by removal of a proton by water, gives the product ester.



All of the steps in this reaction are reversible. Why, then, do the hydrolysis conditions yield the formate ester and not the starting material? The key, as we saw in the preceding section with ester formation and hydrolysis, lies in the overall reaction. Water is present on the left-hand side of the equation and ethanol on the right-hand side. Thus, an excess of water would shift the equilibrium to the right, and an excess of ethanol would shift the equilibrium to the left. In fact, in order to get the reaction to go to the left, water must be removed as it is produced. Depending on the reaction conditions, the hydrolysis may proceed further to the corresponding carboxylic acid.

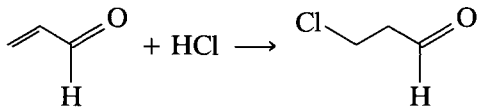
In Problem 3.14.a, we saw that the reaction of an amine with a carbonyl compound in the presence of an acid catalyst can be driven toward the enamine product by removing water from the reaction mixture as it is formed. The reverse of this reaction is an example of the acid hydrolysis of an enamine, a mechanism that is very similar to that of the orthoacetate hydrolysis shown in Example 4.18.

## C. 1,4-Addition

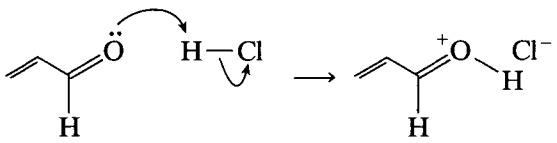
Electrophilic addition to $\alpha,\beta$-unsaturated carbonyl compounds is analogous to electrophilic addition to isolated double bonds, except that the electrophile adds to the carbonyl oxygen, the most basic atom in the molecule. After that, the nucleophile adds to the $\beta$ carbon, and the resulting intermediate enol tautomerizes to the more stable carbonyl compound. These reactions may also be considered as the electrophilic counterparts of the nucleophilic Michael and 1,4-addition reactions discussed in Chapter 3, Section 3.C.

**Example 4.19.** ***Electrophilic addition of HCl to acrolein.***

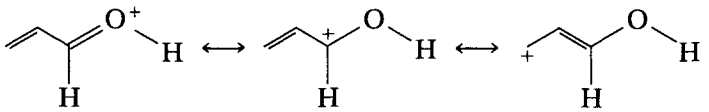
The overall reaction is as follows:



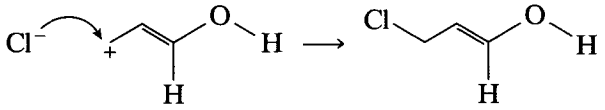
The first step in a mechanism is reaction of the nucleophilic oxygen of the carbonyl group with the positive end of the HCl molecule.



The resulting cation is a resonance hybrid with a partial positive charge on carbon as well as on oxygen:



The electrophilic $\beta$ position now reacts with the nucleophilic chloride ion to give an enol, which then tautomerizes to the keto form.

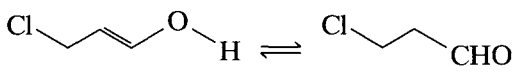


This reaction is the acid-catalyzed counterpart of a 1,4-addition reaction to an $\alpha,\beta$-unsaturated carbonyl compound. Chloride ion, without an acid present, will not add to acrolein. That is, chloride ion is not a strong enough nucleophile to drive the reaction to the right. However, if the carbonyl is protonated, the intermediate cation is a stronger electrophile and will react with chloride ion.

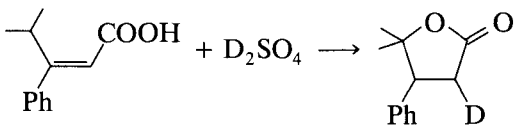
**PROBLEM 4.7**

**Rationalize the regiochemistry of the protonation shown in Example 4.19 by comparing it to protonation at other sites in the molecule.**

**PROBLEM 4.8** **Write a mechanism for the following tautomerization in the presence of anhydrous HCl.**



**PROBLEM 4.9** **Write a step-by-step mechanism for the following transformation.**

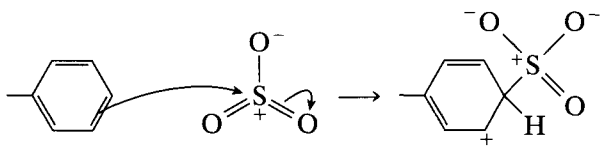


## 7. ELECTROPHILIC AROMATIC SUBSTITUTION

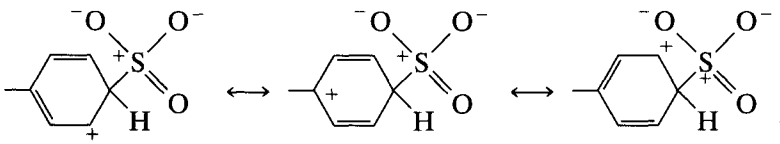
The interaction of certain electrophiles with an aromatic ring leads to substitution. These electrophilic reactions involve a carbocation intermediate that gives up a stable, positively charged species (usually a proton) to a base to regenerate the aromatic ring. Typical electrophiles include chlorine and bromine (activated by interaction with a Lewis acid for all but highly reactive aromatic compounds), nitronium ion, $SO_3$, the complexes of acid halides and anhydrides with Lewis acids (see Example 4.5) or the cations formed when such complexes decompose ($R-\overset{+}{C}=O$ or $Ar\overset{+}{C}=O$), and carbocations.

**Example 4.20.** ***Electrophilic substitution of toluene by sulfur trioxide.***

In this reaction, the aromatic ring is a nucleophile and the sulfur of sulfur trioxide is an electrophile.

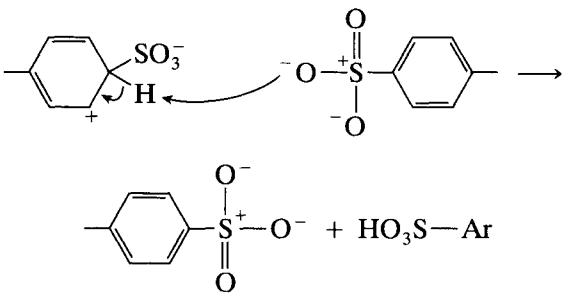


The positive charge on the ring is stabilized by resonance.



4-29-1 4-29-2 4-29-3

A sulfonate anion, acting as a base, can remove a proton from the intermediate to give the product:



Because the aromatic ring acts as a nucleophile, the reaction rate will be enhanced by electron-donating substituents and slowed by electron-withdrawing substituents. Furthermore, the intermediate cation is especially stabilized by an adjacent electron-donating group, as in resonance structure **4-29-2**. Because of this, electrophiles react at positions *ortho* or *para* to electron-donating groups. Such groups are said to be *ortho*- and *para*-directing substituents. Conversely, because electron-withdrawing groups destabilize a directly adjacent positive charge, the electrophile will react at the *meta* position in order to avoid this stabilization. A review of directing and activating–deactivating effects of various substituents is given in Table 4.1.

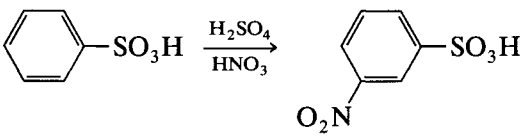
The effect of fluorine, chlorine, or bromine as a substituent is unique in that the ring is deactivated, but the entering electrophile is directed to the *ortho* and *para* positions. This can be explained by an unusual competition between resonance and inductive effects. In the starting material, halogen-substituted benzenes are deactivated more strongly by the inductive effect than they are activated by the resonance effect. However, in the intermediate carbocation, halogens stabilize the positive charge by resonance more than they destabilize it by the inductive effect.

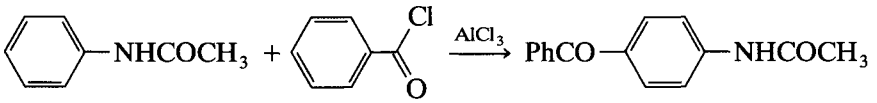
**TABLE 4.1** Influence of Substituents in Electrophilic Aromatic Substitution

| |
|---|
| Strongly activating and *ortho*- or *para*-directing |
| $-NR_2$, $-NRH$, $-NH_2$, $-O^-$, $-OH$ |
| Moderately activating and *ortho* or *para*-directing |
| $-OR$, $-NHCOR$ |
| Weakly activating and *ortho*- or *para*-directing |
| $-R$, $-Ph$ |
| Weakly deactivating and *ortho*- or *para*-directing |
| $-F$, $-Cl$, $-Br$ |
| Strongly deactivating and *meta*-directing |
| $-\overset{+}{S}R_2$, $-\overset{+}{N}R_3$, $-NO_2$, $-SO_3H$, $-CO_2H$, $-CO_2R$, |
| $-CHO$, $-COR$, $-CONH_2$, $-CONHR$, $-CONR_2$, $-CN$ |

**PROBLEM 4.10** **For the following reactions, explain the orientations in the product by drawing resonance forms for possible intermediate carbocations and rationalize their relative stabilities.**

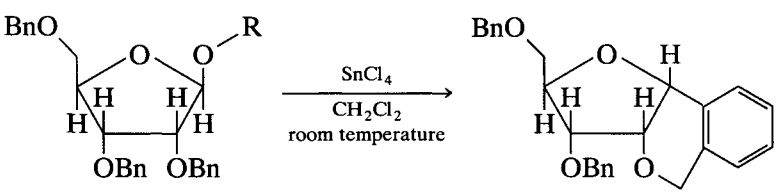
a. The reaction in Example 4.20.

b. 

c. 

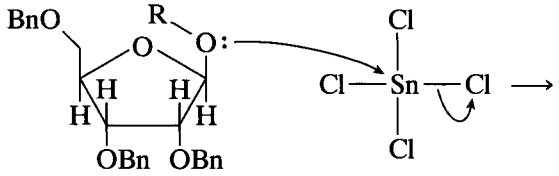
**Example 4.21.** ***A metal-catalyzed, intramolecular, electrophilic aromatic substitution.***

Write a mechanism for the following transformation.

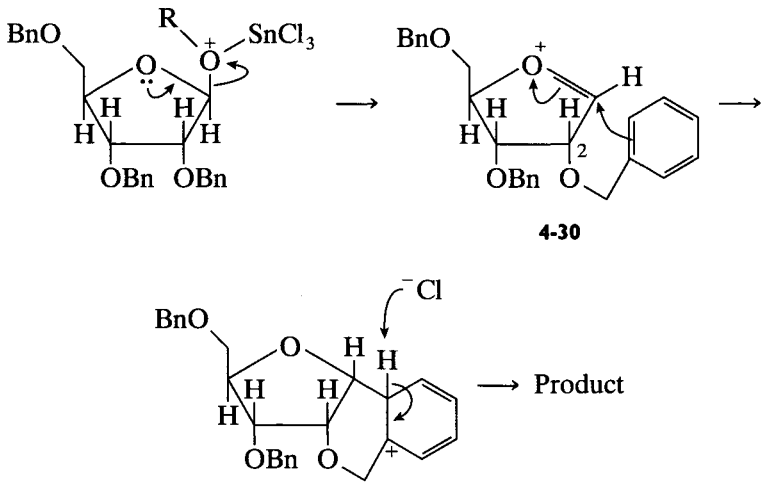


Bn = benzyl ($PhCH_2-$)

Tin(IV) chloride can undergo nucleophilic substitution,



which converts the acetal OR group into a better leaving group. (The positively charged oxygen of the OR group of an acetal is a much better leaving group than the oxygen of an ether because the resulting cation is stabilized by resonance interaction with the remaining oxygen of the original acetal.) After the leaving group leaves, the aromatic ring of a benzyl group at position 2 in **4-30** (suitably situated geometrically for this interaction) acts as a nucleophile toward the positive center. The resulting carbocation then loses a proton to give the product:



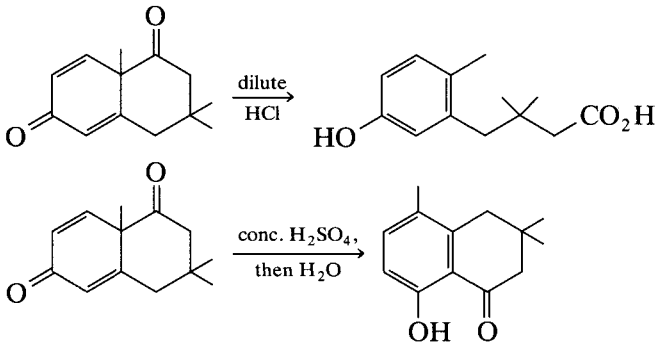
**4-30**

Similar intramolecular electrophilic aromatic substitution reactions are common, especially when five- or six-membered rings are formed.

Martin, O. R. *Tetrahedron Lett.* **1985**, *26*, 2055–2058.

**PROBLEM 4.11 Write step-by-step mechanisms for the following transformations.**

a.

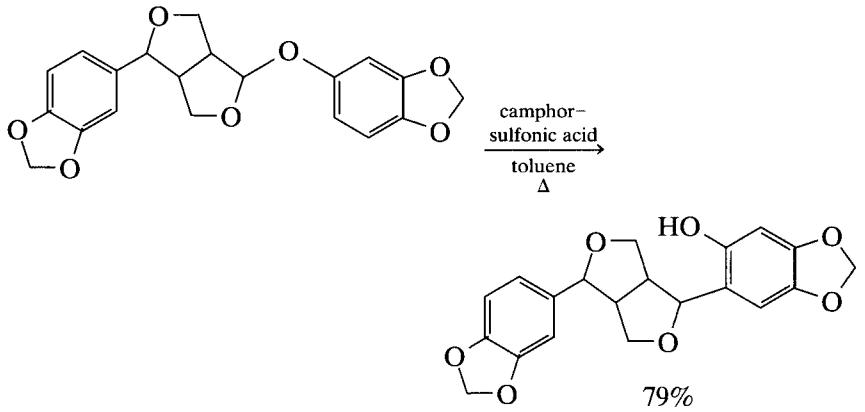



(conc. = concentrated)

The reaction in dilute HCl was discussed in another context in Example 2.11. Modify the mechanism given there to account for the result shown here for concentrated sulfuric acid.

Waring, A. J.; Zaidi, J. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 631–639.

b.



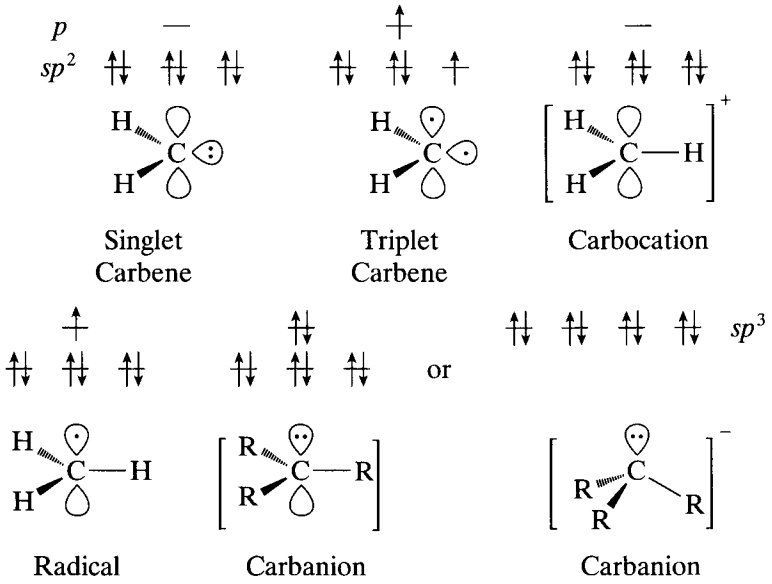

Fukuda, Y.; Isobe, M.; Nagata, M.; Osawa, T.; Namiki, M. *Heterocycles* **1986**, *24*, 923–926.

## 8. CARBENES

Carbenes are very reactive intermediates. Some have been isolated in matrices at low temperatures, but with few exceptions (see *Chem. Eng. News* **1991**, *28*, 19–20) they are very short-lived at ambient temperatures. Although carbenes are often generated in basic media, they usually act as electrophiles.

## A. Singlet and Triplet Carbenes

A carbene is a neutral divalent carbon species containing two electrons that are not shared with other atoms. When these two electrons have *opposite* spins, the carbene is designated a *singlet* carbene; when they have *parallel* spins, the carbene is a *triplet*. In the ground state, a singlet carbene has a pair of electrons in a single orbital, whereas the triplet has two unpaired electrons, each occupying a separate orbital. The designations singlet and triplet originate in spectroscopy.



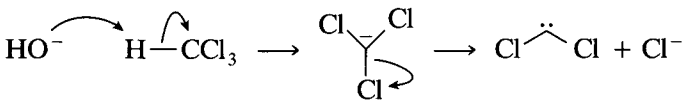

Note that the formal charge on the carbon atom in either a singlet or a triplet carbene is zero; the singlet carbene is *not* a carbanion.

The term *carbenoid* is used to refer to a carbene when the exact nature of the carbene species is uncertain and especially when referring to neutral electron-deficient species that are coordinated with a metal.

## B. Formation of Carbenes

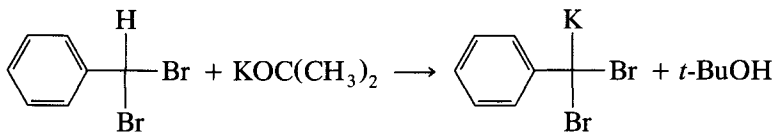
**Example 4.22.** ***Generation of carbenes from alkyl halides and base.***

(1) Dichlorocarbene can be formed from aqueous KOH and chloroform:



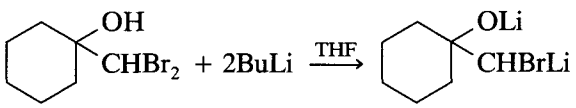
The base removes the acidic proton from chloroform. The resulting anion then loses chloride ion, giving a divalent carbon with two unshared electrons. In this case, the unshared electrons are paired (occupy the same orbital), i.e., dichlorocarbene is a singlet. The carbon of the carbene has no charge.

(2) A carbenoid is formed when potassium *t*-butoxide reacts with benzal bromide in benzene. The reactivity of the carbenoid, **4-31**, is similar to that of phenylbromocarbene. The exact nature of the interaction between the carbenoid carbon and the metal halide, in this case potassium bromide, is not known.



**4-31**

(3) Some alkyl halides react with alkyllithium reagents under aprotic conditions to give carbenoids by a process called "halogen–metal exchange."



**4-32**

In some cases, proton removal from the carbon may predominate over exchange with the halogen. For details, see Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473–485.

**Example 4.23.** ***Generation of $ICH_2ZnI$ (the Simmons–Smith reagent) from methylene iodide and zinc–copper couple.***

When diiodomethane is treated with zinc–copper couple, a carbenoid is formed.

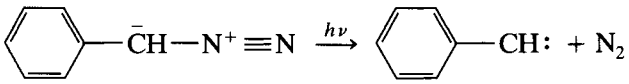
$$CH_2I_2 + ZnCu \longrightarrow ICH_2ZnI$$

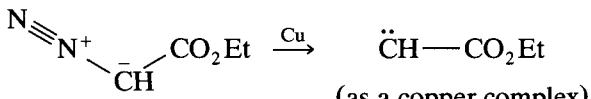
**4-33**

The Simmons–Smith reagent (**4-33**), other carbenoids, and carbenes are very useful in the synthesis of cyclopropanes (see Example 4.25).

**Example 4.24.** ***Generation of carbenes from diazo compounds.***

Loss of nitrogen from a diazo compound can be effected by heat, light, or a copper catalyst. This gives either a carbene (heat or light) or a carbenoid (copper).





(as a copper complex)

## C. Reactions of Carbenes

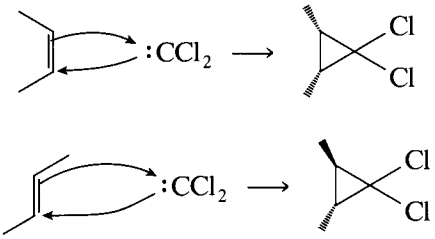
Once generated by the methods outlined in the preceding section, the highly reactive carbene intermediates can react in a number of different ways, including addition, substitution, insertion, rearrangement, and hydrogen or halogen abstraction. Two important reactions involving carbenes are addition to carbon–carbon double and triple bonds to generate cyclopropanes and cyclopropenes, respectively, and electrophilic aromatic substitution (the Reimer–Tiemann reaction), in which electrophilic addition of a carbene is the first step.

### Addition

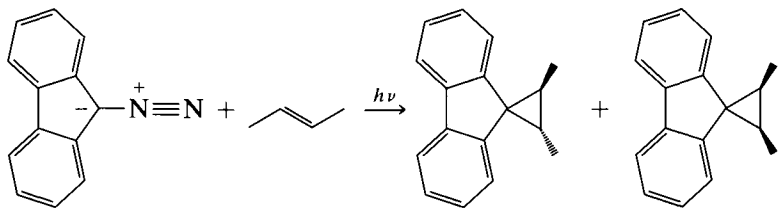
Electrophilic addition of carbenes to carbon–carbon double and triple bonds has been extremely useful synthetically. In many cases, the reaction goes with 100% stereospecificity, so that the stereochemistry about a double bond in the starting material is maintained in the product. Cases in which addition is not 100% stereospecific are rationalized on the basis of a triplet or diradical intermediate. If the triplet carbene is relatively unreactive, the formation of the two new carbon–carbon bonds may be a stepwise process that allows for rotation and, therefore, loss of stereochemistry in the intermediate.

**Example 4.25.** ***Addition of singlet dichlorocarbene to cis-2-butene and trans-2-butene.***

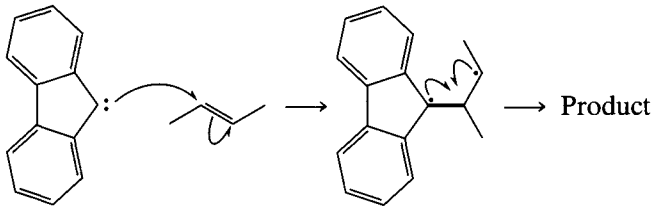
The addition of dichlorocarbene to the double bond of *cis*-2-butene goes with 100% stereospecificity, that is, the only product is *cis*-1,2-dimethyl-3,3-dichlorocyclopropane. The addition of dichlorocarbene to *trans*-2-butene gives only the corresponding *trans* isomer. The stereospecificity of the reaction has been interpreted to mean that dichlorocarbene is a singlet and that both ends of the double bond react simultaneously, or nearly so, with the carbene.




**Example 4.26.** ***A nonstereospecific addition of a carbene.***




Because the reaction is nonstereospecific, the mechanism would be written as a stepwise addition to the double bond by a diradical carbene.



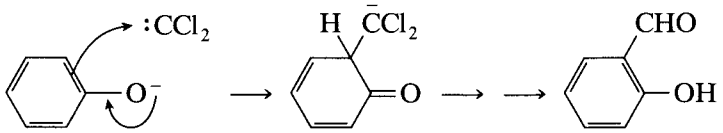

Note that the arrows used to show the flow of unpaired electrons (radicals) have only a half head. Also, the intermediate in the reaction is a diradical. (Radicals are discussed in more detail in Chapter 5.) Rotation about the highlighted single bond takes place fast enough that the stereochemistry of the starting olefin is lost.

### Substitution

Carbenes also add to other nucleophiles, such as hydroxide, thiolate, and phenoxide. The reaction with phenoxide is the classic Reimer–Tiemann reaction.

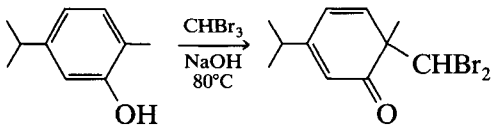
**Example 4.27.** ***The Reimer–Tiemann reaction.***

Phenols react with chloroform in the presence of hydroxide ion in water to give *o*- and *p*-hydroxybenzaldehydes. The steps of the reaction are (1) the formation of dichlorocarbene, as shown in Example 4.22; (2) nucleophilic reaction of the phenoxide with the electrophilic carbene; and (3) hydrolysis.




**Complete the mechanism for Example 4.27 showing the steps leading from the intermediate carbanion to the product *o*-salicylaldehyde.** **PROBLEM 4.12**

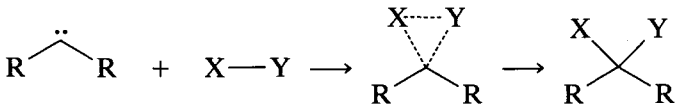
**PROBLEM 4.13 Write a step-by-step mechanism for the following transformation.**




Wenkert, E.; Arrhenius, T. S.; Bookser, B.; Guo, M.; Mancini, P. *J. Org. Chem.* **1990**, *55*, 1185–1193.

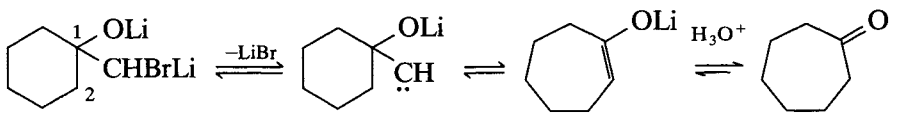
### Insertion

In insertion, as the name suggests, the carbene inserts itself between two atoms. Insertions have been observed into C—H, C—C, C—X, N—H, O—H, S—S, S—H, and M—C bonds, among others. The mechanism of the process is often concerted. A three-centered transition state is usually written for the concerted mechanism:




**Example 4.28.** ***A synthetically useful insertion reaction.***

Carbenoid **4-32** can be generated as shown in Example 4.22. The insertion of **4-32** into the C1—C2 bond leads to the formation of cycloheptanone in 70% yield. Other homologues give even higher yields of ring-expanded products.




**4-32** **4-34**

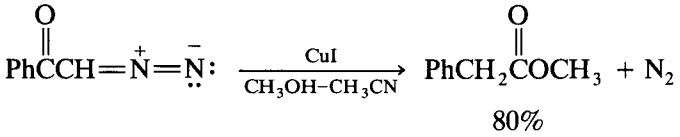
The intermediate enolate, **4-34**, forms the corresponding ketone in acid. From Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6510–6511.

### Rearrangement

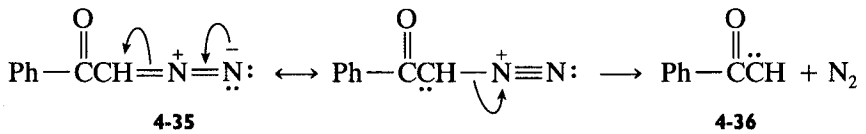
Because of their reactivity, it is frequently difficult to decide whether a free carbene has been generated or whether an electrophilic carbon undergoes a synchronous reaction. It is generally accepted that a free carbene is an intermediate in the Wolff rearrangement, in which a diazoketone rearranges to a highly reactive ketene. The versatile ketene intermediate then reacts to

give the carboxylic acid, ester, or amide by reaction with water, alcohol, or amine, respectively.

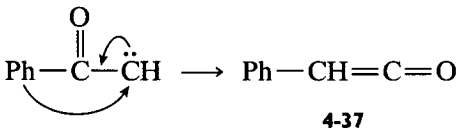
**Example 4.29.** ***The Wolff rearrangement of diazoacetophenone to methyl phenylacetate.***




The mechanism involves decomposition of the diazoketone **4-35** to a carbene **4-36**. The decomposition can be brought about by activation with metal salts, particularly copper and silver, as well as by heat or light.




4-35 4-36




4-37

The carbene then rearranges to the ketene **4-37**. An important feature of the rearrangement is that the migrating group moves with *retention* of configuration. In the example shown, the ester is formed by reaction of the ketene with methanol in the solvent.

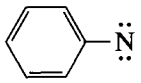
## 9. ELECTROPHILIC HETEROATOMS

A number of reactions involve electrophilic heteroatom species that are analogous to their carbon counterparts. In this section, we will consider electrophilic nitrogen and oxygen species.

## A. Electron-Deficient Nitrogen

### Nitrenes

A nitrene is the nitrogen analogue of a carbene. In other words, it is a neutral, univalent nitrogen that contains two lone pairs of electrons not shared with other atoms.

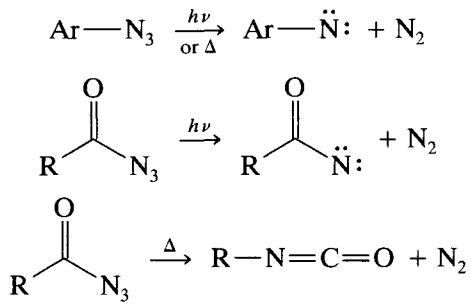


phenyl nitrene

Nitrenes are generated and react very similarly to carbenes, but because of their greater reactivity, the presence of free nitrenes is difficult to demonstrate experimentally.

**Example 4.30.** *Generation of nitrenes.*

Common methods for generating nitrene intermediates are the photolysis and thermolysis of azides. Generation of nitrenes from acyl azides can only be effected photochemically; thermolysis of an acyl azide gives the corresponding isocyanate.



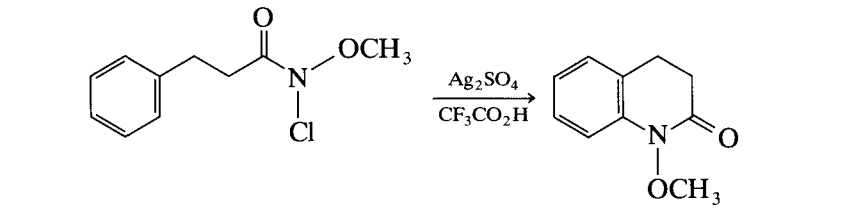
The reactivity of nitrenes is similar to that of carbenes. They readily add to double bonds to give the corresponding three-membered heterocycles, aziridines. Insertion reactions are also common.

### Nitrenium Ions

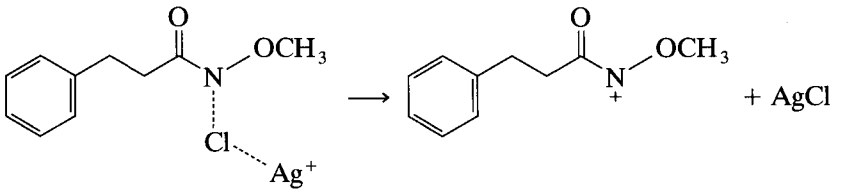
A nitrenium ion is a positively charged divalent nitrogen with one lone pair of electrons. Thus, it is a cation that is isoelectronic with a carbene, a neutral species.

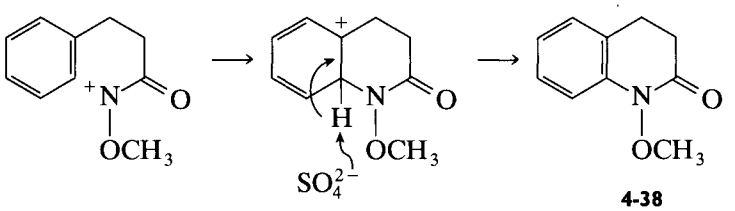
**Example 4.31.** ***Generation and reaction of a nitrenium ion.***

Silver-ion-assisted loss of chloride ion from the starting material gives a nitrenium ion, which acts as an electrophile toward the aromatic ring to give **4-38**.




**4-38**




**4-38**

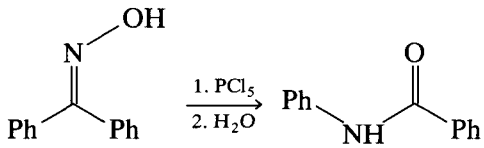
## B. Rearrangements Involving Electrophilic Nitrogen

### The Beckmann Rearrangement

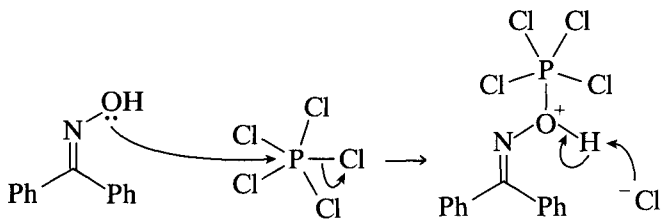
In strong acids, or when treated with reagents such as thionyl chloride or phosphorus pentachloride, an oxime will react to give a rearranged amide. This is known as the Beckmann rearrangement. When the reaction gives products other than amides, these products are referred to as abnormal products. One such abnormal pathway is illustrated in Problem 4.14.

**Example 4.32.** ***Beckmann rearrangement of benzophenone oxime.***

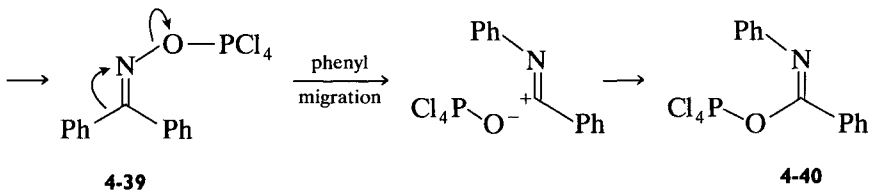
The overall reaction is as follows:




The first two steps of the reaction mechanism convert the original oxime to a derivative, **4-39**. This process converts the hydroxyl group of the oxime into a better leaving group.

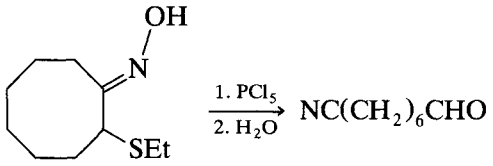



The strongly electron-withdrawing leaving group creates a substantial partial positive charge on nitrogen. The phenyl group, on the side opposite the leaving group, moves with its pair of electrons to the electron-deficient nitrogen as the leaving group leaves. The resulting ions then collapse to form **4-40**. During workup, **4-40** will undergo hydrolysis and tautomerization to the final product, the amide.




**4-39** **4-40**

**Write a step-by-step mechanism for the following reaction.** **PROBLEM 4.14**



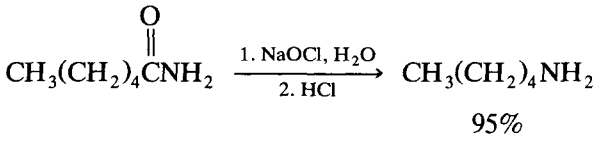

Ohno, M.; Naruse, N.; Torimitsu, S.; Teresawa, I. *J. Am. Chem. Soc.* **1966**, *88*, 3168–3169.

## Nitrogen Analogues of the Wolff Rearrangement

Important rearrangements involving electrophilic nitrogen are the Hofmann, Curtius, and Schmidt rearrangements, which are nitrogen analogues of the Wolff rearrangement discussed in Section 8. In all of these rearrangements, it is possible to write a discrete nitrene intermediate; however, it is generally considered more likely that the reactions proceed through a less reactive intermediate in which rearrangement accompanies loss of the leaving group. The electron deficiency of the nitrogen is due to withdrawal of electron density by a good leaving group. As with the Wolff rearrangement, all of these reactions proceed with *retention* of configuration by the group migrating to nitrogen. Table 4.2 compares rearrangements involving various electron-deficient heteroatom species.

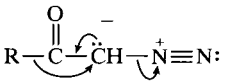
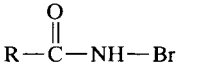
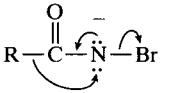
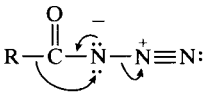
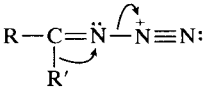
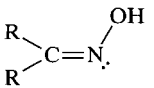
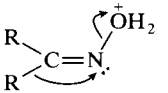
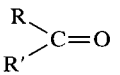
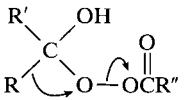
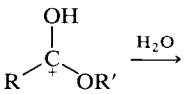
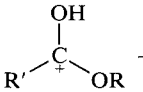
**Example 4.33.** ***The Hofmann rearrangement of hexanamide to pentylamine.***

In the Hofmann rearrangement, a halide leaving group confers electrophilic character on the nitrogen atom.

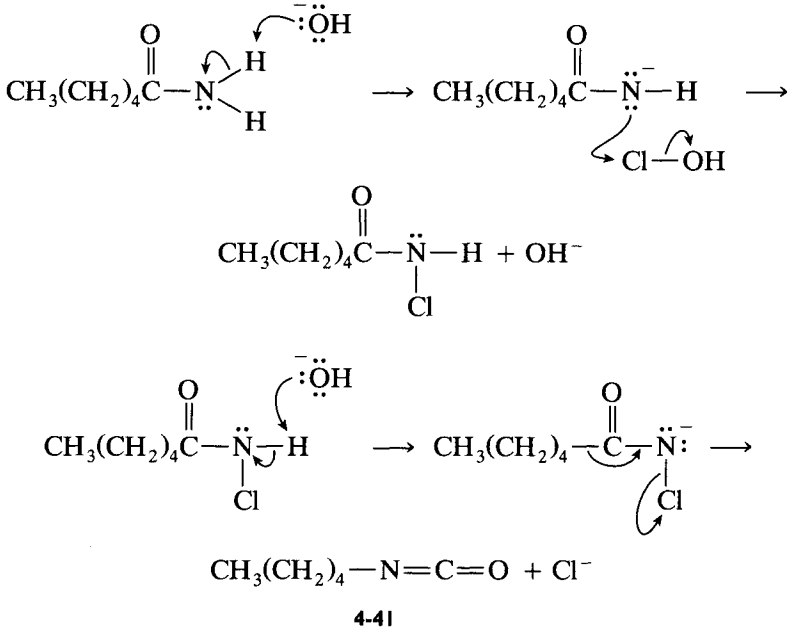



Magnieri, E. *J. Org. Chem.* **1958**, *23*, 2029.

**TABLE 4.2** Parallels in Electrophilic Rearrangements

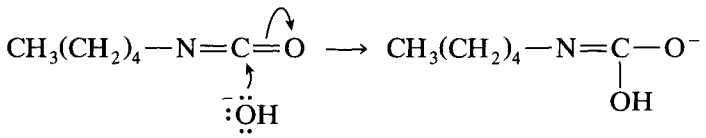
| *Name reaction* | *Starting material* | *Reaction conditions* | *Reactive intermediate* | *Intermediate product* | *Final product* |
|---|---|---|---|---|---|
| Wolff |  | $Ag^+$, $Cu^+$, $\Delta$, $h\nu$ | | $N_2 + O{=}C{=}CHR \xrightarrow{H_2O}$ | $RCH_2CO_2H$ |
| Hofmann |  | $OH^-$, $H_2O$ |  | $Br^- + O{=}C{=}N{-}R \xrightarrow{H_2O}$ | $RNH_2 + CO_2$ |
| Curtius |  | $\Delta$ | | $N_2 + O{=}C{=}N{-}R \xrightarrow{H_2O}$ | $RNH_2 + CO_2$ |
| Schmidt |  | $H^+ + NaN_3$ |  | $N_2 + R{-}\overset{+}{C}{=}N{-}R' \xrightarrow{H_2}$ |  |
| Beckman |  | $H^+$ |  | $H_2O + R{-}\overset{+}{C}{=}N{-}R \xrightarrow{H_2O}$ |  |
| Baeyer–Villager |  | $H^+$, $R''CO_3H$ |  |  |  |
| | | | |  |  |

The first step in the mechanism is formation of the *N*-chloroamide.

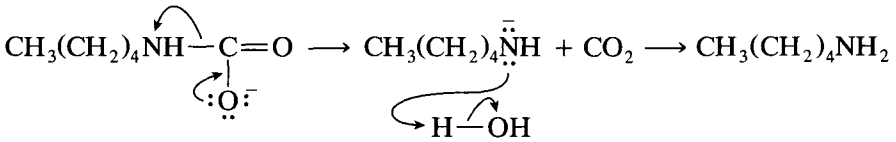


4-41

Because of the electron-withdrawing effect of the chloro group, the remaining hydrogen attached to the amide nitrogen is acidic and easily removed by aqueous base. The tendency of the chloro group to leave with the N—Cl bonding electrons confers electrophilic character on the amide nitrogen, so that as the chloro group departs, the alkyl group moves to compensate for the developing electron deficit on nitrogen, yielding the isocynate **4-41**.



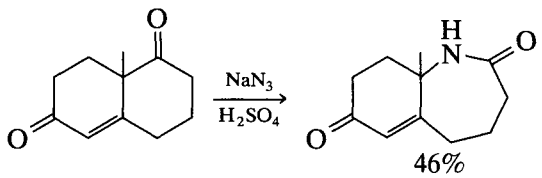
4-41



4-42

Basic hydrolysis of the reactive isocyanate **4-41** leads to an intermediate that tautomerizes under the reaction conditions to give **4-42**, which spontaneously decarboxylates. The irreversible decarboxylation yields the amine, which contains one less carbon (lost as $CO_2$) than the starting material.

**PROBLEM 4.15 Propose a reasonable mechanism for the transformation shown.**

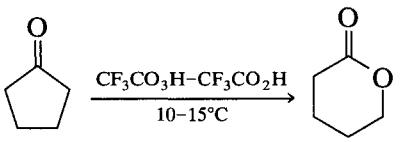



Greco, C. V. *Tetrahedron* **1970**, *26*, 4329.

## C. Rearrangement Involving Electron-Deficient Oxygen

The Baeyer–Villager reaction involves rearrangement of an oxygen-deficient species. Because of the high electronegativity of oxygen, we would not expect a positively charged electron-deficient oxygen, and the reaction is considered to proceed by a concerted mechanism. As in the rearrangement involving electron-deficient nitrogen, the configuration at the migrating carbon is maintained.

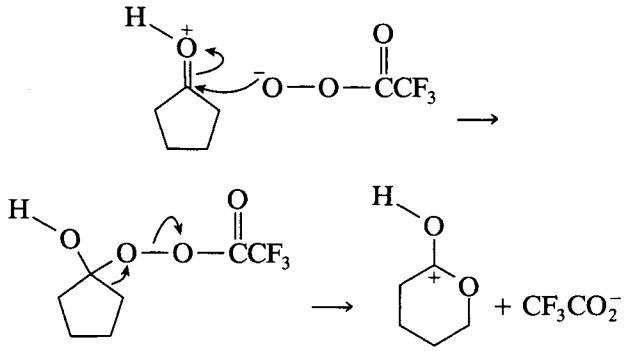
**Example 4.33.** ***Baeyer–Villager oxidation of cyclopentanone to δ-valerolactone.***




81%

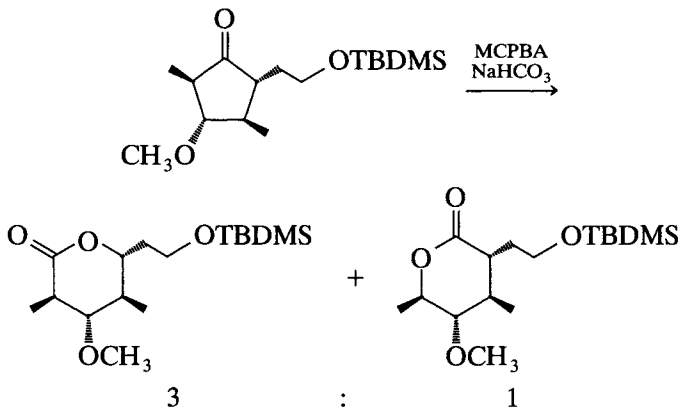
Protonation of the ketone carbonyl is the first step. The generally accepted

mechanism is as follows:



Deprotonation yields the lactone product.

**PROBLEM 4.16** **Baeyer–Villager oxidation of the heavily functionalized cyclopentanone yields a mixture of products. Use a step-by-step mechanism to decide whether this result is unexpected.**

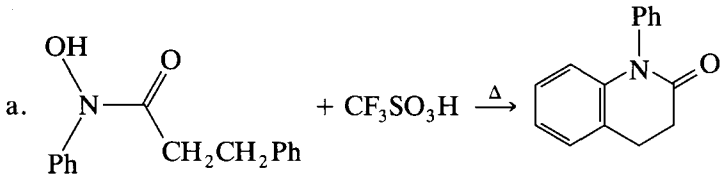


TBDMS = *t*-butyldimethylsilyl
MCPBA = *m*-chloroperbenzoic acid

Clissold, C.; Kelly, C. L.; Lawrie, K. W. M.; Willis, C. L. *Tetrahedron Lett.* **1997**, 8105.

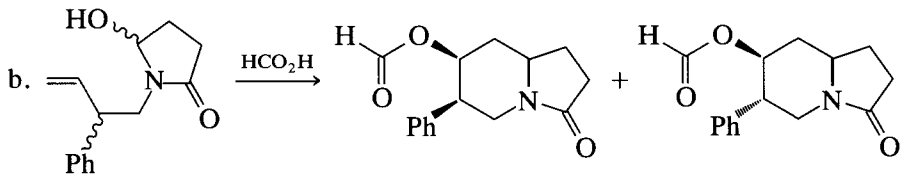
**PROBLEM 4.17 Write step-by-step mechanisms for the following transformations:**

a.



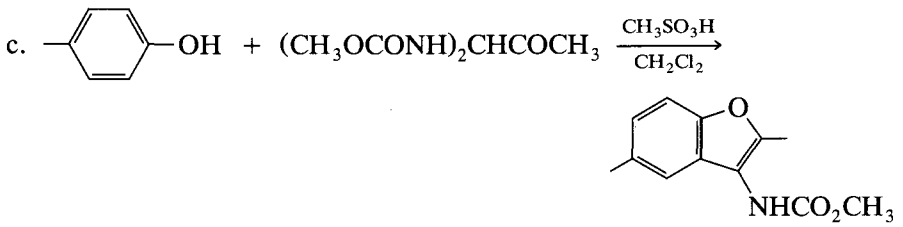
Capozzi, G.; Chimirri, A.; Grasso, S.; Romeo, G. *Heterocycles* **1984**, *22*, 1759–1762.

b.



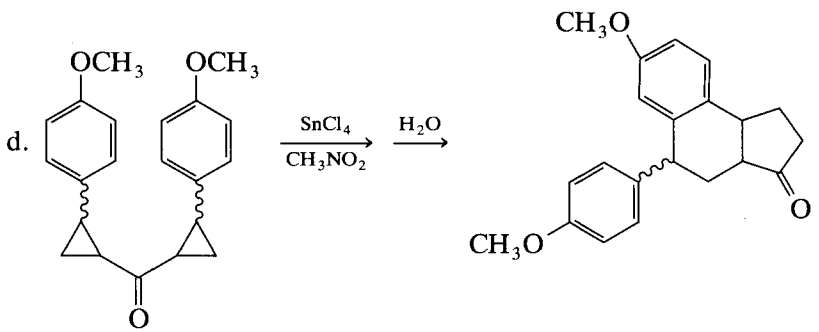
Ent, H.; de Koning, H.; Speckamp, W. N. *J. Org. Chem.* **1986**, *51*, 1687–1691.

c.



Ben-Ishai, D.; Denenmark, D. *Heterocycles* **1985**, *23*, 1353–1356.

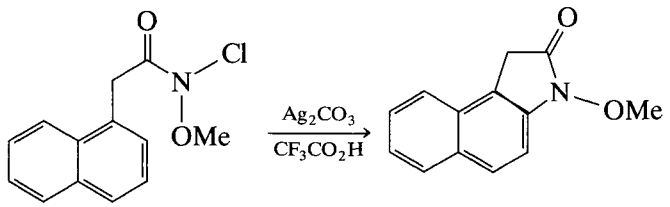
d.



Hantawong, K.; Murphy, W. S.; Boyd, D. R.; Ferguson, G.; Parvex, M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1577–1582.

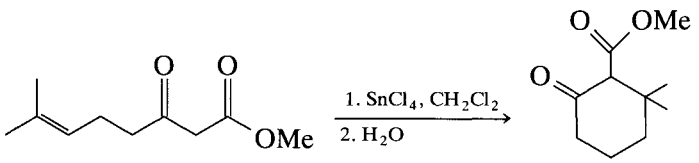
**PROBLEM 4.17**
*continued*

e.




Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728–5729.

f.

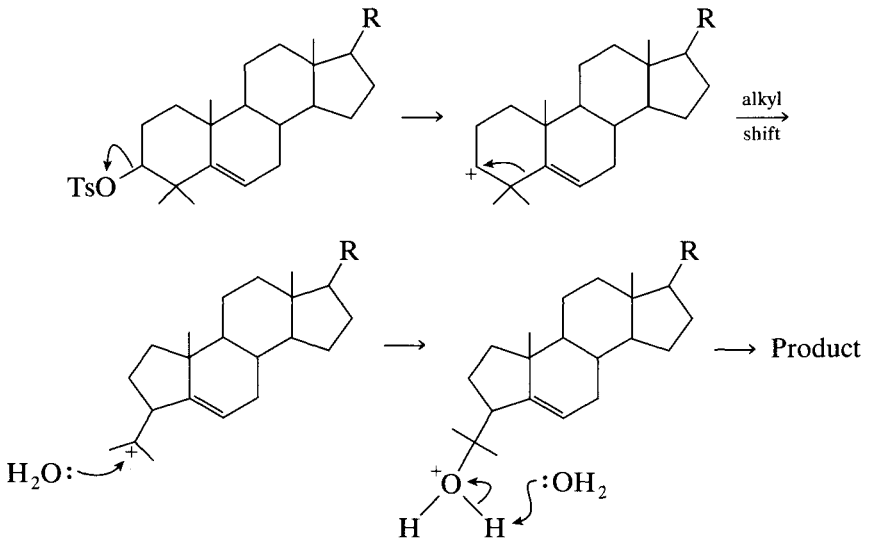



White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939–1948.

## ANSWERS TO PROBLEMS

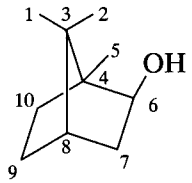
Problem 4.1

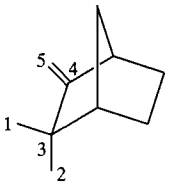
a. This is an ionization, followed by an alkyl shift and nucleophilic reaction of solvent with the electrophilic carbocation intermediate. In other words, it is an example of an $S_N1$ reaction with rearrangement. As noted in Table 3.1, the tosylate anion is an excellent leaving group.



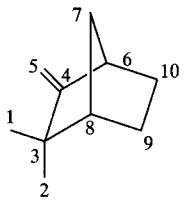
Problem 4.1 *continued*

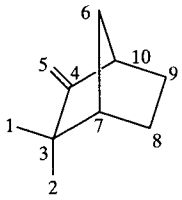
b. Because the hydroxyl group is lost and an alkene is formed, the reaction appears to be a dehydration involving a carbocation rearrangement. Numbering of the carbons in starting material and product is helpful. Numbering of the first five carbons in the product is straightforward because of the methyl carbons.



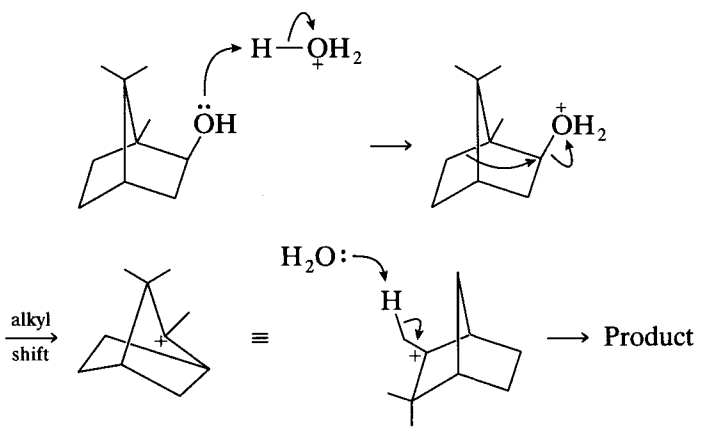

If we minimize bond reorganization there are only two ways to number the remaining carbons of the product:



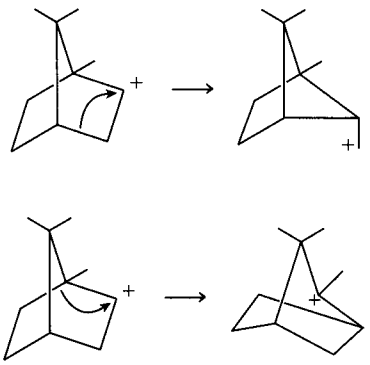

**4-43** **4-44**

A major difference between **4-43** and the starting material is that, at carbon-10 (C-10), a bond to C-4 has been replaced by a bond to C-6. This is equivalent to an alkyl shift of C-10 from C-4 to C-6. In **4-44** at C-6, the bond to C-4 has been replaced by a bond to C-10. This is equivalent to a alkyl shift of C-6 from C-4 to C-10. However, the carbocation will be formed at C-6, and thus this carbon cannot be the one that shifts. Thus, **4-43** must be the product.



Problem 4.1 *continued*

An alternative approach to solving this problem is to start by forming the secondary carbocation at C-6 and then to assess possible 1,2 alkyl shifts that could occur. If we recognize that the relationship of atoms C-1 through C-5 is unchanged in the product, two 1,2 alkyl shifts are possible:

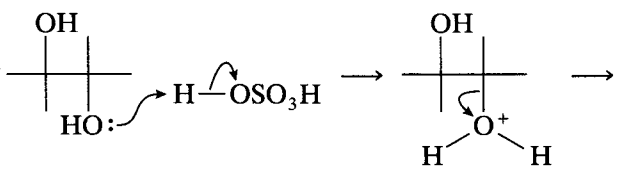


The first leads to formation of a primary carbocation. The instability of the primary carbocation is not so great that it is grounds for eliminating this step from consideration; however, the intermediate ion also contains a four-membered ring, a structural feature not found in the product. The second alkyl shift leads to the carbocation encountered in the mechanism shown previously.

For some reactions, it will be necessary to consider both alkyl and hydride shifts in order to account for the products formed.

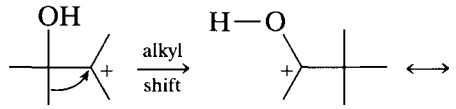
Problem 4.2

The mechanism of this reaction involves protonation of oxygen and loss of water to form a carbocation. Because the molecule is symmetrical, the hydroxyls are equivalent; thus, protonation of either oxygen leads to the product.

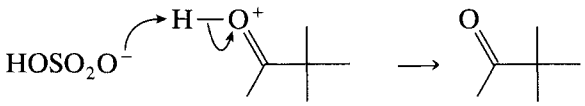



The subsequent alkyl shift gives a carbocation, **4-45**, which is resonance-stabilized by interaction with the adjacent oxygen. Loss of a proton then leads to the product.

Problem 4.2
*continued*

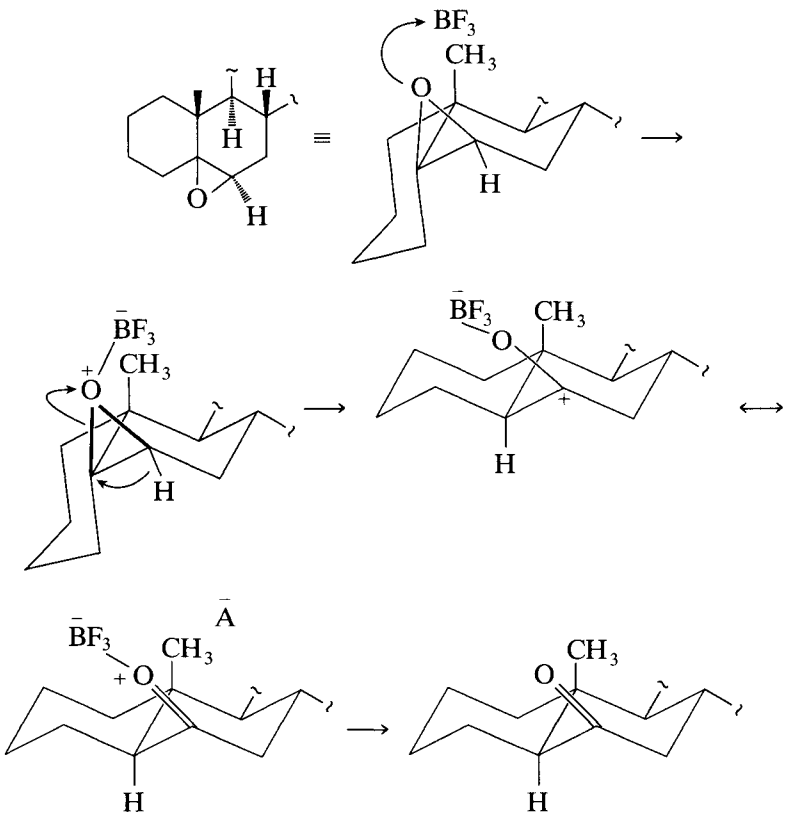



**4-45-1**




**4-45-2**

Problem 4.3 The Lewis acid $BF_3$ can complex with the epoxide oxygen to induce ring opening.



Problem 4.3 *continued*

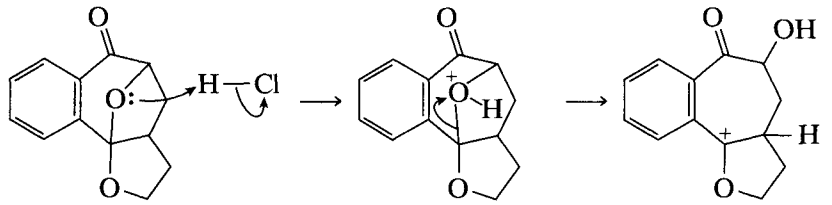
If migration of the hydride and ring opening of the epoxide are concerted, stereospecificity of the reaction is assured. Nucleophilic displacement by ethyl ether (derived from boron trifluoride etherate) removes boron trifluoride to generate the product ketone.

Problem 4.4

There are several possible mechanistic varitions for this reaction. Because the starting material contains several basic oxygens and acid is one of the reagents, protonation is a reasonable first step. Dimethyl ether more basic than acetophenone by only 0.5 p$K_a$ units (see Appendix C). An acetal would be expected to be less basic than an ether because of the electron-withdrawing effect of the second oxygen. Thus, protonation at both the acetal oxygen of the center ring and the carbonyl oxygen will be examined. (Protonation of the other acetal oxygen is unlikely to lead to product, because the ring containing this oxygen is not rearranged in the final product.)

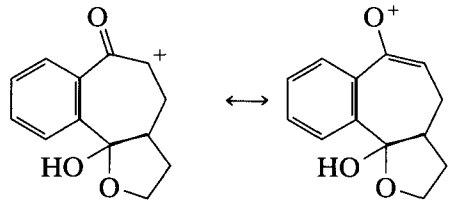
***Mechanism 1***

In this sequence, initial protonation of the acetal oxygen in the center ring is considered.




**4-46**

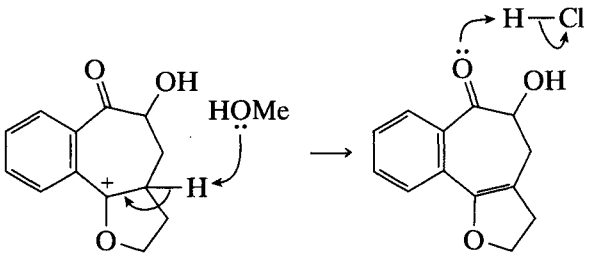
Ring opening of the protonated intermediate could produce either cation **4-46** or cation **4-47** depending upon which bond is broken. Carbocation **4-46** is stabilized by resonance with both the aromatic ring and the adjacent ether oxygen. Carbocation **4-47** is a hybrid of only two resonance forms, and **4-47-2** is quite unstable because the positive oxygen does not have an octet of electrons. Thus, the ring-opening reaction to give **4-46** is preferred.




**4-47-1** **4-47-2**

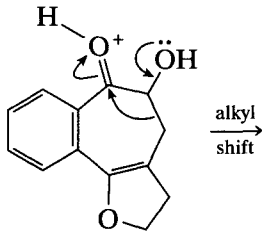
Problem 4.4 *continued*

Reaction of **4-46** continues with elimination of a proton to form a double bond, followed by protonation of the carbonyl group.

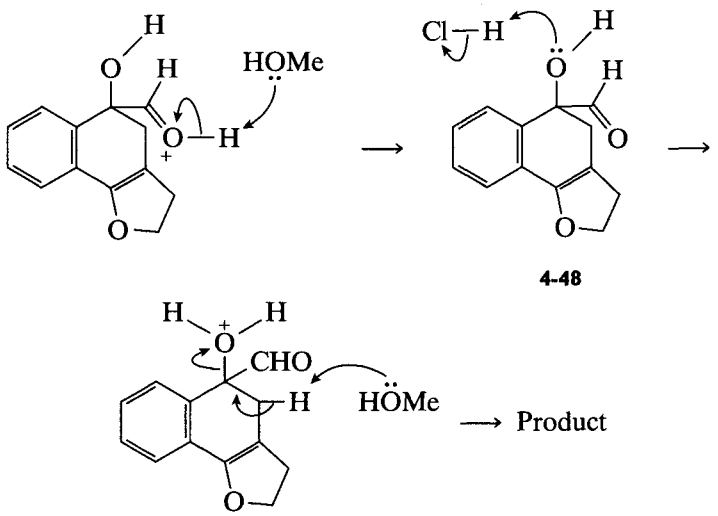


**4-46**

Then an alkyl shift occurs, followed by a deprotonation.




Finally, a dehydration takes place, forming the product.




**4-48**

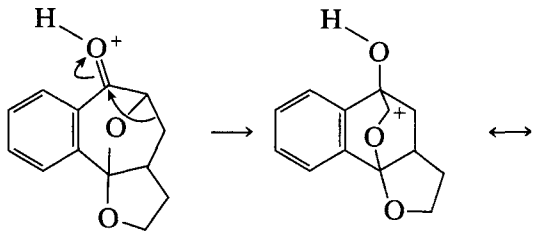
Problem 4.4 *continued*

In this sequence (mechanism 1), methanol was consistently used as the base, because data in Appendix C show that it is a stronger base than chloride ion.

***Mechanism 2***

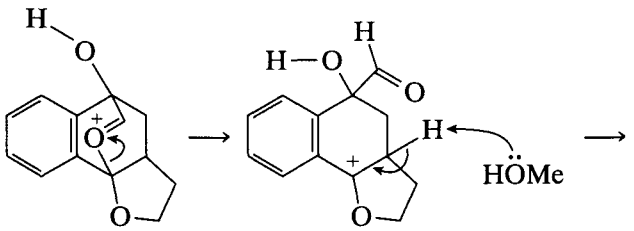
Mechanism 2 starts with protonation of the carbonyl oxygen to produce cation **4-49**.

An alkyl shift gives cation **4-50**, which is resonance-stabilized. This cation

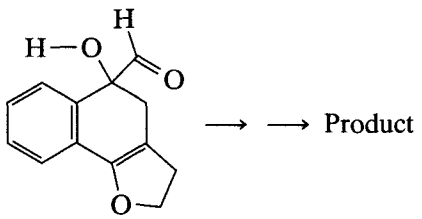


**4-49** **4-50-1**

then undergoes bond cleavage to form **4-51**, which is stabilized in the same manner as **4-46** in mechanism 1. Loss of a proton gives **4-48**, which is also an intermediate in mechanism 1.



**4-50-2** **4-51**

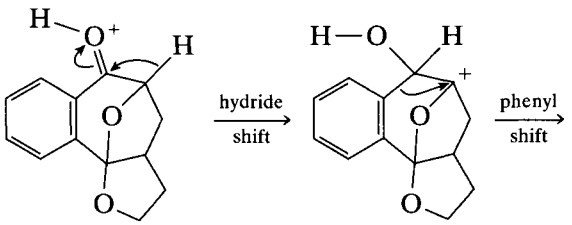


**4-48**

Problem 4.4
*continued*

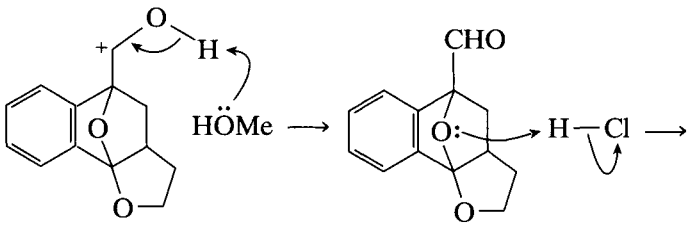
***Mechanism 3***

Intermediate **4-49** of mechanism 2 undergoes a hydride shift, instead of an alkyl shift, to give the following:

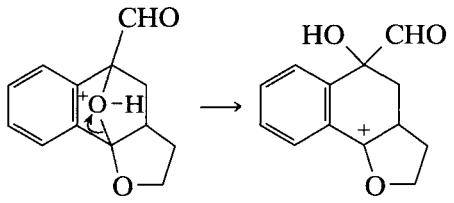



**4-49** **4-52**

A phenyl shift gives the cation, **4-53**, which can lose a proton to give the aldehyde functional group. The acetal oxygen in the center ring can be protonated and open to give cation, **4-51**, which behaves as shown previously in mechanism 2.




**4-53**



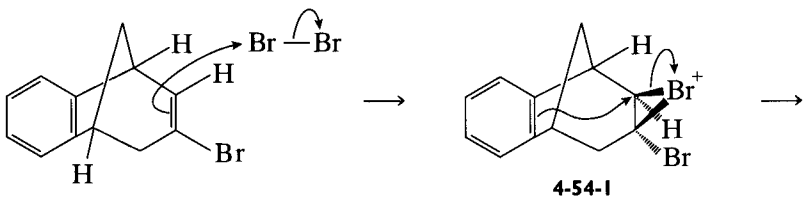

**4-51**

Problem 4.4 *continued*

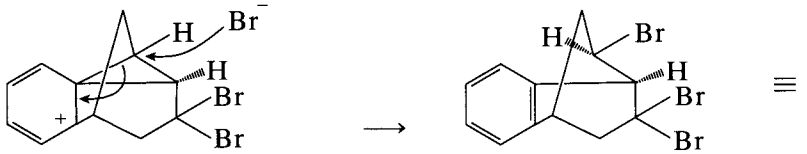
The problem with this mechanism is that the likelihood of forming a carbocation at the position shown in intermediate **4-52** is vanishingly small. Several factors combine to make this cation very unstable. First, although it is tertiary, the carbocation is at a bridgehead position and is constrained from assuming the planar geometry of an $sp^2$ hybridized carbocation. The bridgehead location also precludes resonance stabilization by the adjacent bridging oxygen, which nevertheless has a destabilizing inductive effect. Finally, there is a hydroxyl group on the carbon adjacent to the cationic center, and its inductive effect would further destabilize the carbocation in **4-52**. Because of these factors this would not be considered a viable mechanism.

Problem 4.5

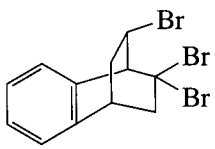
a. The formation of **4-23** could involve formation of a bromonium ion, **4-52**, similar to **4-14**, **4-15**, and **4-18**. This ion undergoes an aryl shift and then reacts with bromide to give the product. The bromonium ion must form on the *exo* side for the rearrangement to take place because the migrating aryl group must enter from the side opposite the leaving bromo group.



**4-54-I**



**4-23**

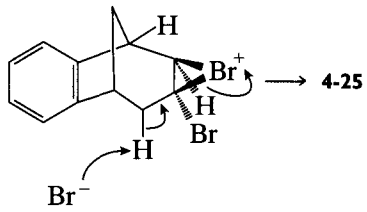


**4-23**

Problem 4.5
*continued*

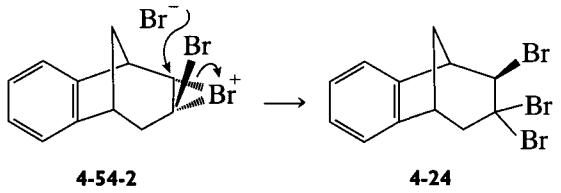
In the last step of the preceding sequence, the bromide ion enters on the side opposite the phenonium ion, in analogy to the stereochemistry of reaction of bromide ion with a bromonium ion.

There are several possible explanations for the different result at higher temperatures. One is that the bromonium ion forms on both the *exo* and *endo* sites. Reaction of the *exo* bromonium ion gives **4-23**, as before, and **4-25** is formed in an elimination reaction.

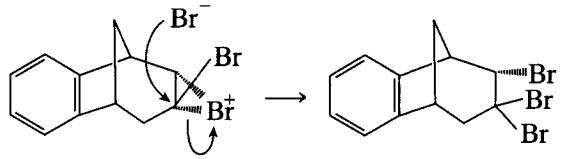



**4-54-1**

Reaction of the *endo* bromonium ion gives the isomers, **4-24**.



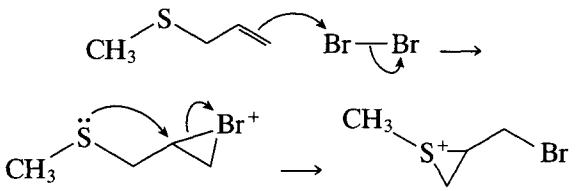

**4-54-2** **4-24**




**4-54-2** **4-24**

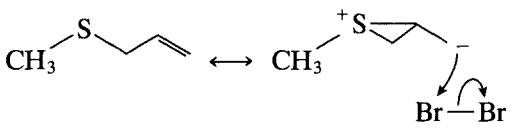
Another explanation is that at the higher temperature, only the *exo* bromonium ion **4-54-1** forms, but that under these conditions **4-54-1** can rearrange to give **4-23**, undergo elimination to form **4-25**, or react with bromide ion approaching from the *endo* side to give the two isomers **4-24**.

b. The displacement of Br by sulfur in the intermediate bromonium ion, **4-55**, is similar to the ring closure in Problem 3.4a. Problem 4.5 *continued*



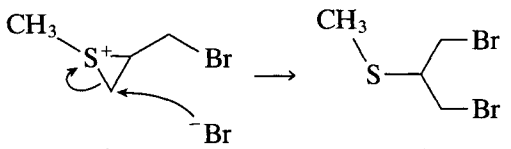
**4-55** **4-56**

Representing the reaction as follows would be incorrect. The doubly charged structure **4-57** is not a resonance form of the starting material because the positions of the atoms and the bond angles of the sigma bonds are different. Also, because it is not stabilized by resonance, **4-57** would be very unstable.



**4-57**

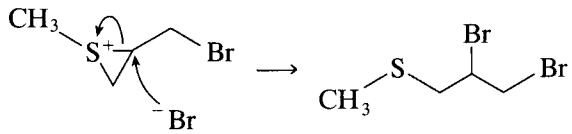
At low temperatures, the three-membered-ring episulfonium ion, **4-56**, which resembles a bromonium ion, reacts with bromide only at the primary carbon. The product of this $S_N2$ reaction is determined by the reaction rate, which is faster at the primary carbon than at the secondary carbon. This is a reaction in which product formation is rate-controlled.



**4-56** **4-58**

Problem 4.5
*continued*

At elevated temperatures, **4-58** is in equilibrium with **4-56**. Under these conditions, **4-56** also reacts at the secondary carbon to give **4-59**. Because **4-59** is more stable than **4-58**, its reverse reaction to **4-56** is slower, and **4-59** accumulates. Thus, at higher temperatures, product formation is equilibrium-controlled.



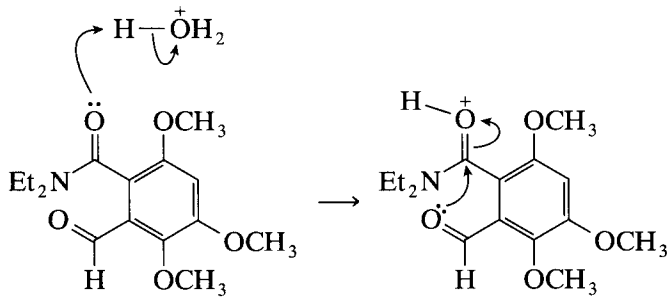

**4-56** **4-59**

Problem 4.6

a. This reaction involves loss of the diethylamino group of the amide and ring closure with the aldehyde to form the hydroxylactone product. Because the timing of the ring closure is open to question, two possible mechanistic sequences are given.

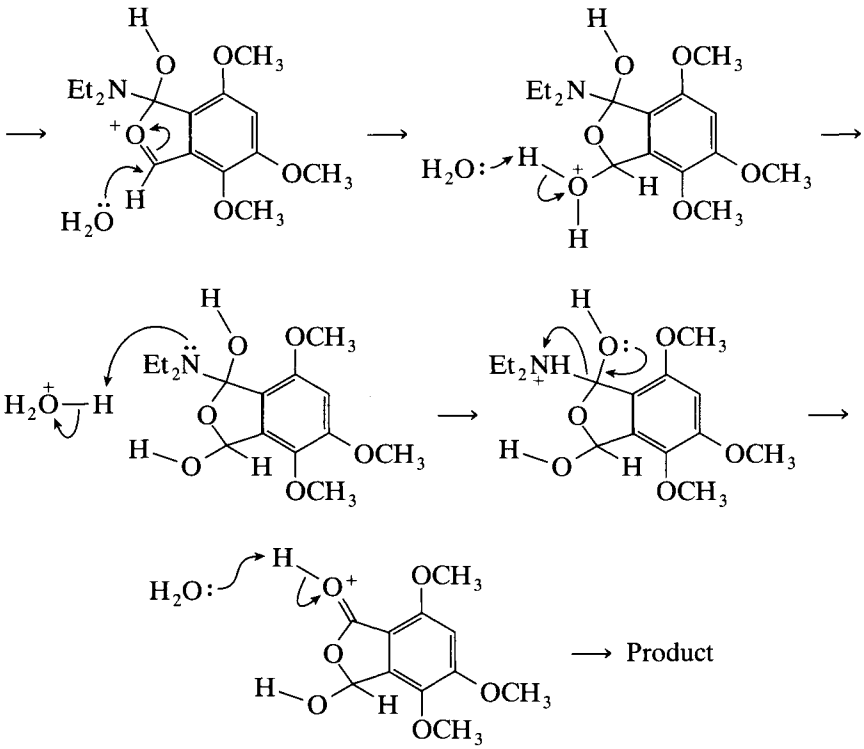
***Mechanism 1***

In this mechanism, the second ring is formed early. The carbonyl oxygen of the amide is protonated, and then the oxygen of the aldehyde adds to this protonated functional group to form a new ring.



Problem 4.6 *continued*

The four steps, after participation of the aldehyde oxygen, are (1) nucleophilic reaction of water with the most electrophilic carbon; (2) loss of a proton; (3) protonation of the nitrogen; and (4) loss of diethylamine. Writing the steps in this order avoids formation of more than one positive charge in any intermediate.

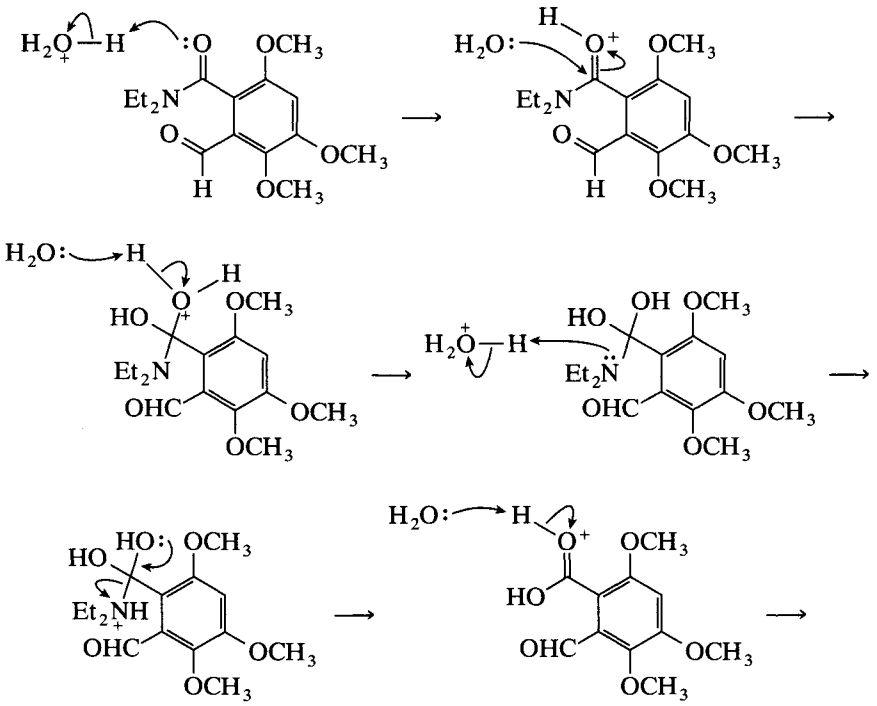



4-60

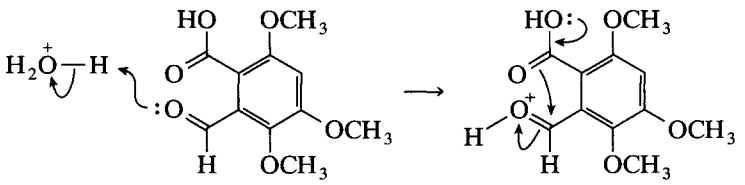
***Mechanism 2***

Another possibility is hydrolysis of the amide to a carboxylic acid followed by closure with the aldehyde. The hydrolysis of the amide mimics the steps in Example 4.16.

Problem 4.6
*continued*



Because it is easier to protonate an aldehyde than a carboxylic acid (compare benzoic acid and benzaldehyde in Appendix C), the ring closure would be written best as protonation of the aldehyde oxygen followed by nucleophilic reaction of the carboxylic acid carbonyl oxygen. The carbonyl oxygen acts as the nucelophile because a resonance-stabilized cation is produced. If the hydroxyl oxygen acts as a nucleophile, the cation is not resonance-stabilized.

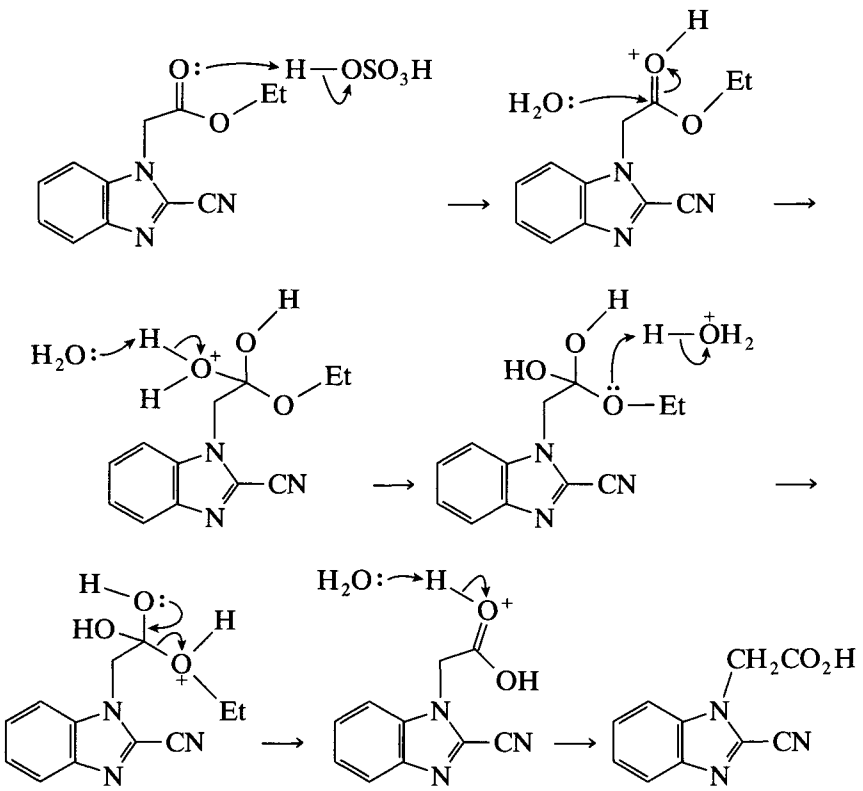


**4-60**

Problem 4.6 *continued*

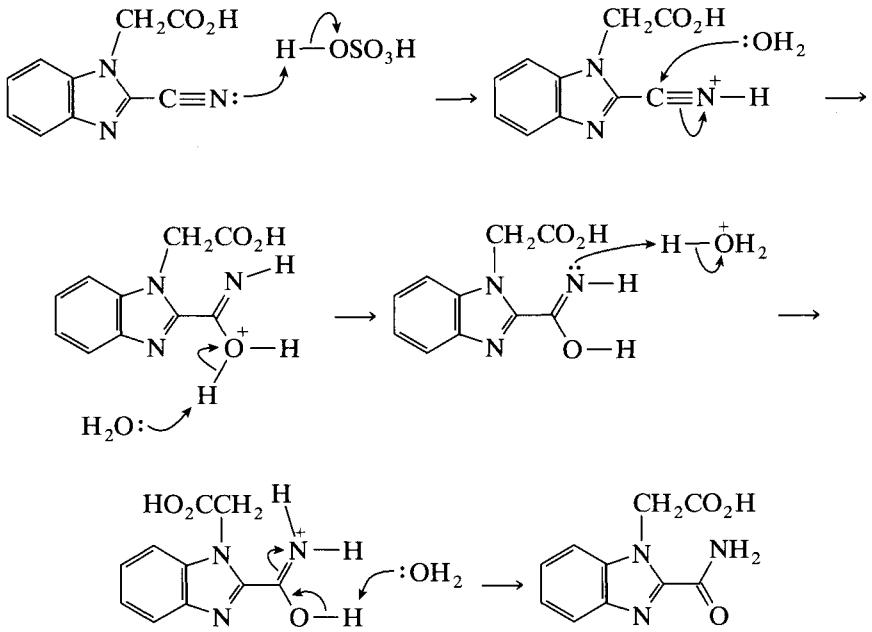
The last step is the same as that for mechanism 1. Mechanism 1 seems better than mechanism 2 because no tetrahedral intermediate is formed at the amide carbon prior to cyclization. The amide position is sterically congested, because it is flanked by *ortho* substituents. A tetrahedral intermediate ($sp^3$-hybridized carbon) adds to the congestion and might be of such high energy that its formation would be unlikely.

b. Both the ester and nitrile undergo hydrolysis. (There are many acids present. The strongest acids, $H_3O^+$ and $H_2SO_4$, can be used interchangeably.) Normally, esters are hydrolyzed more rapidly than nitriles, so that the ester will be hydrolyzed first.

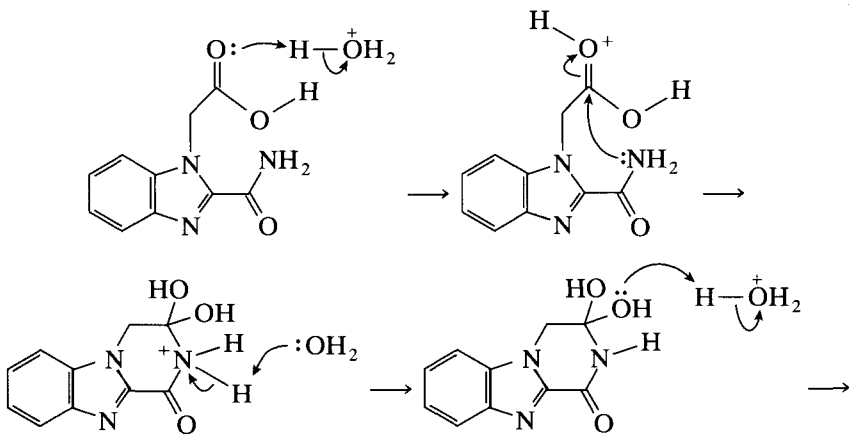


Hydrolysis of the nitrile produces the imino form of the amide, which readily tautomerizes by the usual mechanism to form the amide.

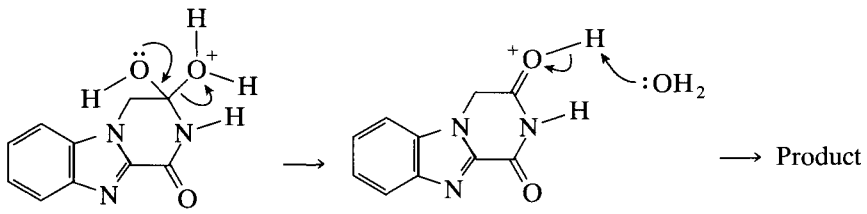
Problem 4.6
*continued*



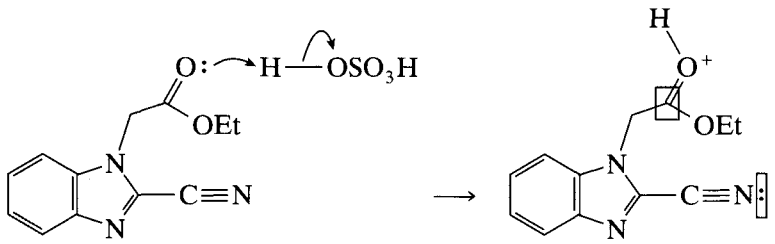
If reaction conditions are controlled, the hydrolysis of nitriles can be stopped at the amide stage. In this case, once the amide is produced, the nitrogen will react as a nucelophile with the protonated carbonyl of the acid. Because a six-membered-ring transition state is involved, this intramolecular reaction is very favorable.



Problem 4.6
*continued*



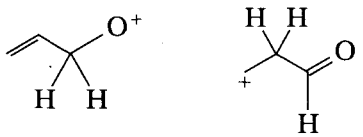

Reaction of the nitrile, acting as a nucleophile, with the electrophilic protonated ester is unlikely as a ring-forming reaction. Because of the linearity of the nitrile group, it is difficult for the lone pair of electrons on nitrogen to reach close enough to overlap the *p* orbital on the carbon of the carbonyl group. (See the boxed groups on the last structure in the sequence.) Also, because the lone pair of electrons on the nitrile occupies an *sp* orbital, these electrons would be much less nucleophilic than the lone pair occupying a *p* orbital on the amide nitrogen.




Problem 4.7

None of the cations produced by protonation at the carbons of acrolein is as stable as the cation produced by protonation at oxygen. We will consider the possibilities.

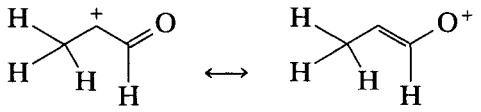
Protonation of the aldehyde carbonyl carbon gives cation **4-61**. This is a very unstable intermediate. It is not stabilized by resonance, and the positive oxygen lacks an octet of electrons. Notice that the double bond and the positive oxygen are not conjugated because they are separated by an $sp^3$-hybridized carbon.




**4-61** **4-62**

Problem 4.7 *continued*

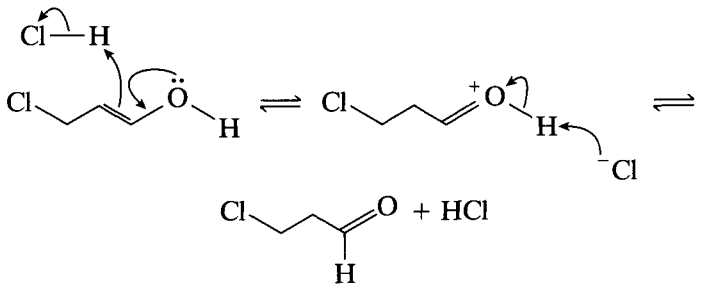
The intermediate produced by protonation at the $\alpha$ carbon also gives a very unstable primary cation, **4-62**, which is not stabilized by resonance. Protonation at the $\beta$ carbon gives a delocalized cation, **4-63**, but the resonance form **(4-63-2)** is especially unstable because the oxygen has a positive charge and does not have an octet of electrons.



**4-63-1** **4-63-2**

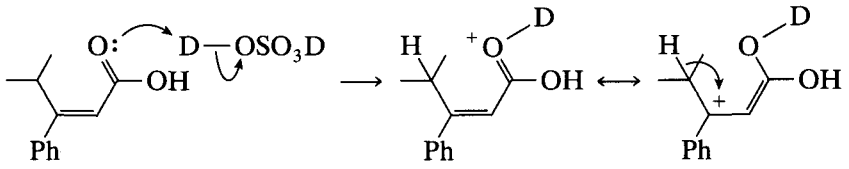
Problem 4.8

HCl is a catalyst for the transformation, so it must be regenerated at some point in the mechanism.



Problem 4.9

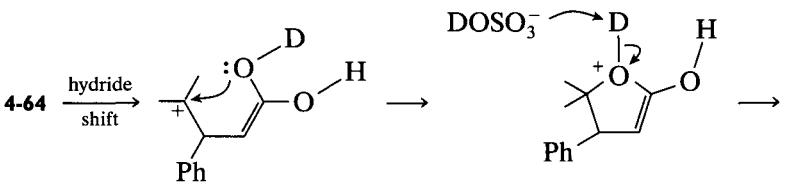
By analogy to Example 4.19 and Problem 4.7, protonation at the carbonyl group, rather than at the double bond, of the starting material will give a more stable cation. (That is not to say that all reactions occur via a mechanism involving formation of the most stable carbocation. But if the most stable cation leads to product, that is the one to use.)



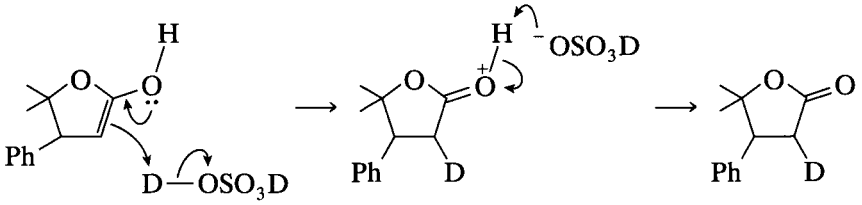
**4-64-1** **4-64-2**

Problem 4.9
*continued*

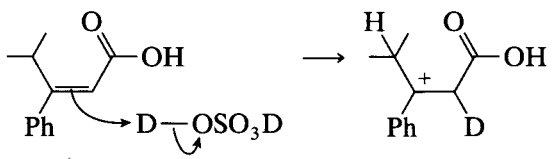
The carbocation formed initially, **4-64**, can undergo a hydride shift to give a tertiary carbocation. The oxygen of the OH or OD group reacts as a nucleophile with the electrophilic carbocation. In order for the ring to form, the oxygen that reacts must be the one on the same side of the double bond as the carbocation. In **4-65**, this happens to be the OD oxygen, but because these two oxygens can equilibrate rapidly under the reaction conditions, the oxygen *cis* to the alkyl group could just as easily be protonated as deuterated.




Intermediate **4-66** undergoes acid-catalyzed tautomerization to give the product.




There is another cation that could undergo the same rearrangement as this one. This cation could be formed by direct protonation of the double bond with Markovnikoff regiospecificity:

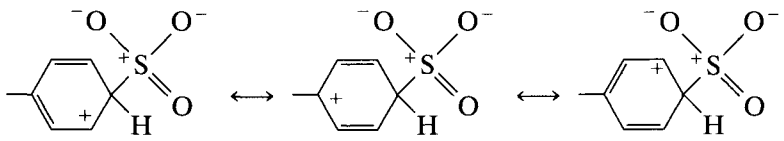


Problem 4.9 *continued*

The remaining steps in this mechanism would be very similar to those of the first. However, the first mechanism is better because the carbocation formed initially is more highly stabilized by resonance and, thus, should form faster.

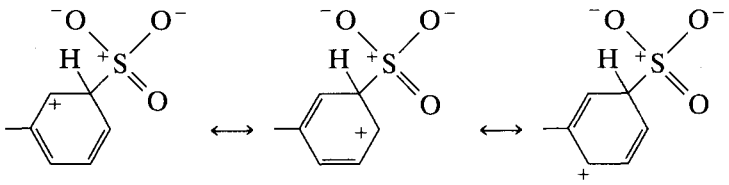
Problem 4.10

a. The intermediate, formed by reaction of the electrophile at the *para* position, has three resonance forms. Form **4-67** is especially stable because the positive charge is next to an alkyl group, which stabilizes positive charge by the inductive effect and by its polarizability.



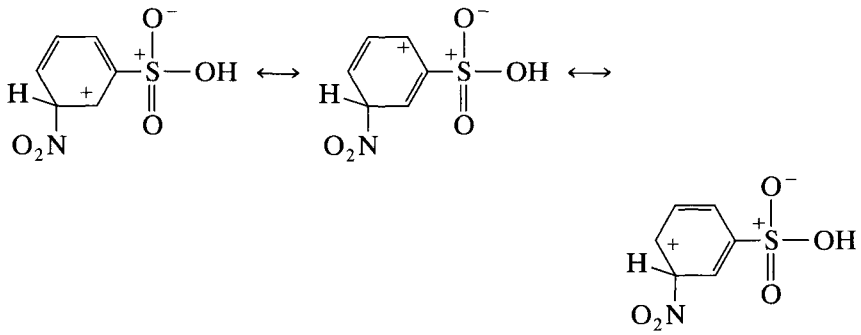
**4-67**

Reaction of the electrophile at the *ortho* position would give an intermediate of essentially the same stability. However, reaction of the electrophile at the *meta* position gives an intermediate, **4-68**, in which the positive character cannot be located at the alkyl group position. Thus, this intermediate is not as stable and is not formed as rapidly as the intermediates from reaction at either the *ortho* or *para* position.



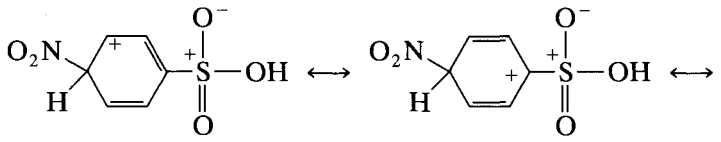
**4-68**

b. The intermediate, formed by reaction of a nitronium ion at the *meta* position, does not have positive charge on the carbon bearing the positively charged sulfur of the sulfonic acid group.

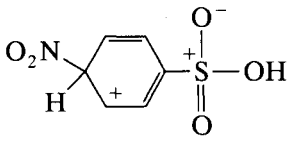


Problem 4.10 *continued*

The intermediates, formed by electrophilic reaction at the *ortho* or *para* positions, are not as stable as the intermediate formed by reaction at the *meta* position because, for *ortho* and *para* attack, one of the three resonance forms has positive charge on the carbon bearing the positively charged sulfur of the sulfonic acid group. For example, for the intermediate resulting from reaction at the *para* position we can draw three resonance forms. Of these **4-69-2** is particularly unstable because of the destabilizing effect of two centers of positive charge in close proximity. Because the intermediate involved in *meta* substitution lacks this unfavorable interaction, it is more stable and *meta* substitution is favored.



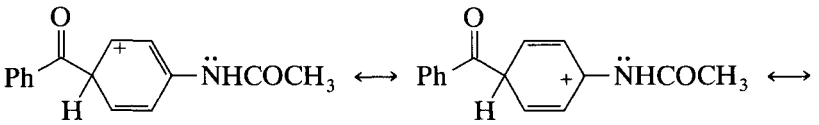
**4-69-1** **4-69-2**



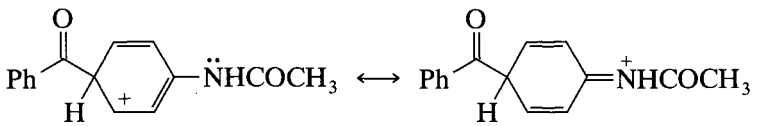
**4-69-3**

For reaction at the *ortho* position, the resonance forms of the resulting intermediate are destabilized in the same way as those that result from reaction at the *para* position.

c. The intermediate, formed by reaction of the electrophile at the *para* position, has a resonance form, **4-70-2**, with positive character at the substituent position. This means that the unshared pair of electrons on the nitrogen of the acetamido group can overlap with the adjacent positive charge, as shown in **4-70-4**.



**4-70-1** **4-70-2**

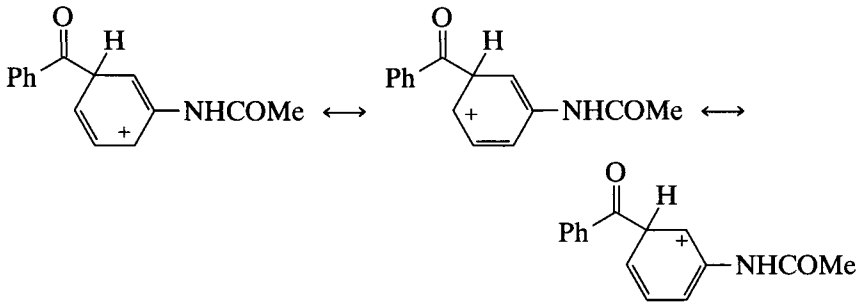


**4-70-3** **4-70-4**

This extra delocalization of the positive charge adds to the stability of the

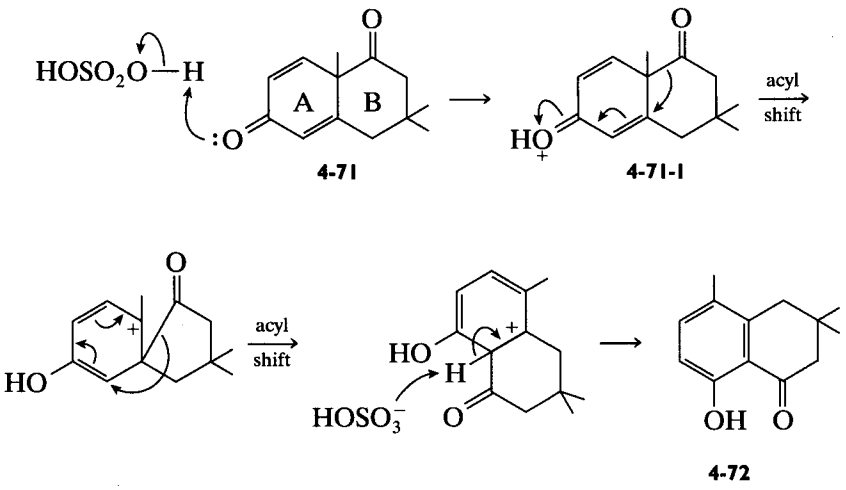
Problem 4.10 *continued*

intermediate. On the other hand, if the electrophile reacts at the *meta* position, the positive charge cannot be placed on the nitrogen.



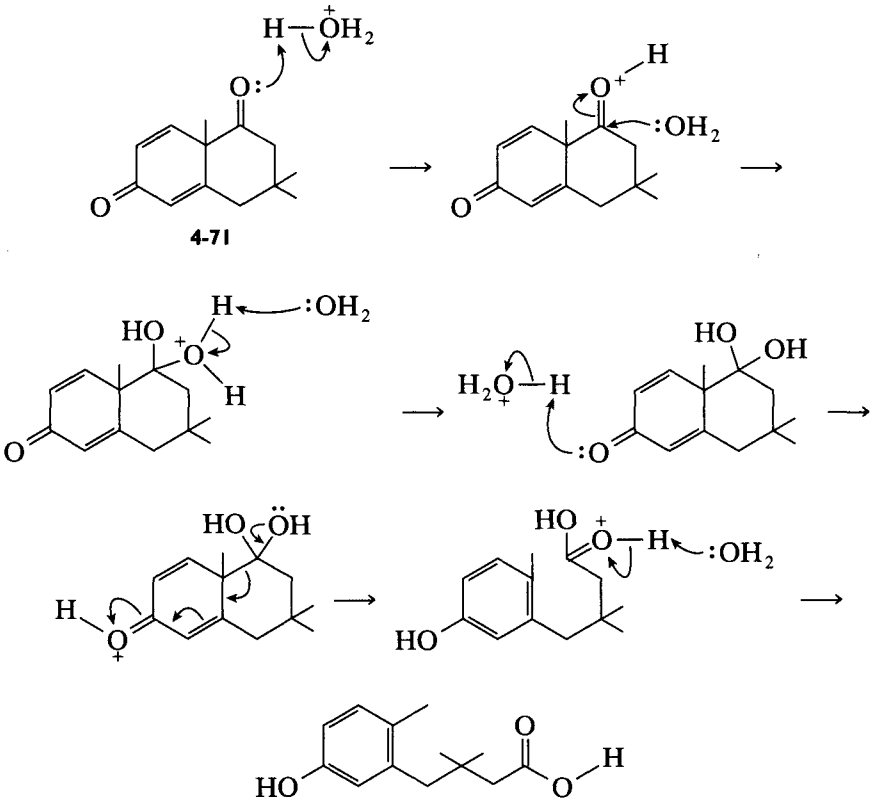
Problem 4.11

a. The mechanism in sulfuric acid might occur by the steps typical for a dienone–phenol rearrangement. Protonation of the A-ring carbonyl gives a more highly resonance-stabilized intermediate than protonation of the B-ring carbonyl.



Formation of the product, **4-73**, formed in dilute HCl requires cleavage of the B ring. A mechanism involving the formation of the hydrate of the keto group in the B ring, followed by ring opening, is shown next. (Example 2.11 shows a slightly different possibility.)

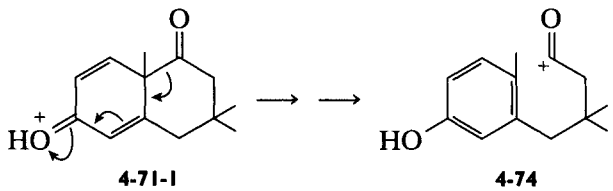
Problem 4.11
*continued*



4-71

4-73

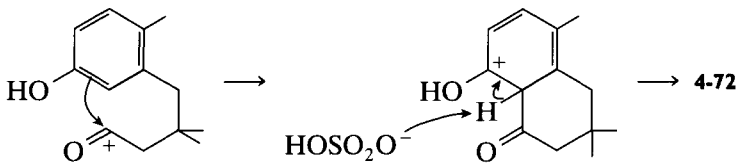
The mechanism in dilute acid suggests an alternative route to **4-72** in the stronger acid, sulfuric acid, in which initial cleavage of the B ring occurs. In this pathway, the ring of the intermediate cation **4-71-1** can open to give the acylium ion, **4-74**.



4-71-1 4-74

Rewriting **4-74**, with the acylium ion in proximity to the position *ortho* to the hydroxyl group clarifies the intramolecular acylation reaction that forms a six-membered ring.

Problem 4.11
*continued*

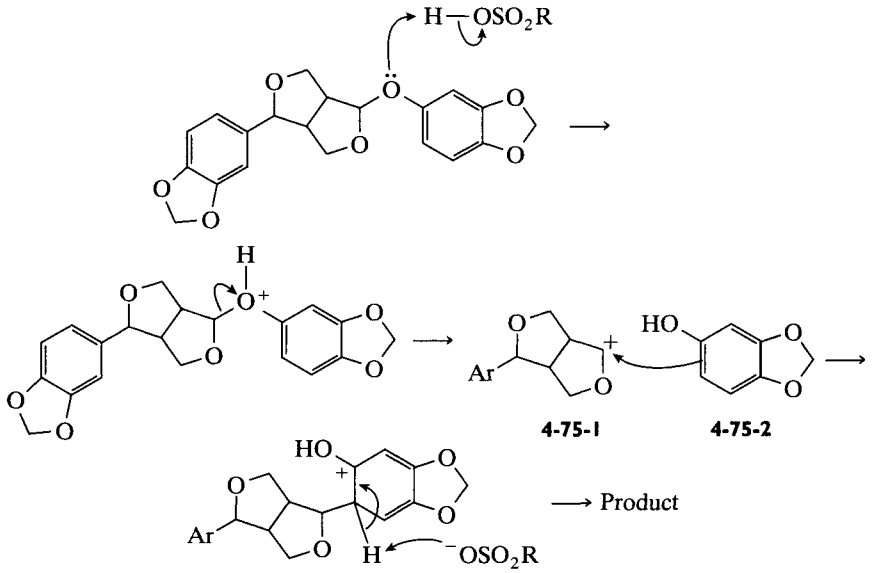



4-74

The acylium ion would have a longer lifetime in concentrated sulfuric acid than in aqueous hydrochloric acid because the concentration of water in the former acid is extremely low. In aqueous hydrochloric acid, the starting ketones are more likely to be in equilibrium with their hydrates, and the intermediate acylium ion might never form. If it does form, it will react so rapidly with the nucleophilic oxygen of water that the electrophilic aromatic substitution cannot occur.

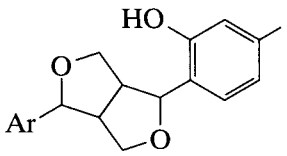
Experimental data in the cited paper support the opening of the B ring in concentrated as well as dilute acid. It was found that on treatment with sulfuric acid, **4-73** and **4-71** both react to give **4-72** at the same rate. However, the alternative mechanism involving successive acyl shifts appears to occur in trifluoroacetic acid. In this medium, **4-71** rearranges to **4-72**, but **4-73** does not give **4-72**. This means that **4-73** cannot be an intermediate in the reaction. Consequently, the mechanism involving opening of ring B is ruled out, and the acyl shift mechanism is a reasonable alternative.

b. The reaction proceeds by a cleavage–recombination reaction.



Problem 4.11 *continued*

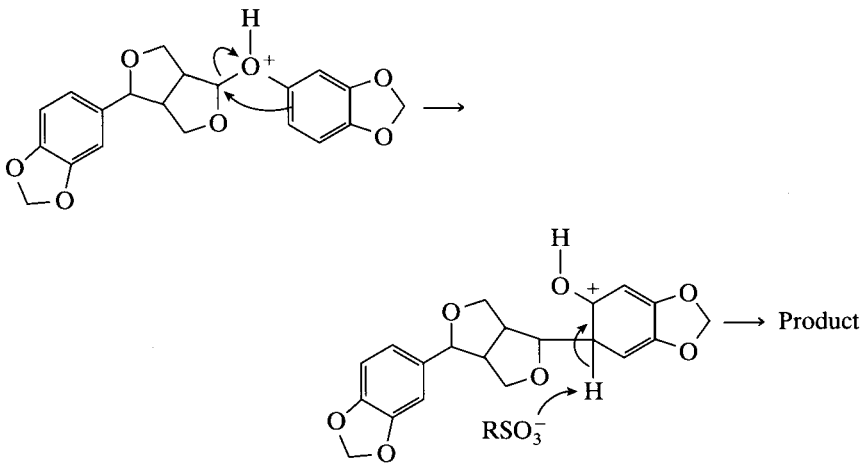
Support for the formation of **4-75-1** and **4-75-2** comes from a crossover experiment reported in the paper. In the presence of *m*-cresol, **4-76** was obtained.




**4-76**

This product is formed by capture of the intermediate carbocation **4-75-1** by the added *m*-cresol. Loss of a proton gives **4-76**. Furthermore, as the concentration of *m*-cresol increases, the amount of **4-76** increases. This supports the idea that the *m*-cresol is competing with **4-75-2** for **4-75-1**. The term, crossover experiment, refers to the fact that **4-75-1** reacts with an external reagent rather than **4-75-2**, its co-cleavage product.

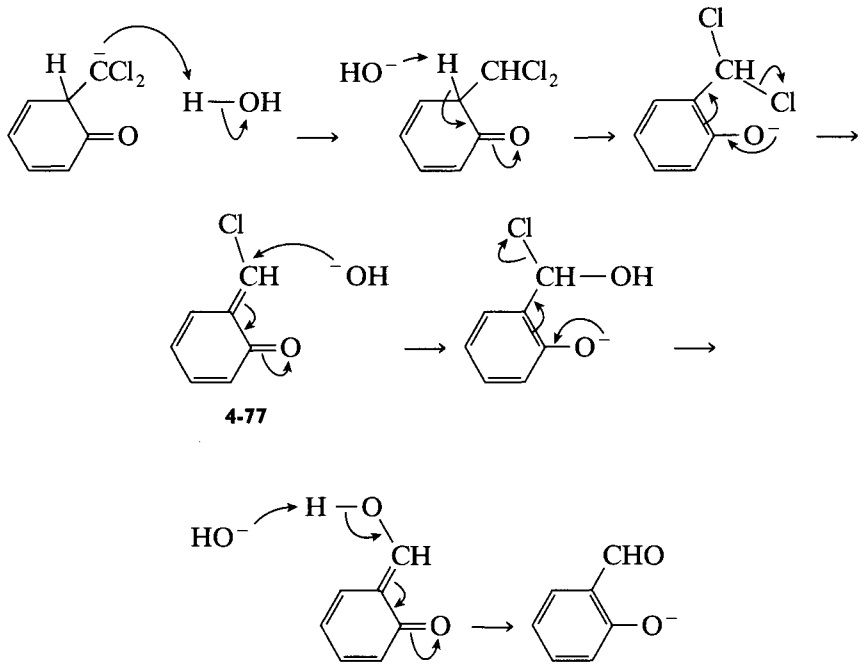
The occurrence of crossover rules out the following mechanism:




Problem 4.12

The intermediate anion picks up a proton: removal of the proton on the $sp^3$-hybridized carbon $\alpha$ to the carbonyl group gives the phenolate ion. The phenolate loses chloride ion to give **4-77**, which undergoes addition of hydroxide at the carbon at the *ortho* position. Loss of the remaining chloride and removal of a proton gives the product phenolate.

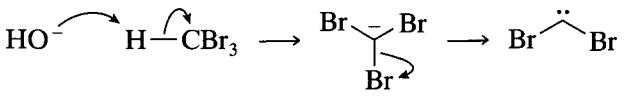
Problem 4.12
*continued*



**4-77**

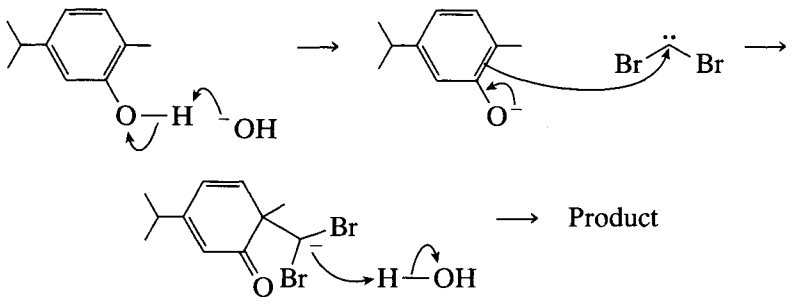
Acidic workup will give the phenol itself.

Problem 4.13 Dibromocarbene can be produced from bromoform and base:



Phenolate, formed in the basic medium, reacts as a nucleophile with the electrophilic carbene. The resulting anion is protonated by water to give the product.

Problem 4.13
*continued*

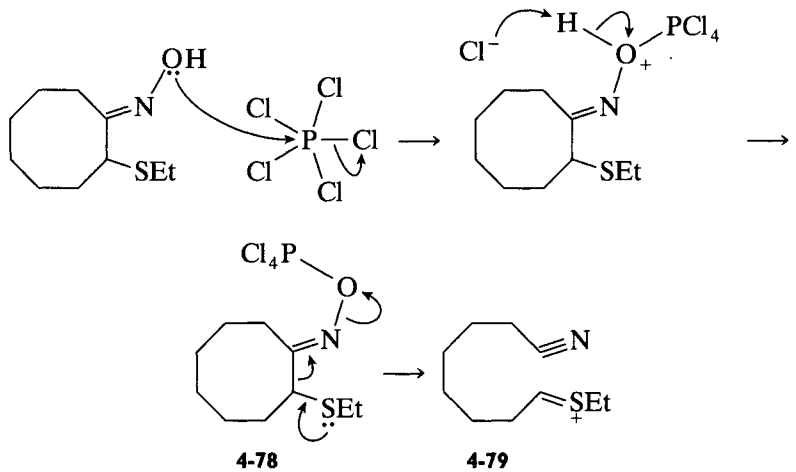



Problem 3.4b gives a subsequent reaction of this product and its literature reference.

An alternative mechanism with the ring acting as an electrophile and the carbene as a nucleophile would be incorrect. The dihalocarbenes are quite electrophilic. Also, because the phenol readily forms a salt with sodium hydroxide, the aromatic ring would not be electrophilic.

Problem 4.14

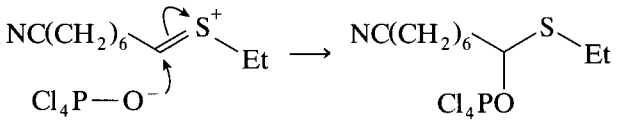
This reaction is a fragmentation, which often accompanies a Beckmann rearrangement. Reaction of the hydroxyl group with phosphorus pentachloride converts it into a better leaving group. In **4-78**, instead of an alkyl group migration, the ring bond on the side opposite the leaving group cleaves, producing a ring-opened cation, **4-79**. This mimics the stereochemical requirement of the Beckmann rearrangement.




**4-78** **4-79**

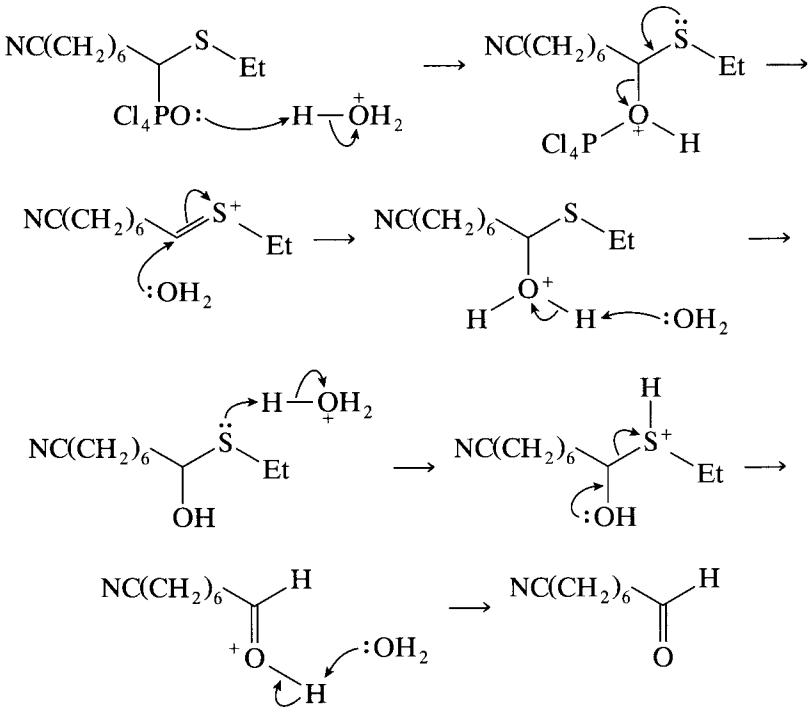
Problem 4.14
*continued*

The electrophilic cation, **4-79**, reacts with a nucleophile at carbon to give the neutral derivative, **4-80**.

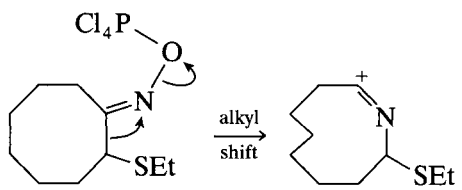


**4-79** **4-80**

The product, **4-80**, will undergo hydrolysis readily when the reaction is worked up in water. This hydrolysis is acid-catalyzed because the phosphorus compounds in the reaction mixture are acidic.



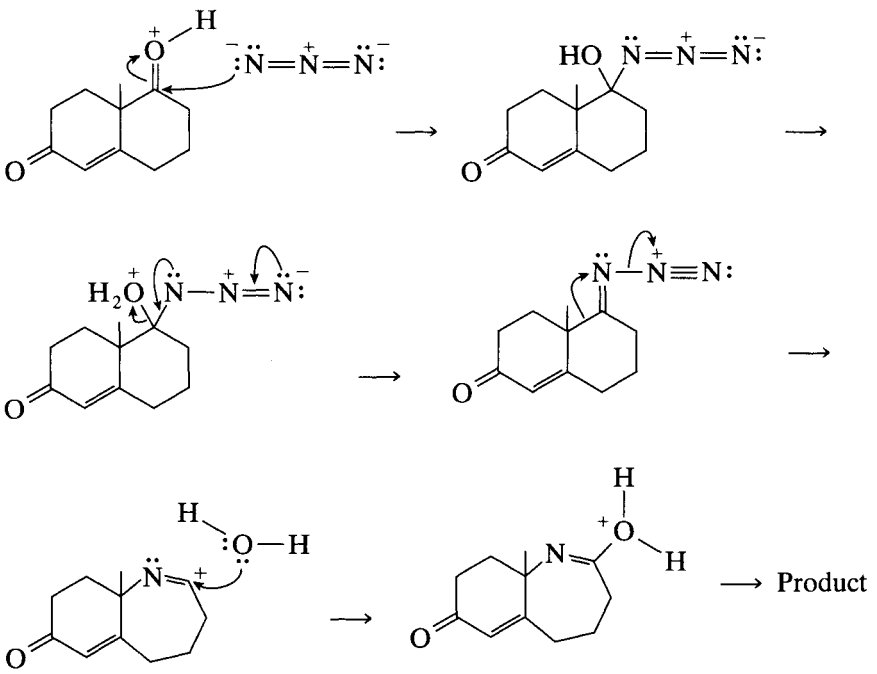
One student wrote an alternative mechanism that involved ring expansion of **4-78** rather than fragmentation. Problem 4.14 *continued*




**4-78**

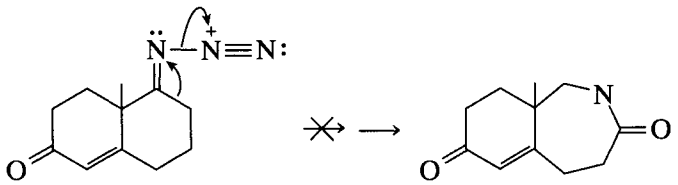
This is a good step because it is the normal Beckmann rearrangement. However, to get from this intermediate to the open-chain product took a fairly large number of "creative" steps. Application of Occam's razor suggests that the initial fragmentation occurs early in the mechanism.

The initial step is a protonation, followed by nucleophilic reaction of azide ion. Problem 4.15



Problem 4.15 *continued*

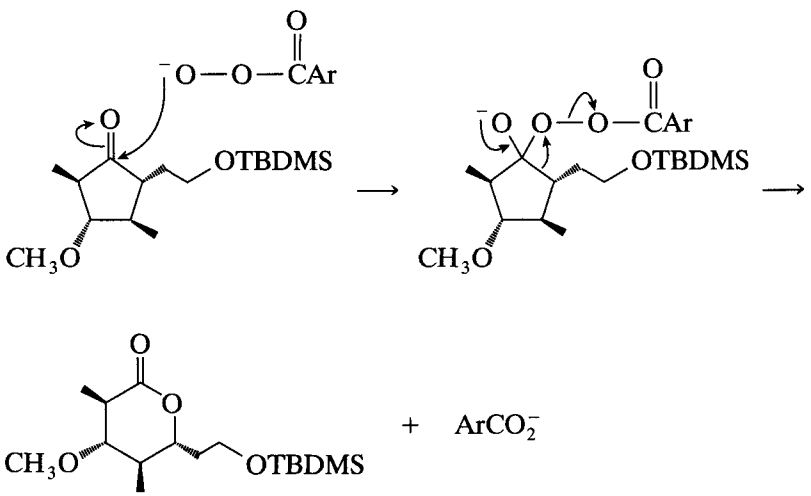
The reaction is a Schmidt reaction and its mechanism closely resembles that of the Beckman and Wolff rearrangements. The final step is deprotonation, followed by tautomerization to the lactam. Note that the alternate lactam formed by migration of the secondary carbon was not found.



One might expect that reaction could also occur at the $\alpha$-$\beta$-unsaturated keto group, and, depending on the reaction conditions, several different products were formed by reaction at this site. The course of reaction when there are two similar functional groups present in a molecule frequently is difficult to predict. The authors of the article cited offer rationalizations for the formation of the various products of the reaction.

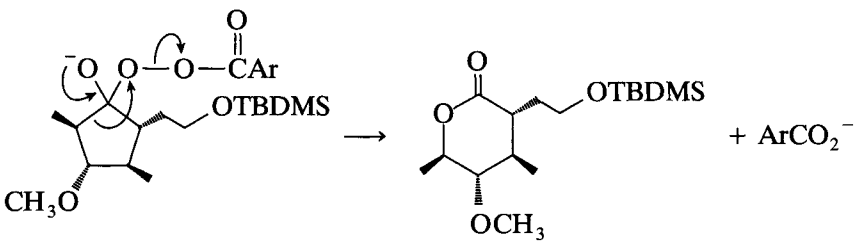
Problem 4.16

In the presence of $NaHCO_3$, deprotonation of the peracid is the first step, followed by nucleophilic attack on the carbonyl group:

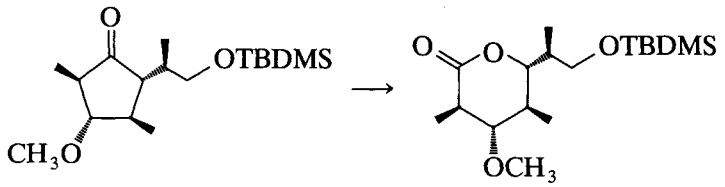


Problem 4.16 *continued*

The minor product is formed by migration of the other alkyl substituent. Note that both products are formed with retention of configuration at the migrating carbon.




There is no readily apparent reason why one group should migrate in preference to the other. The rearrangement of a closely related structure that differs only in the side-chain substitution is regiospecific:



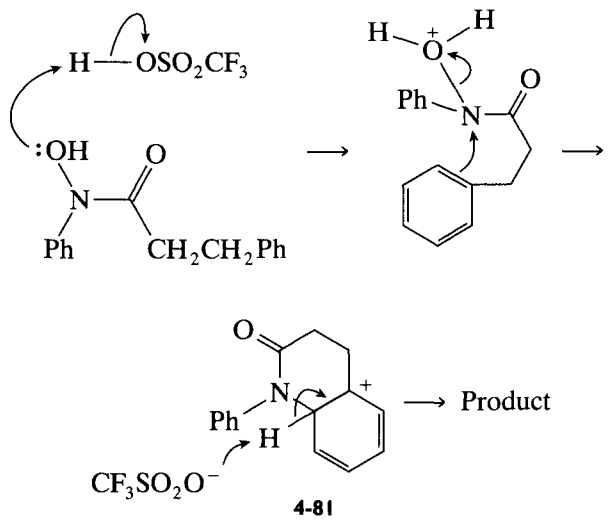

sole product

The reaction is buffered by $NaHCO_3$ to prevent hydrolysis of the TBDMS protecting group by the acid produced in the course of the reaction.

Problem 4.17

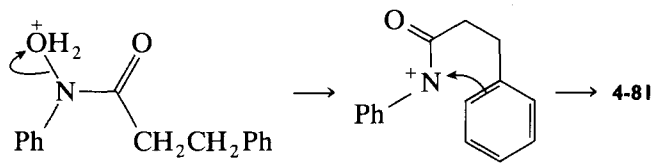
a. Trifluoromethanesulfonic acid is a very strong acid, and the most basic atom in the amide is the carbonyl oxygen. Protonation of the carbonyl group is a likely process, but it is not one that leads to product. That is, protonation of the hydroxyl oxygen is on the pathway to product, whereas protonation of the carbonyl oxygen is not. The nitrogen bearing the protonated hydroxyl group can act as an electrophile, and the phenyl ring, situated to form a favorable six-membered ring, can act as a nucleophile.

Problem 4.17
*continued*

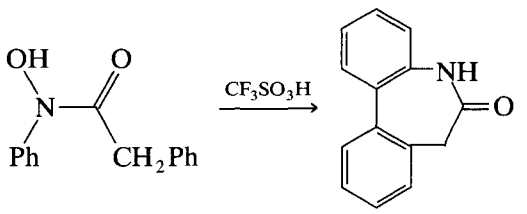



**4-81**

In an alternate mechanism, water leaves the protonated starting material prior to involvement of the nucleophile (the aromatic ring). This gives a nitrenium ion, which acts as the electrophile. Cyclization leads to the same intermediate carbocation, **4-81**, as before.



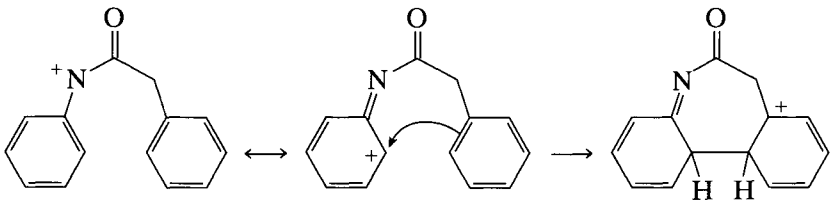

The following reaction in trifluoromethanesulfonic acid provides support for initial formation of positive nitrogen (Endo, Y.; Ohta, T.; Shudo, K.; Okamoto, T. *Heterocycles* **1977**, *8*, 367–370).




76%

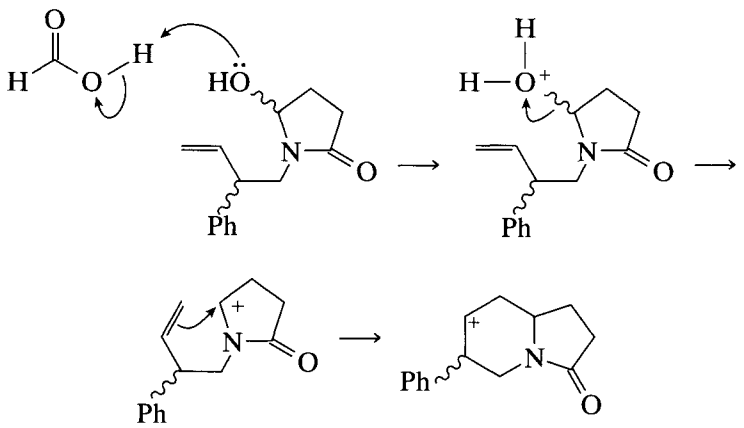
Problem 4.17 *continued*

This reaction is an electrophilic aromatic substitution in which one benzene ring acts as the electrophile and the other benzene ring acts as the nucleophile. In order to develop substantial positive charge in the electrophilic ring (a driving force for the reaction), resonance must occur. This requires prior loss of water. The intermediate nitrenium ion and the direction of the substitution reaction are shown:



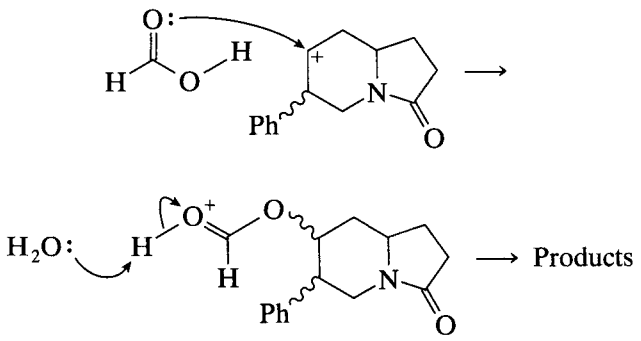
Formation of the product requires loss of a proton to regenerate a neutral compound and tautomerization to regenerate the other benzene ring.

b.



Nucleophilic reaction of formic acid at the electrophilic carbocation can be either *cis* or *trans* to the phenyl group in the bicyclic intermediate and leads to the two products.

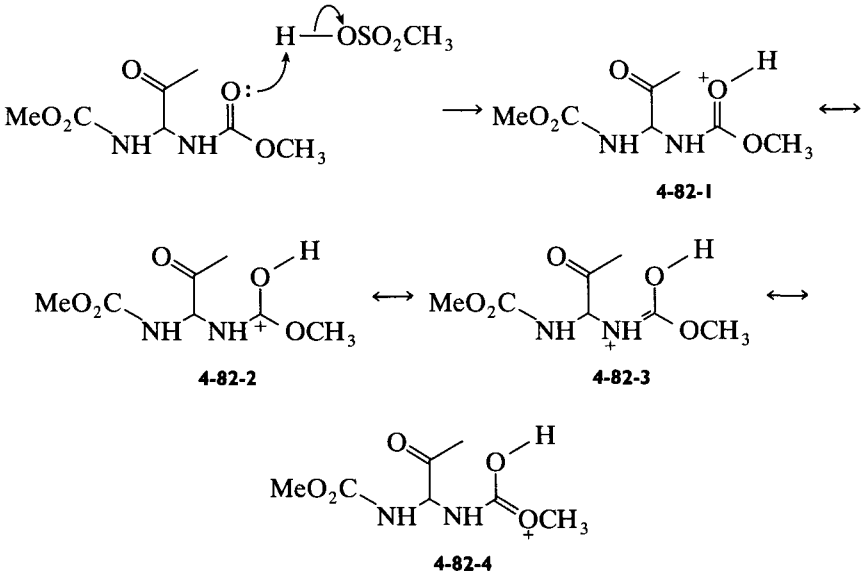
Problem 4.17
*continued*




c. There are several different mechanistic sequences that might lead to the product.

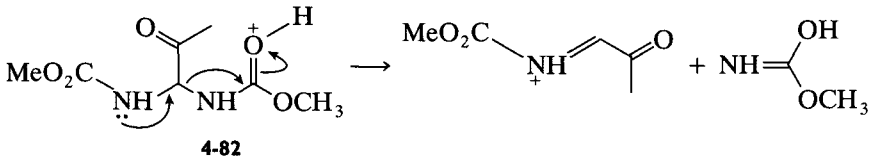
***Mechanism 1***

The two equivalent amide carbonyl oxygens are the most basic atoms in the starting materials. Protonation of one of these oxygens gives a carbocation, **4-82**, which is stabilized by delocalization onto oxygen and nitrogen as well as onto carbon.

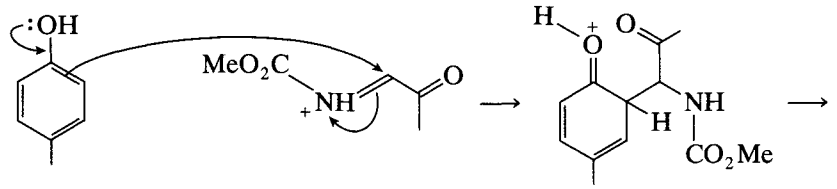


Problem 4.17 *continued*

The intermediate, **4-82**, can decompose to give a new electrophile, with which the nucleophilic phenol then reacts.

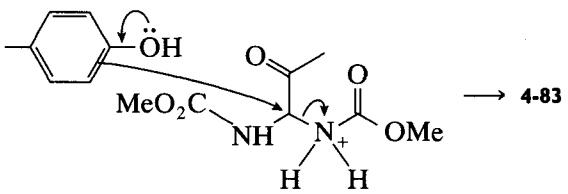


**4-82**



**4-83**

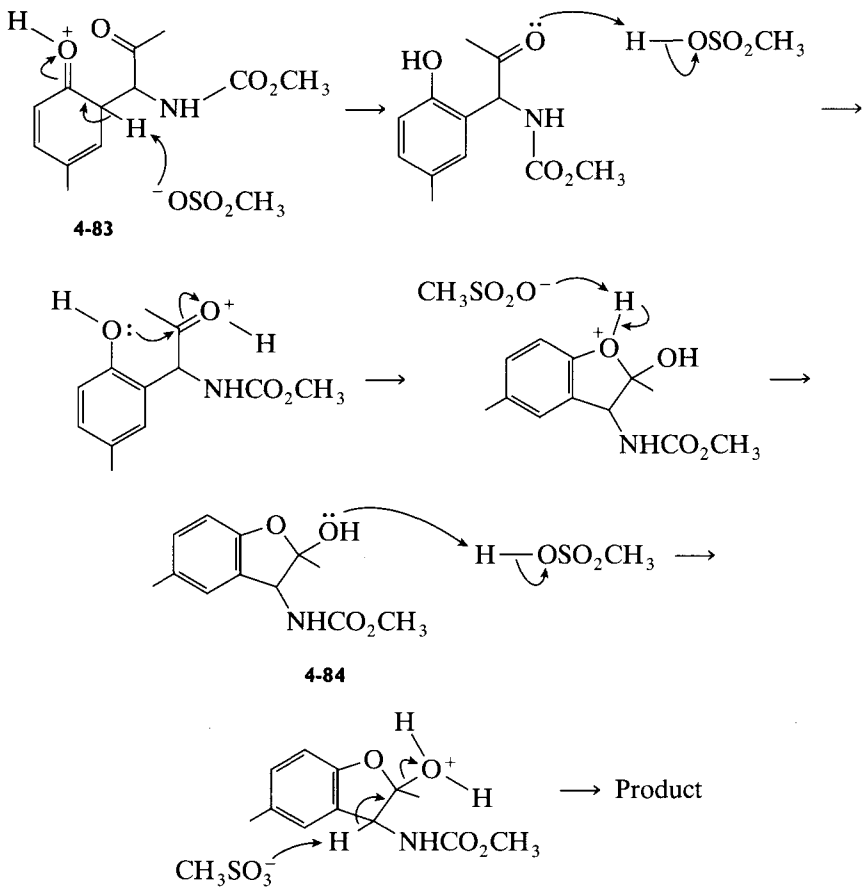
An alternative mechanism to **4-83** might be protonation of one of the nitrogens in the starting material, followed by nucleophilic reaction of the phenol with the carbon bearing the protonated leaving group ($S_N2$ reaction). However, this carbon is quite sterically congested, so that this is not an attractive option.



After aromatization of **4-83** and protonation of the keto carbonyl, cycliza-

Problem 4.17 *continued*

tion can occur:

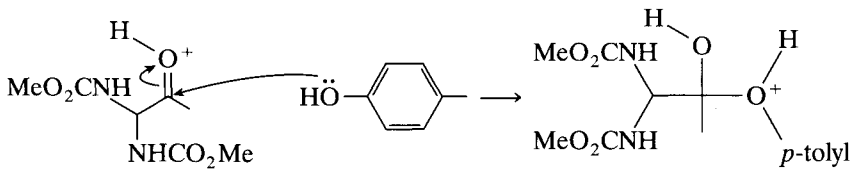


4-83

4-84

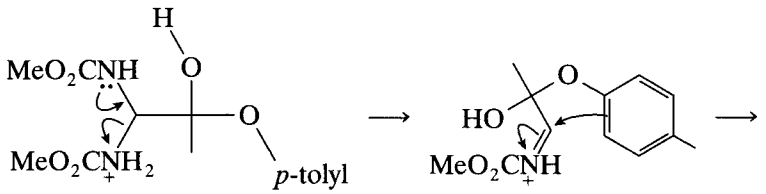
*Mechanism 2*

If the keto group in the starting material were protonated, the phenolic oxygen could react as a nucleophile at the carbonyl carbon.

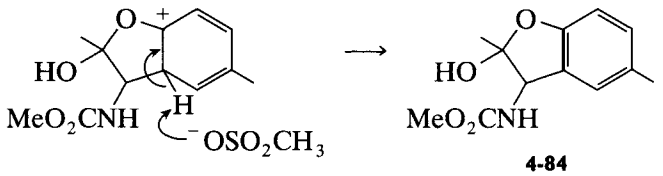


Problem 4.17 *continued*

Following proton loss from the positive oxygen and protonation of one of the amide nitrogens, intermediate **4-85** is formed. This intermediate can lose methyl carbamate to form **4-86**, in which the ring acts as a nucleophile.




**4-85** **4-86**



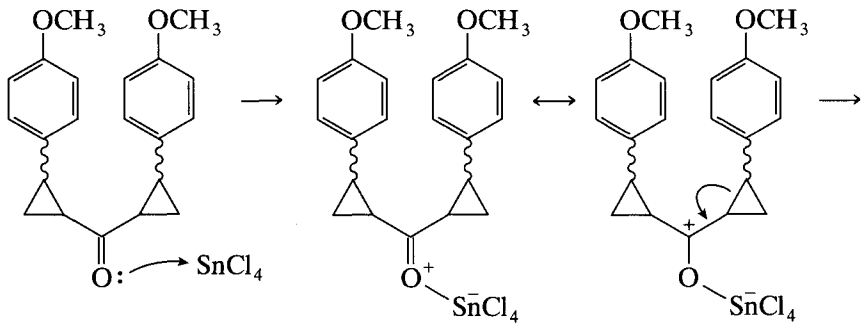

**4-84**

Loss of a proton gives **4-84**, which undergoes dehydration as in mechanism 1.

d. The tin intermediate can be written as either the product of a nucleophilic displacement on tin, or as an expanded orbital on tin, as in **4-87**.

***Mechanism 1***

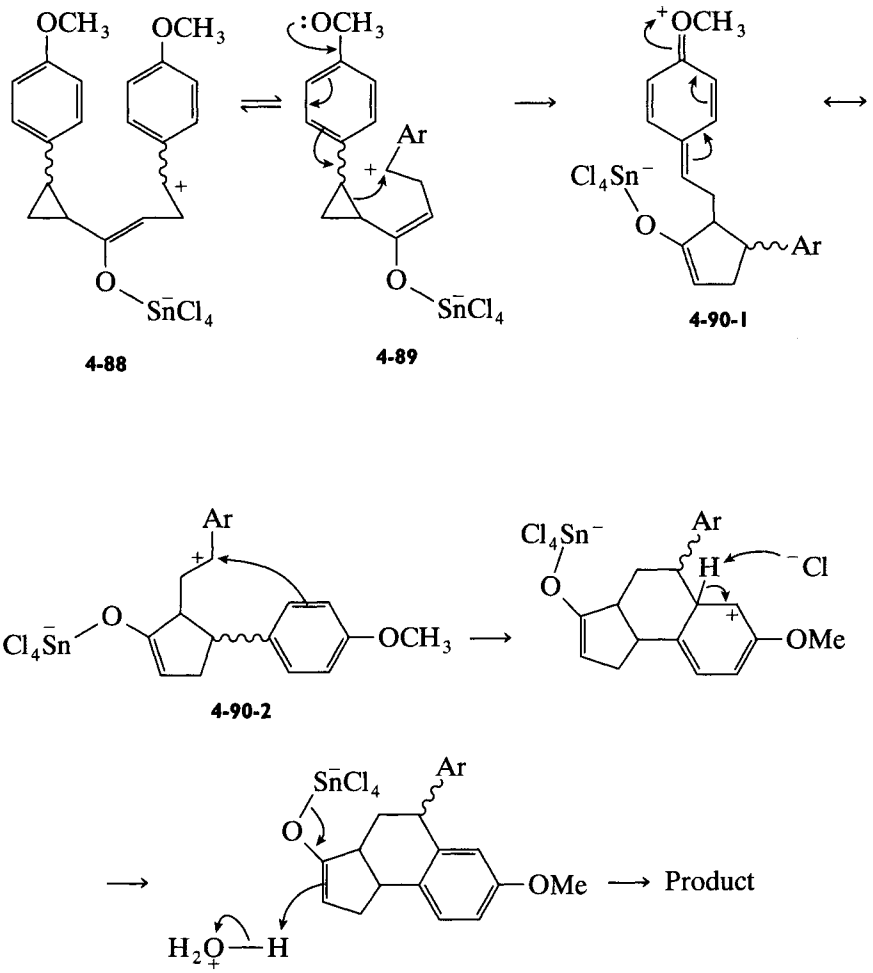
Ring opening occurs readily in the cyclopropyl-substituted cation, **4-87**, to give **4-88**. The driving forces are release of the strain energy of the three-membered ring and stabilization of the resulting cation by the *p*-methoxyphenyl group.




**4-87**

Problem 4.17 *continued*

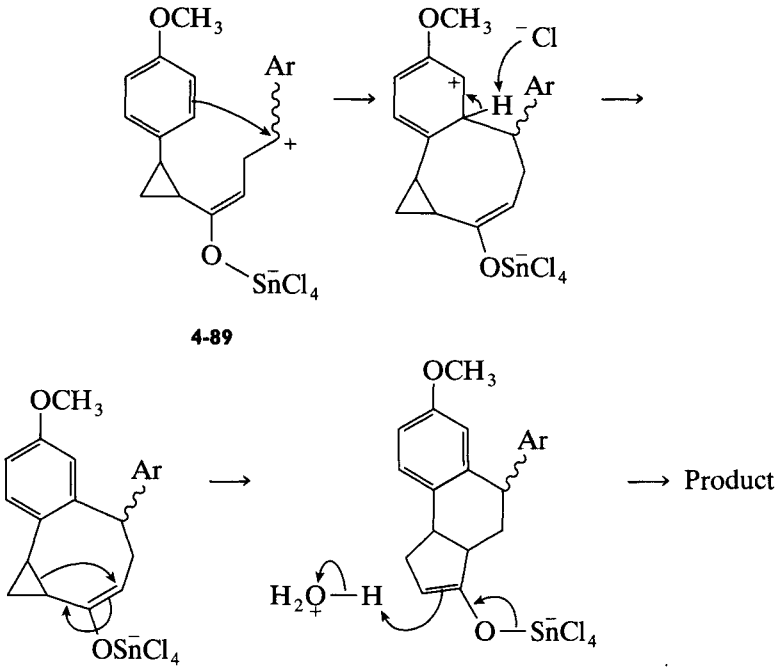
Intermediate **4-88** must equilibrate with the *cis* isomer, **4-89**, which undergoes further ring opening and cyclization to **4-90**, with the same driving forces as the reaction of **4-87** to give **4-88** (Ar = aryl).



Problem 4.17
*continued*

***Mechanism 2***

An alternative mechanism involves formation of an eight-membered-ring intermediate from **4-89**:




**4-89**

Formation of the eight-membered ring is entropically less favorable than mechanism 1. Another advantage of mechanism 1 is that the methoxy group participates in resonance stabilization of the positive charge produced when the five-membered ring is formed. Direct participation of the methoxy group is not possible in the intermediates formed in mechanism 2.

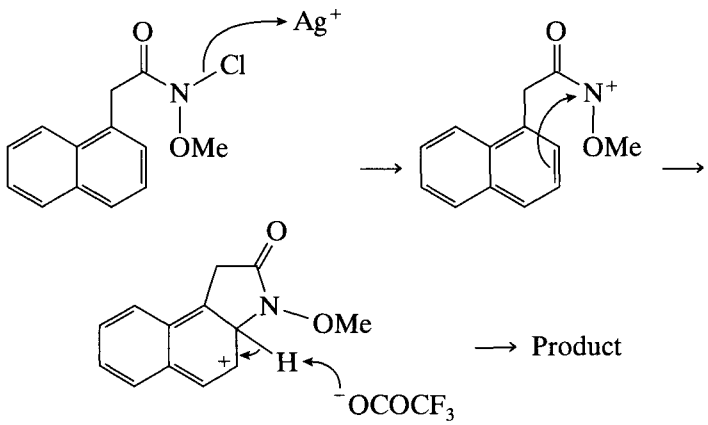
The source of chloride ion, used as a base in these mechanisms, would be the following equilibrium:

$$ROSnCl_4 \rightleftharpoons ROSnCl_3 + Cl^-$$

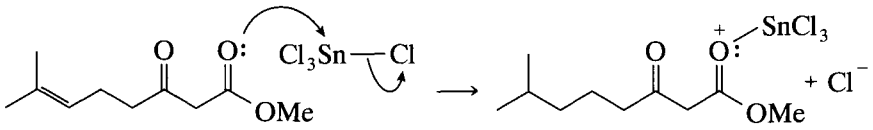
Nitromethane is the sole solvent for the reaction.

Problem 4.17 *continued*

e. Silver ion coordinates with the chlorine and increases its ability to act as a leaving group. After the positive center (a nitrenium ion) has been created, an intramolecular electrophilic aromatic substitution takes place.

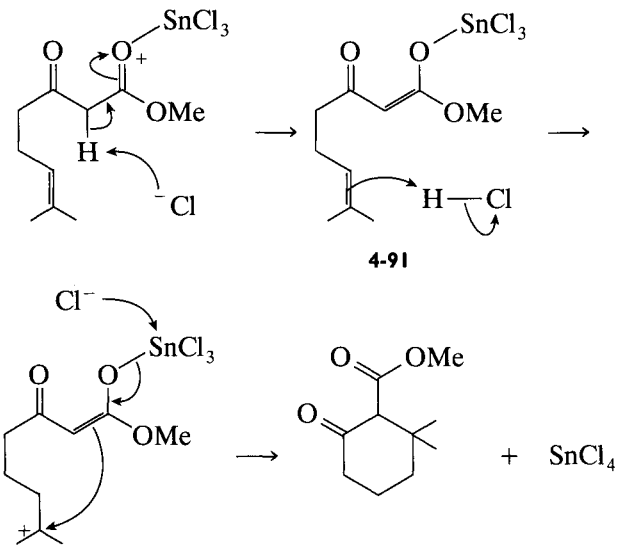



f. The nucleophilic ester carbonyl oxygen reacts with the electrophilic tin(IV) chloride. Loss of a proton from the intermediate formed initially gives **4-91**.



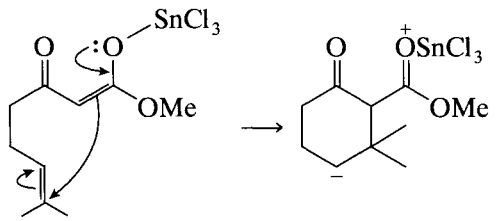

The HCl that is produced can add in a regiospecific manner to the isolated double bond, giving a tertiary carbocation. An intramolecular nucleophilic reaction with this cation generates the product.

Problem 4.17
*continued*




4-91

The following would *not* be a good mechanistic step because the anion that is generated is so unstable. Also, we would not expect such a strong base to be formed in a strongly acidic medium.




4-91

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