Reactions of Nucleophiles and Bases

I. NUCLEOPHILIC SUBSTITUTION

The classification within this section is based on the structural (rather than the mechanistic) relationship between the starting materials and products. Mechanistically, all of the reactions considered in this section involve nucleophilic substitution as the first step, *except for* aromatic substitution via the aryne mechanism, which involves elimination followed by nucleophilic addition.

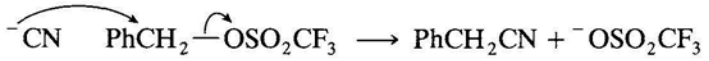
A. The S_N2 Reaction

The S_N2 reaction is a concerted bimolecular nucleophilic substitution at carbon. It involves an electrophilic carbon, a leaving group, and a nucleophile. The partial positive charge on the electrophilic carbon is due to the electron-withdrawing effect of the electronegative leaving group. This partial positive charge can be augmented by the presence of other electron-withdrawing groups attached to the electrophilic carbon, and the presence of such groups enhances reaction at the electrophilic center. For example, α-halocarbonyl groups react much faster than simple alkyl halides

The S_N2 reaction occurs only at sp^3-hybridized carbons. The relative reactivities of carbons in the S_N2 reaction are $CH_3 > 1° > 2° \gg 3°$, due to steric effects. Methyl, 1° carbons, and 1° and 2° carbons that also are allylic, benzylic, or α to a carbonyl group are especially reactive.

Example 3.1. ***The S_N2 reaction: A concerted process.***

The electrons of the nucleophile interact with carbon at the same time that the leaving group takes both of the electrons in the bond between carbon and the leaving group. This particular example involves both a good leaving group and a good nucleophile.



Leaving Groups

Usually, the less basic the substituent, the more easily it will act as a leaving group. This is because both basicity and leaving group ability are related to the stability of the anion involved. Frequently, these are both related to charge dispersal in the anion, with greater charge dispersal being associated with greater stability of the ion. In looking at Table 3.1, we see that the best leaving groups are those for which resonance, inductive effects, or size results in distribution of any negative charge.

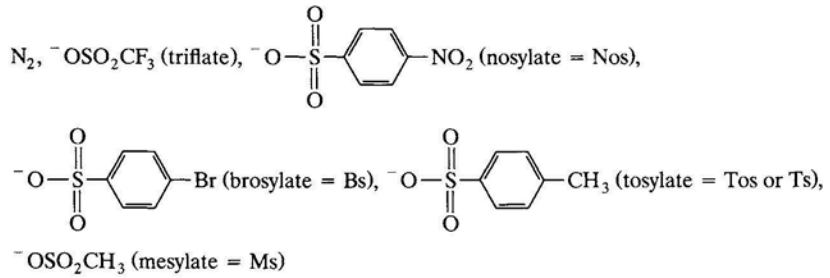
Relative leaving group abilities also depend upon the solvent and the nature of the nucleophile. For example, negatively charged leaving groups will be stabilized by interactions with protic solvents, so that protic solvents will increase the rate of bond breaking for these groups. Although these effects are important in modifying reaction conditions and yields, they rarely are large enough to completely change the mechanism by which a reaction proceeds, and we will not consider them here in detail.

Hydride (H^-) rarely acts as a leaving group. Exceptions are the Cannizzaro reaction and hydride abstraction by carbocations. ***Hint 3.1***

The S_N2 reaction rarely occurs with poor leaving groups. However, in other reactions, such as the nucleophilic substitution of carboxylic acid

TABLE 3.1 Leaving Group Abilities

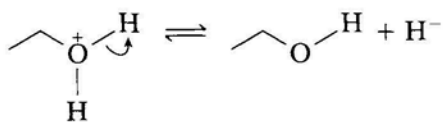
Excellent



Good	Fair
I^-, Br^-, Cl^-, SR_2	OH_2, NH_3, $^-OCOCH_3$ (acetate = OAc)
Poor	**Very Poor**
F^-, ^-OH, ^-OR	$^-NH_2$, ^-NHR, $^-NR_2$, R^-, H^-, Ar^-

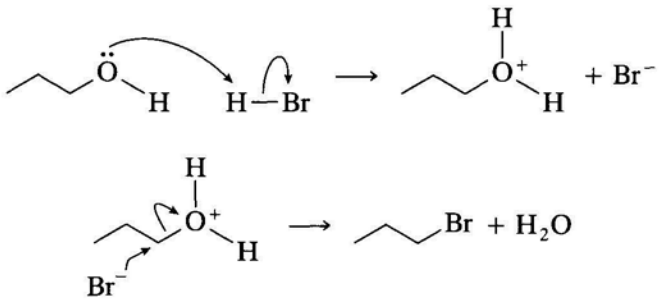
derivatives (see Sections 1.B and 3), reactions with a poor leaving group like OH^- or RNH^- are encountered more frequently. Hydroxide may act as a leaving group, but only when there is considerable driving force for the reaction, as in certain elimination reactions where the double bond formed is stabilized by resonance (see Ex. 3.10).

PROBLEM 3.1 **Explain why the following mechanistic step in the equilibrium between a protonated and an unprotonated alcohol is a poor one.**

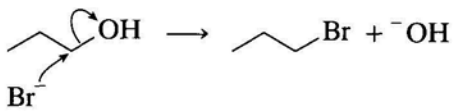


Example 3.2. ***The S_N2 reaction of an alcohol requires prior protonation.***

The alcohol oxygen is protonated before substitution takes place. Thus, the leaving group is a water molecule, a fair leaving group, rather than the hydroxide ion, a poor leaving group.



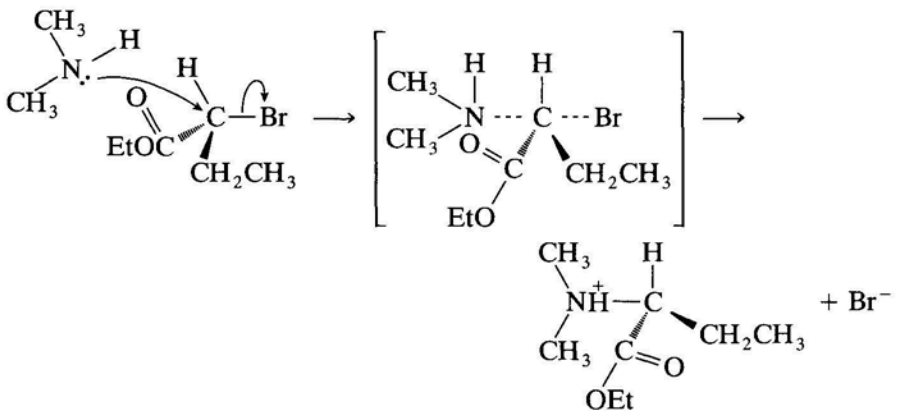
A poorer mechanistic option would show hydroxide as the leaving group:



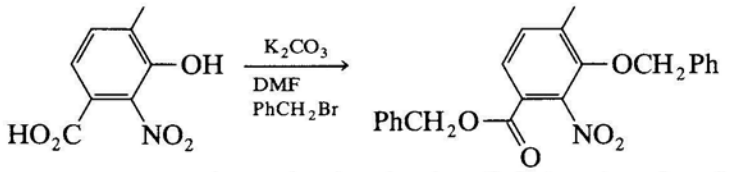
Stereochemistry

The S_N2 reaction always produces 100% inversion of configuration at the electrophilic carbon. Thus, as shown in Example 3.3, the nucleophile approaches the electrophilic carbon on the side opposite the leaving group (there is a 180° angle between the line of approach of the nucleophile and the bond to the leaving group).

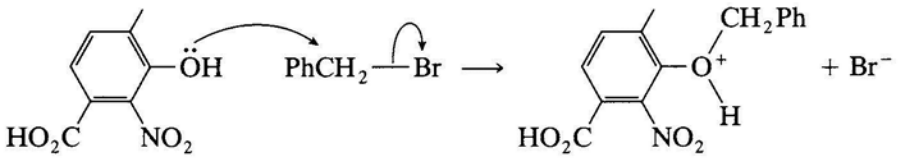
Example 3.3. ***Stereochemistry of the S_N2 reaction.***



PROBLEM 3.2 **Consider the following synthesis, which involves alkylation of the phenolic oxygen (attachment of the benzyl group onto the oxygen).**

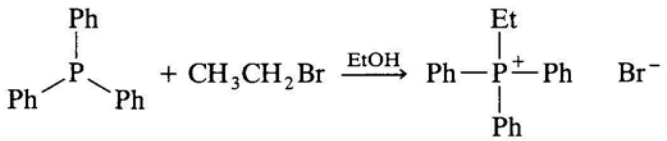


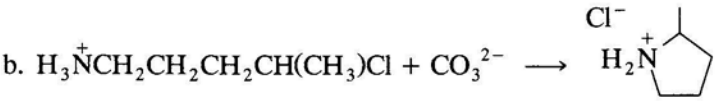
Propose a more reasonable mechanism for the alkylation than that shown in the following step. Formation of the product would involve deprotonation of the positively charged oxygen.

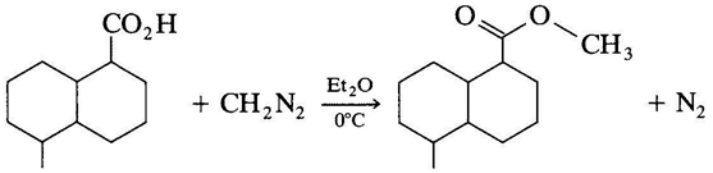


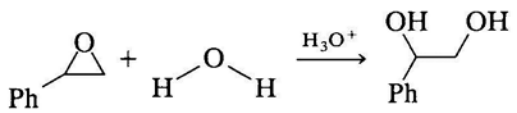
Pena, M. R.; Stille, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 5417–5424.

PROBLEM 3.3 **Pick out the electrophile, nucleophile, and leaving group in each of the following reactions and write a mechanism for the formation of products.**

a. 

b. 

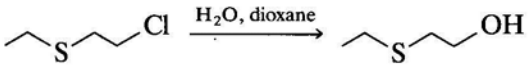
c. 

d. 

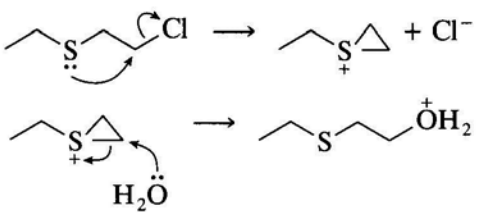
Neighboring Group Participation

On occasion, a molecule undergoing nucleophilic substitution may contain a nucleophilic group that participates in the reaction. This is known as the *neighboring group effect* and usually is revealed by *retention of stereochemistry* in the nucleophilic substitution reaction or by an *increase in the rate* of the reaction.

Example 3.4. ***Neighboring group participation in the hydrolysis of ethyl 2-chloroethyl sulfide.***

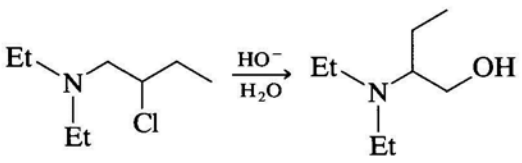


The hydrolysis of the chlorosulfide proceeds to give the expected product. However, the reaction is 10,000 times faster than the reaction of the corresponding ether, $ClCH_2CH_2OCH_2CH_3$. This rate enhancement has been credited to the ready formation of a cyclic sulfonium ion due to intramolecular displacement of chloride by sulfur, followed by rapid nucleophilic reaction of water with the intermediate sulfonium ion.

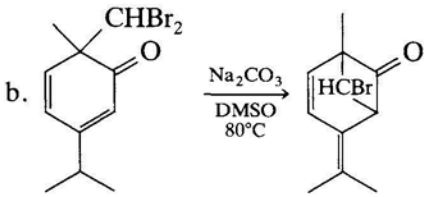


Other groups that exhibit this behavior include thiol, sulfide, alkoxy (RO^-), ester, halogen, and phenyl.

Write step-by-step mechanisms for the following transformations: **PROBLEM 3.4**

a. 

PROBLEM 3.4
continued

b. 

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

B. Nucleophilic Substitution at Aliphatic sp^2 Carbon (Carbonyl Groups)

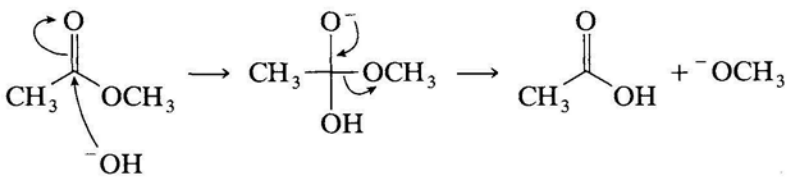
The familiar substitution reactions of derivatives of carboxylic acids with basic reagents illustrate nucleophilic substitution at aliphatic sp^2 carbons.

The mechanisms of these reactions

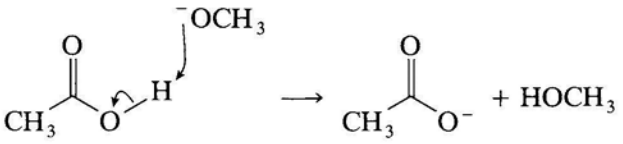
involve two steps: (1) addition of the nucleophile to the carbonyl group and (2) elimination of some other group attached to that carbon. Common examples include the basic hydrolysis and aminolysis of acid chlorides, anhydrides, esters, and amides.

Example 3.5. ***Mechanism for hydrolysis of an ester in base.***

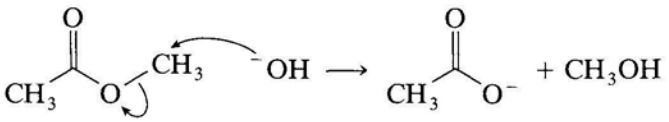
Unlike the one-step S_N2 reaction, the hydrolysis of esters in base is a two-step process. The net result is substitution, but the first step is nucleophilic addition to the carbonyl group, during which the carbonyl carbon becomes sp^3-hybridized. The second step is an elimination, in which the carbonyl group is regenerated as the carbon rehybridizes to sp^2.



This is followed by removal of a proton from the acid, by the methoxide ion, to yield methanol and the carboxylate ion:



Another possible mechanism for this hydrolysis is an S_N2 reaction at the alkyl carbon of the ester:



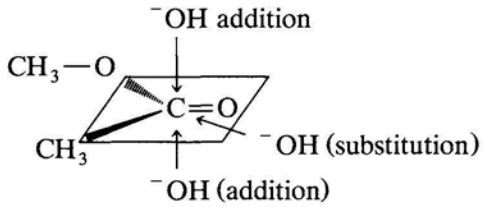
This single-step mechanism appears reasonable, because carboxylate is a fair leaving group and hydroxide is a very good nucleophile. However, labeling studies rule out this mechanism under common reaction conditions. The two-step mechanism must be favored because the higher mobility of the π electrons of the carbonyl group makes the carbonyl carbon especially electrophilic.

Hint 3.2

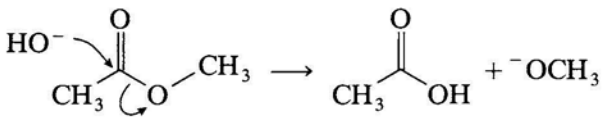
Direct nucleophilic substitution at an sp^2-hybridized center is not likely under common reaction conditions. Thus, nucleophilic substitution reactions at such centers usually are broken into two steps. (For exceptions to this hint, see Dietze, P.; Jencks, W. P. *J. Am. Chem. Soc.* **1989,** *111*, 5880–5886, and references cited therein.

There are several reasons why direct substitutions occur at sp^2-hybridized centers less readily than at sp^3 centers. First, because there is more *s* character in the bond to the leaving group, this bond is stronger than the

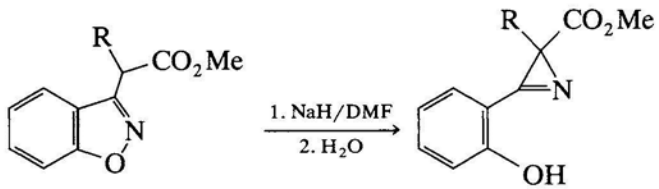
corresponding bond to an sp^3-hybridized carbon. Second, the greater mobility of the π electrons at an sp^2 center increases the likelihood that the interaction will cause electron displacement. Third, because of the planar configuration of the substituents around an sp^2 center, there is strong steric interference to the approach of a nucleophile to the side opposite the leaving group. On the other hand, in the addition of a nucleophile to the carbonyl group, the nucleophile approaches perpendicular to the plane of the sp^2 orbitals so that there is maximum overlap with the π electron system. This means that the relatively unhindered addition step occurs in preference to direct substitution.

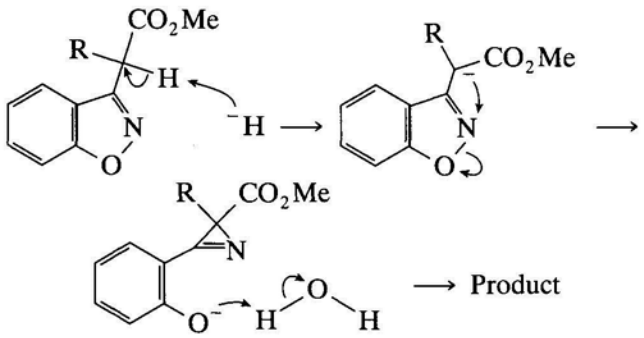


Thus, the mechanism for basic hydrolysis of an ester would *not be written* as follows:



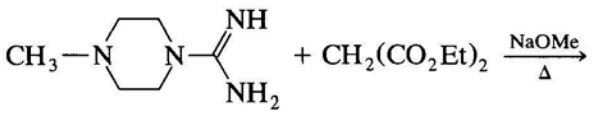
PROBLEM 3.5 **Consider the mechanism shown for the following transformation. Propose a more reasonable alternative.**

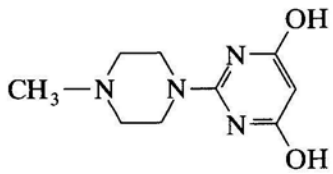




PROBLEM 3.6 **Write step-by-step mechanisms for the following transformations:**

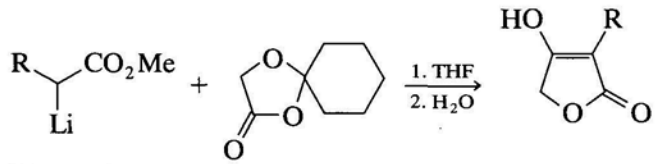
a.





Gueremy, C.; Audiau, F.; Renault, C.; Benavides, J.; Uzan, A.; Le Fur, *J. Med. Chem.* **1986**, *29*, 1394–1398.

b.

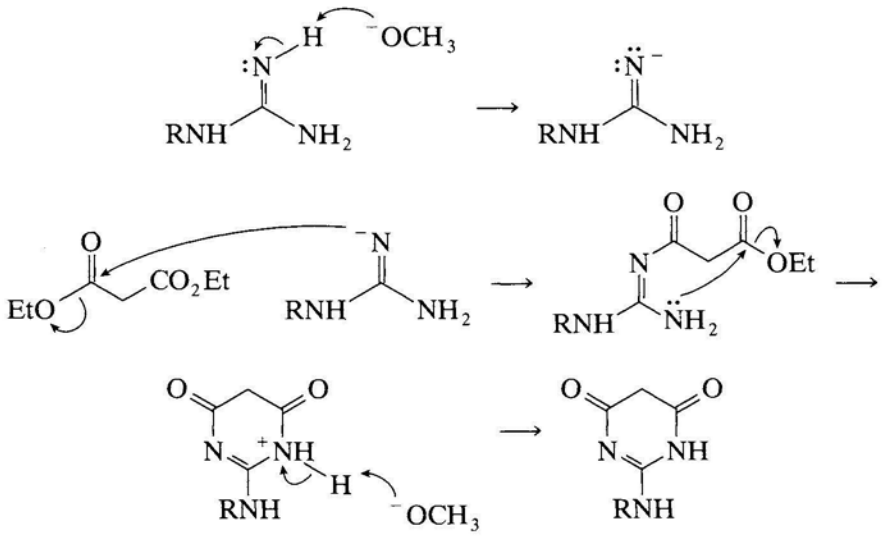


Ramage, R.; Griffiths, G. J.; Shutt, F. E.; Sweeney, J. N. A. *J. Chem. Soc., Perkin Trans. I* **1984**, 1539–1545.

c. Critically evaluate the following partial mechanism for the reaction

PROBLEM 3.6 *continued*

given in part a:



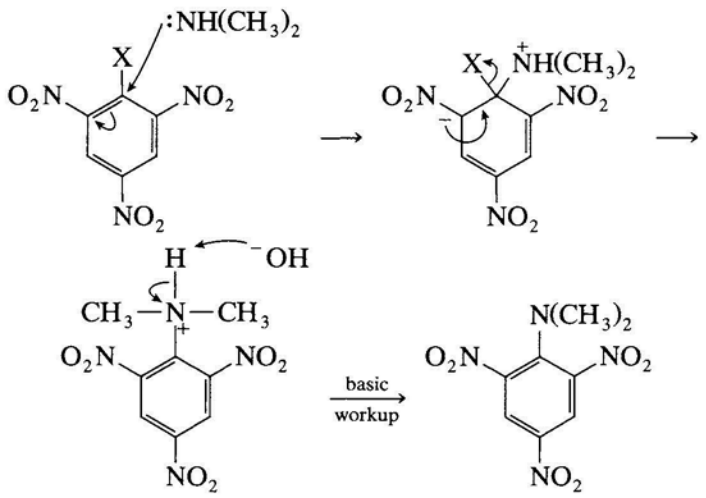
C. Nucleophilic Substitution at Aromatic Carbons

There are two mechanisms for nucleophilic aromatic substitution. Both occur in two important steps. In one mechanism, an addition is followed by an elimination. In the other mechanism, an elimination is followed by an addition.

Addition – Elimination Mechanism

The addition–elimination mechanism generally requires a ring activated by electron-withdrawing groups. These groups are especially effective at stabilizing the negative charge in the ring when they are located at positions *ortho* and/or *para* to the eventual leaving group.

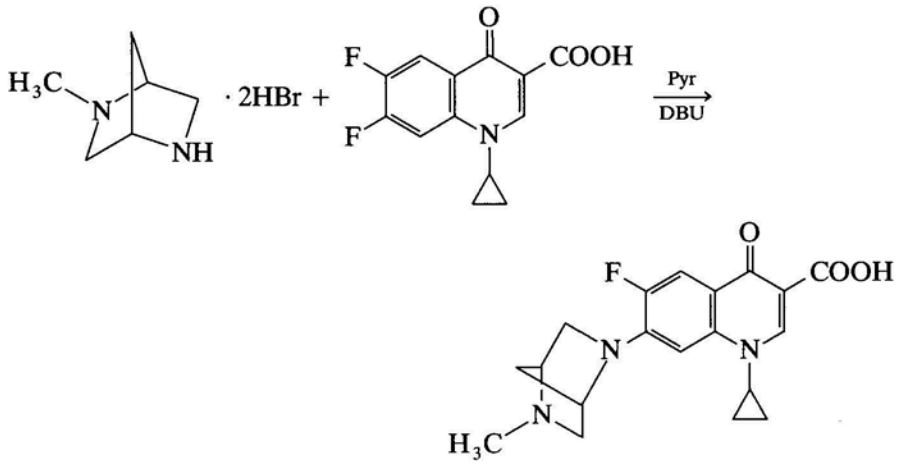
Example 3.6. ***Relative reactivity in the addition–elimination mechanism.***



When X = halogen, the observed relative reactivities of the starting materials are F > Cl > Br > I. This indicates that the first step is rate-determining because the greater the electron-withdrawing power of the halogen (see Table 1.2), the more it increases the electrophilicity of the aromatic ring, making it more reactive to nucleophiles. If the second step were rate-determining, the relative reactivities would be reversed, because the relative abilities of the leaving groups are $I^- > Br^- > Cl^- > F^-$.

By drawing the appropriate resonance forms, show that the negative charge in the intermediate anion in Example 3.6 is stabilized by extensive electron delocalization. **PROBLEM 3.7**

PROBLEM 3.8 **Write a step-by-step mechanism for the following transformation:**

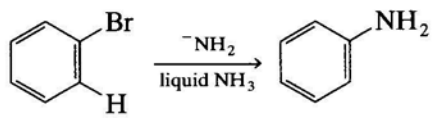


Braish, T. F.; Fox, D. E. *J. Org. Chem.* **1990**, *55*, 1684–1687. [This is the last step in the synthesis of danofloxicin, an antibacterial. Pyr (or Py) is a common acronym for pyridine; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene. A good reference for the translation of acronyms is Daub, G. H.; Leon, A. A.; Silverman, I. R.; Daub, G. W.; Walker, S. B. *Aldrichim. Acta* **1984**, *17*, 13–23.]

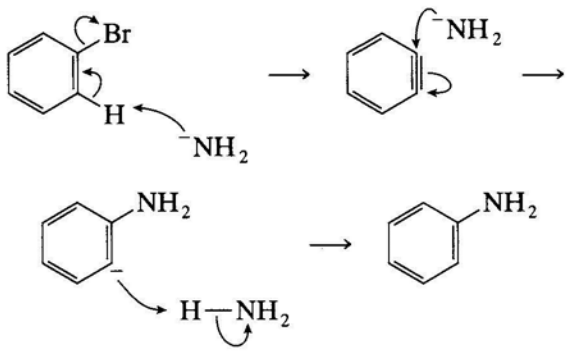
Elimination – Addition (Aryne) Mechanism

In reactions that proceed by the elimination–addition mechanism (often called the aryne mechanism), the bases used commonly are stronger than those used in reactions proceeding by the addition–elimination mechanism. Also, in this reaction, the aromatic ring does *not* need to be activated by electron-withdrawing substituents, although a reasonable leaving group (usually a halide) must be present.

Example 3.7. ***An elimination–addition mechanism—aryne intermediate.***



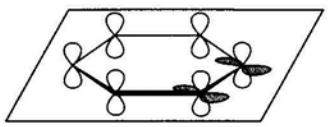
The following mechanism can be written for this reaction:



The intermediate with a triple bond is called benzyne. For substituted aromatic compounds, this type of intermediate is called an aryne. In benzyne, the ends of the triple bond are equivalent, and either can react with a nucleophile.

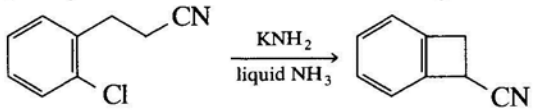
The triple bond in an aryne is not a normal triple bond. The six-membered ring does not allow the normal linear configuration of two *sp*-hybridized carbon atoms and their substituents. Thus, the carbons remain sp^2-hybridized, and the triple bond contains the σ bond, the π bond, and a third bond formed by overlap of the sp^2-hybridized orbitals that formerly bonded with the bromine and hydrogen atoms. This third bond is in the plane of the benzene ring and contains two electrons.

The rate-determining step can be either proton removal or departure of the leaving group, depending on the acidity of the proton and the ability of the leaving group. In many cases, the relative rates are so close that the reaction cannot be distinguished from a concerted process.



PROBLEM 3.9 **Assume that in Example 3.7, the carbon bound to the bromine in bromobenzene is labeled by enrichment with ^{13}C. Where would this label be found in the product aniline?**

PROBLEM 3.10 **Write a step-by-step mechanism for the following transformation:**



Bunnett, J. F.; Skorcz, J. A. *J. Org. Chem.* **1962**, *27*, 3836–3843.

2. ELIMINATIONS AT SATURATED CARBON

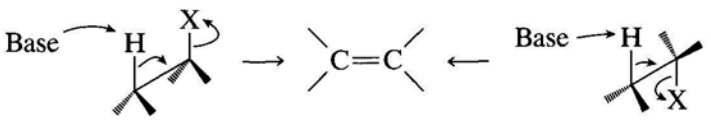
Important eliminations at saturated carbon are the E2 (bimolecular elimination) and Ei (intramolecular elimination) processes.

A. E2 Elimination

The E2 reaction is a concerted process, with a bimolecular rate-determining step. In this case, "concerted" means that bonding of the base with a proton, formation of a double bond, and departure of the leaving group all occur in one step.

Stereochemistry

The stereochemistry is usually *anti*, but in some cases is *syn*. The term *anti* means that the proton and leaving group depart from opposite sides of the bond, which then becomes a double bond. That is, the dihedral angle (measured at this bond) between their planes of departure is 180°. If they depart from the same side (the dihedral angle is 0°), the stereochemistry of the elimination is called *syn*.

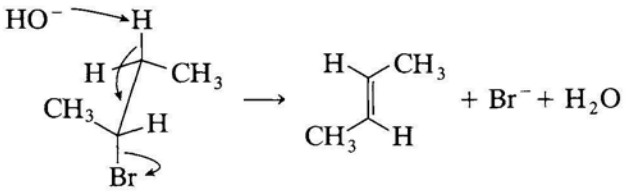


syn elimination
(dihedral angle 0°)

anti elimination
(dihedral angle 180°)

Example *An anti-E2 elimination.*

The dihedral angle between the proton and bromide is 180°, so this is an *anti* elimination.

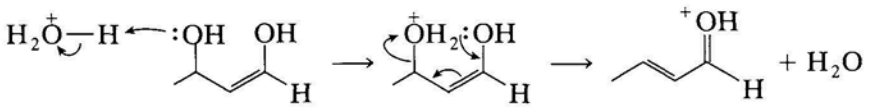


Leaving Groups

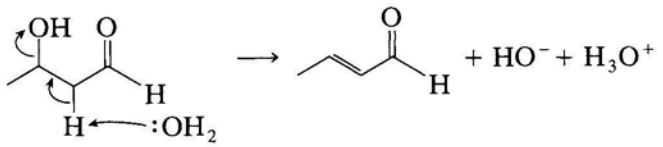
The nature of the leaving group influences whether the reaction proceeds by an E2 mechanism. An excellent leaving group like $CH_3SO_3^-$ (mesylate) will favor competing reactions that proceed through a carbocation. Poor leaving groups, due to their failure to react, will allow competing reactions via anionic mechanisms.

Example 3.9. ***In an acid-catalyzed elimination of water from an alcohol, water is the leaving group.***

The mechanism for an elimination step in the acid-catalyzed aldol condensation is written as follows:

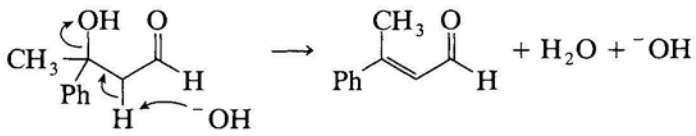


The following step is less likely for the formation of an α,β-unsaturated aldehyde in acid (see Hint 2.5):



Example ***Under some conditions, hydroxide can act as a leaving group.***

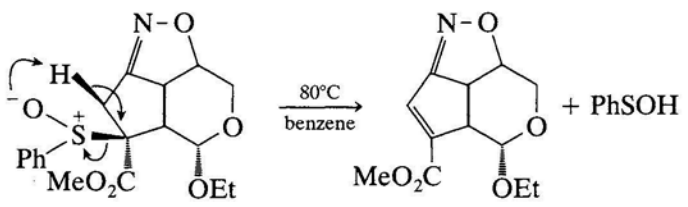
A 3-hydroxyaldehyde (or ketone) will undergo elimination under basic conditions if the double bond being formed is especially stable, e.g., conjugated with an aromatic system. Such eliminations can occur under the reaction conditions of the base-promoted aldol condensation. An example is the formation of 3-phenyl-2-butenal by an E2 elimination from 3-hydroxy-3-phenylbutanal.



B. Ei Elimination

In another type of elimination reaction, called Ei or intramolecular, the base, which removes the proton, is another part of the same molecule. Such eliminations from amine oxides or sulfoxides have five-membered-ring transition states. These transition states are more stable with *syn* than with *anti* orientations of proton and leaving group, producing very high *syn* stereoselectivity.

Example 3.11. ***An Ei reaction: Pyrolytic elimination from a sulfoxide.***



Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280–5282.

Write a mechanism for the following reaction. What is the other product? **PROBLEM**