S_N1 Substitution Reactions

In Chapter 4, S_N2 reactions were defined and presented in the context of the various conditions necessary for such reactions to take place. However, as mentioned in the introductory comments of Chapter 4, there are additional fundamental mechanistic types relevant to organic chemistry that are essential to understand in order to advance in this subject. In this chapter, discussions of organic chemistry reaction mechanisms are advanced to the study of S_N1 reactions. While conditions required for S_N1 reactions to proceed are quite different from those essential for S_N2 reactions, the products of S_N1 reactions, in many cases, resemble those derived from S_N2 mechanisms. Additionally, unlike S_N2 reactions, S_N1 reaction mechanisms allow routes for unwanted or, in some planned cases, preferred side reactions.

5.1 WHAT IS AN S_N1 REACTION?

As discussed in Chapter 4, an S_N2 reaction proceeds with the **S**ubstitution of a leaving group by a **N**ucleophile leading to the S_N designation. Because this mechanism proceeds with the initial approach of two species, it is referred to as a bimolecular reaction. The involvement of **2** species enhances the mechanistic designation to S_N2. Extrapolating from this definition, an S_N1 reaction also proceeds with the **S**ubstitution of a leaving group by a **N**ucleophile leading to the S_N designation. However, unlike S_N2 reactions, S_N1 reactions proceed through initial dissociation of the leaving group from the starting material as shown in Scheme 5.1. This occurs because of differences in reactants and reaction conditions as compared to those relevant to S_N2 processes. Once the leaving group has dissociated, the resulting **carbocation** (a carbon atom possessing a positive charge) is free to react
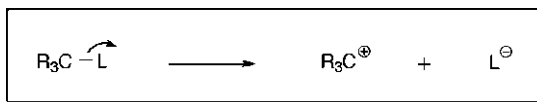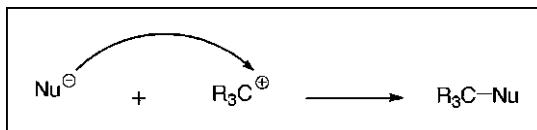
Scheme 5.1 *Initial phase of an S_N1 reaction involves dissociation of a leaving group from the starting molecule, generating a carbocation.*


Scheme 5.2 *Second phase of an S_N1 reaction involves reaction of a carbocation with a nucleophile generating a new product.*

with a nucleophile as shown in Scheme 5.2. Because the initial step in this reaction involves a single molecule dissociating from its leaving group, the initial stage of this process is considered a unimolecular reaction. The involvement of only **1** species in the initial phase of the reaction enhances the mechanistic designation to S_N1.

Because, with S_N1 reactions, a reactive carbocation is formed before incorporation of a nucleophile, other products may form in addition to the simple substituted materials anticipated. These additional products arise from the specific properties of carbocations. The properties of carbocations and their related mechanistic outcomes are presented in the following sections.

5.2 HOW ARE S_N1 REACTIONS INITIATED?

In order for an S_N1 reaction to proceed, initial formation of a carbocation is required. A primary method for the formation of carbocations occurs during solvolysis reactions.
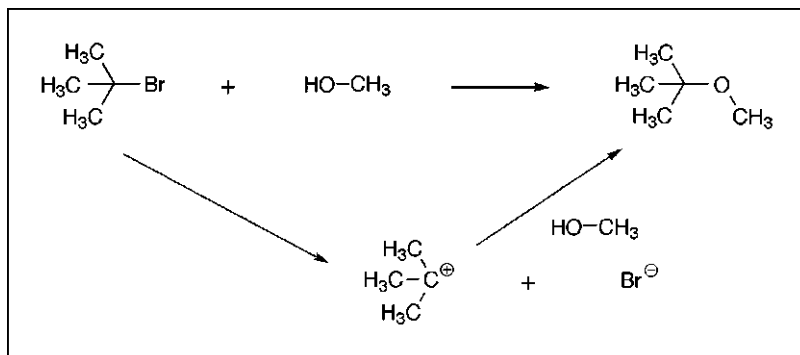
Scheme 5.3 *Solvolysis of tert-butylbromide in methanol produces MTBE via an S_N1 mechanism.*
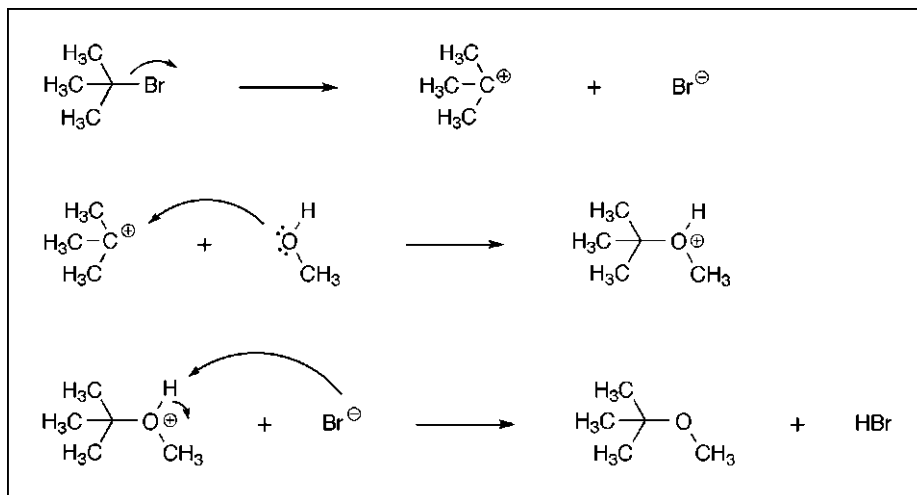
Scheme 5.4 *Explanation of the solvolysis of* tert-*butylbromide in methanol using arrow pushing.*

Solvolysis reactions, illustrated in Scheme 5.3, involve the reaction of an organic molecule with the surrounding solvent. Furthermore, these reactions generally proceed through initial separation of a carbocation from its leaving group followed by reaction of the carbocation with a surrounding solvent molecule forming a new compound. The example shown in Scheme 5.3 illustrates these steps for the reaction of *tert*-butylbromide with methanol, forming methyl *tert*-butylether (MTBE).

As shown in Scheme 5.4, the above-described solvolysis reaction can be explained using arrow pushing. Specifically, initial separation of the bromide leaving group from the *tert*-butyl cation proceeds with electrons residing on the bromide anion. Subsequent reaction of the *tert*-butyl cation with lone pairs of electrons donated by the solvent (methanol) molecules results in the formation of a new carbon–oxygen bond. Dissociation of hydrogen from the resulting oxonium (oxygen cation) ion liberates the product (MTBE) and hydrobromic acid. As a direct reference to the definition of S_N1 reactions, it is important to recognize that the first step (the rate-limiting step) involves only *tert*-butylbromide, thus rendering this step **unimolecular**.

In general, solvolysis reactions occur under circumstances where a molecule possessing an exceptionally good leaving group is dissolved in a polar solvent. Under these conditions, the polarity of the solvent renders formation of the carbocation more favorable by selectively solvating either the carbocation, its accompanying anion, or both. Once the carbocation is separated from its anion, it may undergo typical S_N1 reactions as discussed in the following paragraphs. Additionally, as shown in Scheme 5.5, the reaction illustrated
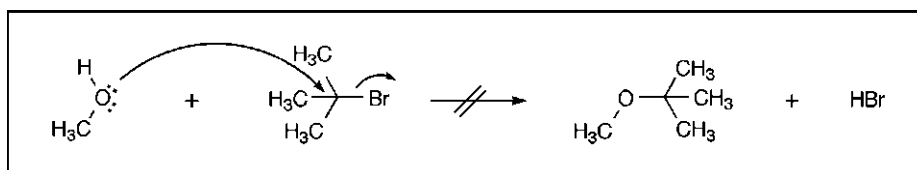
Scheme 5.5 *Methanol will not react with* tert-*butylbromide via an* S_N2 *mechanism.*

in Scheme 5.4 will not proceed by an S_N2 mechanism because of the steric bulk of the start-ing *tert*-butylbromide. Additional discussions surrounding the influence of steric factors are presented in Chapters 3 and 4.

5.3   THE CARBOCATION

As defined in the previous sections of this chapter, carbocations are positively charged carbon ions. However, simply defining this unique species of cations without exploring its associated properties does little to promote understanding of S_N1 reactions and the related side reactions observed for this mechanistic type. Therefore, this section focuses on the nature, stability, and reactivity of carbocations as explained using arrow pushing. While the alluded to side reactions include both **elimination** reactions and **rearrange-ments**, only rearrangements are presented in this chapter. Discussions focused on elimin-ations are found beginning in Chapter 6.

### 5.3.1   Molecular Structure and Orbitals

Before delving into more details regarding the reactive nature and stability of carbocations, it is important to understand the structure of these species. Recall that S_N2 reactions occur at carbon atoms bearing four substituents. Furthermore, recall that electrophilic carbon centers participating in S_N2 reactions are tetrahedral in geometry with all bond angles measuring approximately $109.5°$ – the tetrahedral bond angle. This equal spacing, illustrated in Figure 5.1, is only possible if the natures of all four bonds connecting the central carbon atom to its four substituents are identical.

Since an understanding of **orbital** theory is critical to understanding organic reaction mechanisms, *review of the material presented in primary organic chemistry textbooks is essential*. For the purposes of the discussions presented herein, recall that ground-state first-row elements (including C, N, and O) all possess one *s* **orbital** and three *p* **orbitals**. Figure 5.2 illustrates the shapes of *s* and *p* orbitals.

If we consider methane (CH_4), we find that not only does the central carbon atom possess four hydrogen substituents, these four hydrogens are equally spaced in a tetrahedral
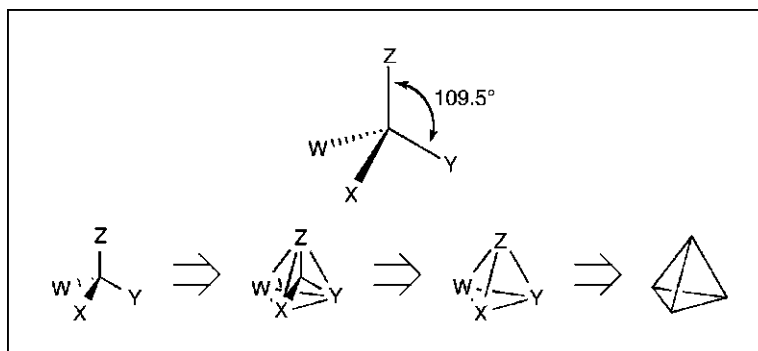
Figure 5.1   *Fully substituted carbon atoms present substituents in tetrahedral arrangements.*
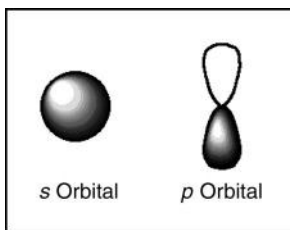
Figure 5.2 *s orbitals are spherical and p orbitals are shaped like hourglasses.*

arrangement with equal bond lengths. As *s* **orbitals** and *p* **orbitals** are spatially different, this level of structural equality cannot be explained through bonding with one *s* orbital and three *p* orbitals. Instead, this equality is explained by combining the single *s* orbital with the three *p* orbitals forming four equal sp^3 **hybrid orbitals**. Figure 5.3 illustrates the various hybrid orbitals involved in most chemical bonds found in organic chemistry.

Expanding upon Figure 5.3, an *sp* **hybrid orbital** is made up of one part *s* orbital and one part *p* orbital. Furthermore, an sp^2 **hybrid orbital** is made up of one part *s* orbital and two parts *p* orbital. Finally, an sp^3 **hybrid orbital** is made up of one part *s* orbital and three parts *p* orbital. In cases such as *sp* and sp^2 hybridization where only a subset of the three *p* orbitals are used in forming hybrid orbitals, the unhybridized *p* orbitals are utilized in the formation of double and triple bonds.

While the present discussions focus on **orbital hybridization** relative to bonds between atoms, it is important to recognize that nonbonding electron pairs (lone pairs) also participate in orbital hybridization. Thus, as illustrated in Figure 5.4 and relating to sp^3-hybridized centers, for the purposes of determining orbital hybridization, lone pairs can be treated as bonds between a central atom and nothing.

As alluded to in Figure 5.3, sp^3 hybridization occurs when a central atom possesses a total of four substituents comprised of any combination of atoms and lone pairs.

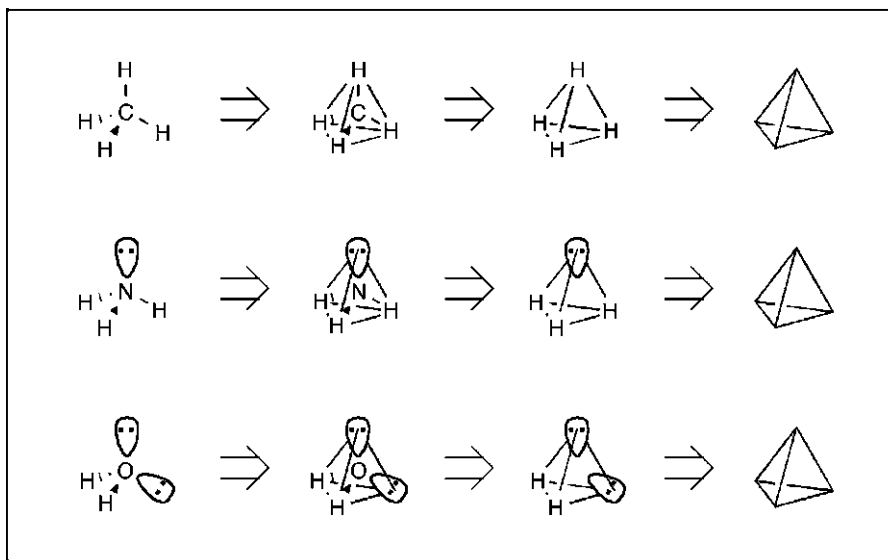**Figure 5.3** *Hybrid orbitals result from combinations of s and p orbitals.*

Figure 5.4   *Like substituents, lone pairs influence molecular geometry.*

Furthermore, sp^2 hybridization occurs when a central atom possesses a total of three substituents comprised of any combination of atoms and lone pairs. Finally, sp hybridization occurs when a central atom possesses a total of two substituents comprised of any combination of atoms and lone pairs. While thus far attention has been focused on the tetrahedral nature of sp^3-hybridized atoms, exploring the geometric consequences of sp^2 and sp-hybridized atoms reveals very different spatial relationships between substituents. Specifically, as shown in Figure 5.5, the three substituents of an sp^2-hybridized atom adopt a **trigonal planar** relationship with bond angles of $120°$ and all substituents residing in the same plane. Furthermore, the two substituents of an sp-hybridized atom adopt a **linear** relationship with bond angles of $180°$.

Having addressed the geometric consequences of orbital hybridization, the above discussions can now be related to carbocations. Recalling the rules relating the number of substituents to specific orbital hybrids, we recognize that a carbocation possesses a maximum of three substituents and is thus rendered as no more than sp^2 hybridized. Furthermore, the carbocation positive charge resides in an unoccupied p orbital. The trigonal planar structure of an sp^2-hybridized carbocation is illustrated in Figure 5.6 and enhanced with the placement of a p orbital at the cationic center.

Having established the three-dimentional structure of carbocations as planar, we can now study the **stereochemical progression** of S_N1 reactions as compared to S_N2 reactions. As shown in Scheme 5.6, the stereochemical course of an S_N2 reaction is well defined because **nucleophilic displacement** of a leaving group proceeds with inversion of stereochemistry. Thus, the stereochemical outcome is defined by the stereochemistry of the starting material. As for S_N1 reactions, since the step required for initiation of these reactions involves formation of a planar species, incoming nucleophiles have equal access to both sides of the reactive carbocation. As shown in Scheme 5.7, this results in complete elimination of
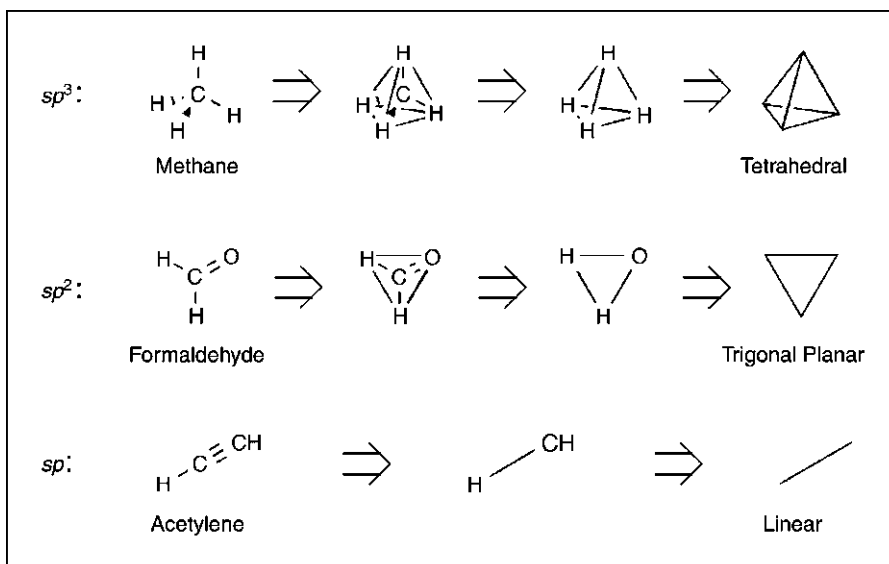
Figure 5.5 *Different orbital hybridizations result in different molecular geometries.*
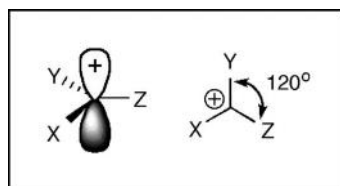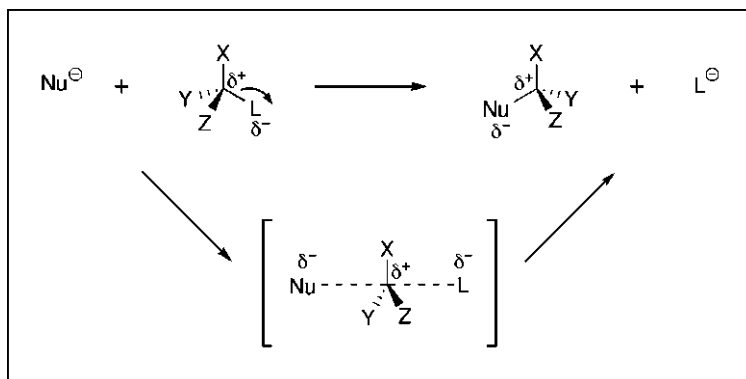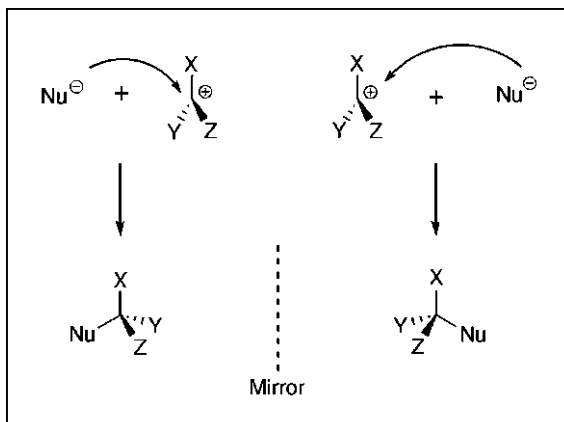

Figure 5.6 *sp²-hybridized carbocations possess trigonal planar geometries.*

Scheme 5.6 *Stereochemical courses of S_N2 reactions are defined by the stereochemical configuration of the starting materials. One product is formed.*

Scheme 5.7 *Stereochemical identities of starting materials subjected to S_N1 reactions are lost due to the planarity of reactive carbocations. Two products are formed.*

stereochemical control over these reactions. Thus, where S_N2 reactions on **stereochemically pure** starting materials proceed with generation of a single stereoisomer, S_N1 reactions proceed with complete loss of **stereochemical identity** even when the starting material is stereochemically pure. Specifically, an S_N2 reaction on a chiral starting material yields **one chiral product**, and an S_N1 reaction on a chiral starting material yields a **racemic mixture** of two stereoisomers.

5.3.2 Stability of Carbocations

As alluded to at the beginning of this section, carbocations generated during S_N1 mechanisms are subject to **side reactions** that include eliminations and rearrangements. Considering the possibility of these side reactions, one must question the *stability* of carbocationic species. To clarify, if carbocations were inherently stable, they would not be readily subject to additional transformations. Having already addressed the structure of carbocations, attention can now be focused on the factors influencing stability.

In studying carbocations, it is important to recognize that **tertiary carbocations** are more stable than **secondary carbocations**. Furthermore, secondary carbocations are more stable than **primary carbocations**. This relationship, shown in Figure 5.7, results from an effect known as **hyperconjugation**. Specifically, hyperconjugation, illustrated in
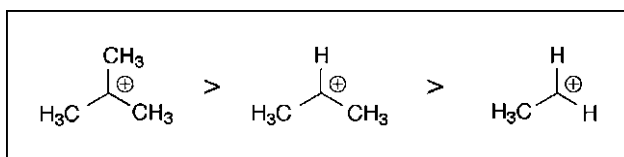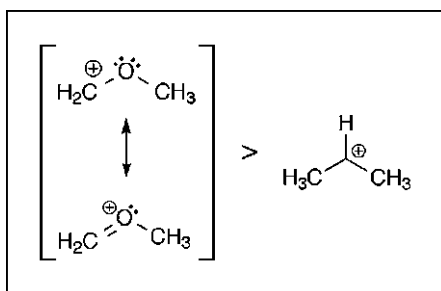

Figure 5.7 *Tertiary carbocations are more stable than secondary carbocations, and secondary carbocations are more stable than primary carbocations.*
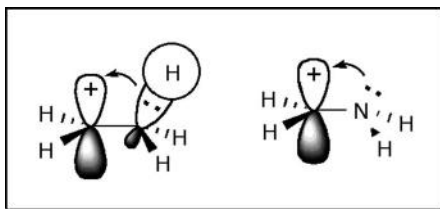
Figure 5.8 *Hydrogen atom s orbitals can donate electron density to adjacent cationic centers as can heteroatoms bearing lone electron pairs.*


Figure 5.9 *Heteroatoms stabilize carbocations better than hyperconjugation effects.*

Figure 5.8, defines the ability of a hydrogen atom to donate electron density from its *s* orbital to sites of neighboring electron deficiency. This effect is similar to the stabilization of carbocations bearing heteroatoms with lone electron pairs. Thus, the greater number of carbon–hydrogen bonds located adjacent to a positive charge, the greater the stability of the cation.

As hyperconjugation can be related to **cationic stabilization** by neighboring lone pairs, relationships between these types of effects must be noted. As shown in Figure 5.9, heteroatom-induced stabilization is a stronger effect than hyperconjugation.

With the understanding that hyperconjugation and heteroatoms both stabilize cations through resonance effects, the influence of full conjugation to sites of unsaturation deserves mention. As shown in Figure 5.10, direct conjugation is generally a stronger effect than hyperconjugation. This effect is illustrated with an allylic carbocation compared to a secondary carbocation. However, if we consider a tertiary carbocation, as shown in Figure 5.11, this trend is reversed, thus emphasizing that while resonance stabilization is good, it is not as good as the stabilization obtained by having three alkyl groups associated with the cation.
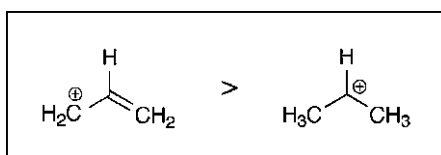
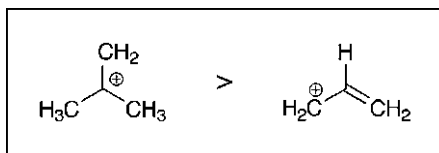**Figure 5.10** *Allylic carbocations are more stable than secondary carbocations.*

Figure 5.11   *Tertiary carbocations are more stable than allylic carbocations.*

5.4   CARBOCATION REARRANGEMENTS

Having addressed the structure and stability of carbocations, discussions will now be directed to the specific **side reactions** to which carbocations are subject. Specifically, this section focuses on rearrangements of carbocations known as **hydride shifts** and **alkyl shifts**.

5.4.1   1,2-Hydride Shifts

Recalling the role played by hyperconjugation in the stabilization of carbocations, a more detailed examination of this phenomenon is warranted. Looking at Figure 5.6, we note that carbocations are planar with an unoccupied *p* orbital extending both above and below the plane of the ion. Furthermore, looking at Figure 5.8, the electrons in a carbon–hydrogen bond adjacent to a carbocation can conjugate toward the positive charge residing in the vacant *p* orbital. This donation of electron density can only occur if the carbon–hydrogen bond is aligned with the vacant *p* orbital, as shown in Figure 5.12 using several perspective views. Specifically, the carbon–hydrogen bond must lie in the same plane as the vacant *p* orbital.
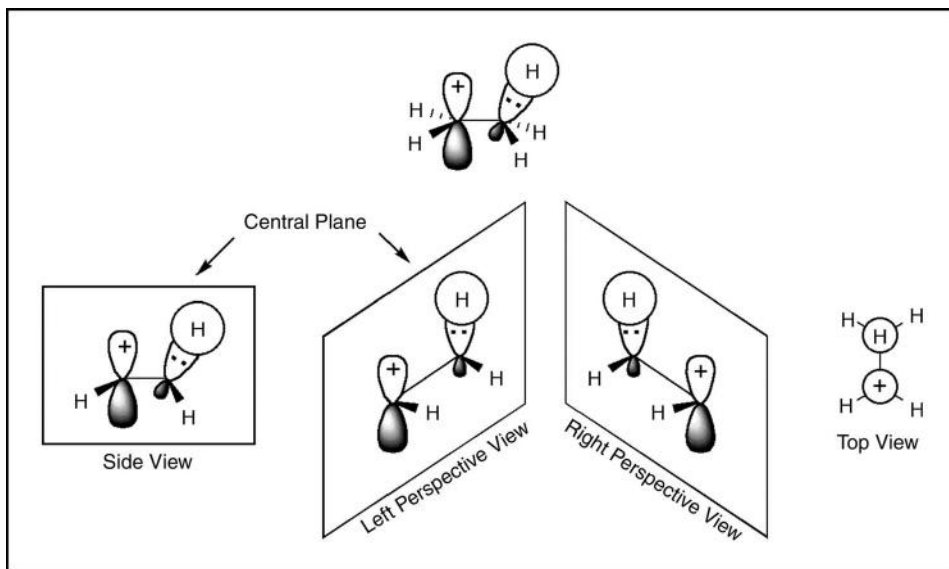

Figure 5.12   *Hyperconjugation occurs when a carbon–hydrogen bond lies in the same plane as a carbocation's vacant* p *orbital.*
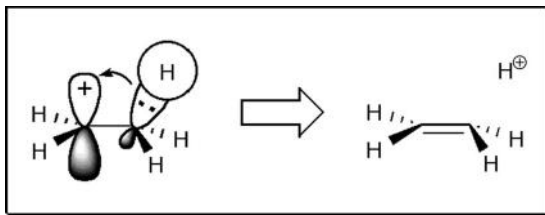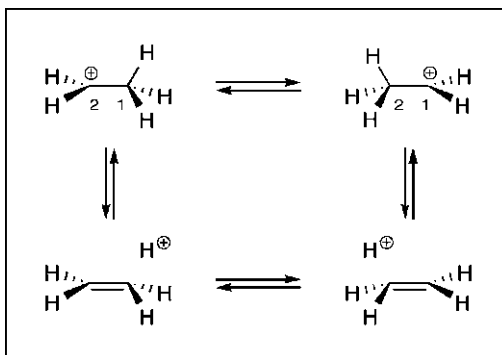
Figure 5.13 *Hyperconjugation can be viewed as formation of a pseudo-double-bond.*

Scheme 5.8 *Hyperconjugation leads to migration of hydrogen atoms through a 1,2-hydride shift.*

When the **alignment** of a carbon–hydrogen bond with a vacant *p* orbital takes place allowing for hyperconjugation, a "pseudo-double-bond" develops. As illustrated in Figure 5.13, this can be envisioned as a double bond with a closely associated hydrogen ion.

If, as shown in Figure 5.13, hyperconjugation results in the formation of species possessing both double-bond character and associated hydrogen ions, **equilibrium-controlled migration** of the associated hydrogen ion can be expected. This transformation, shown in Scheme 5.8, is known as a **1,2-hydride shift** and results in the migration of a proton from carbon 1 to carbon 2.

While the example illustrated in Scheme 5.8 shows equilibrium between two chemically identical carbocations, there are factors influencing the direction of these transformations when applied to more complex systems. If we consider Scheme 5.9, we notice that the positive charge migrates exclusively to the tertiary center, reflecting the increased stability of tertiary carbocations over primary carbocations. In general, where 1,2-hydride shifts are possible, rearrangement of less stable carbocations to more stable carbocations is expected.

5.4.2 1,2-Alkyl Shifts

Moving from discussion of 1,2-hydride shifts to **1,2-alkyl shifts**, it is important to remember that hydride shifts occur much more readily than the corresponding alkyl shifts. In fact, as a general rule, alkyl shifts will not occur unless a hydride shift cannot take place.

Among the most famous examples of a reaction involving a 1,2-alkyl shift is the **pinacol rearrangement**. This reaction, shown in Scheme 5.10, results in the conversion of a **vicinal diol** to a ketone.
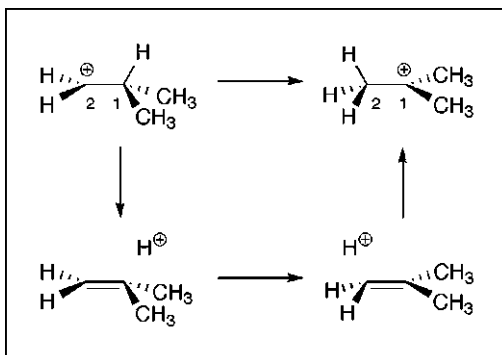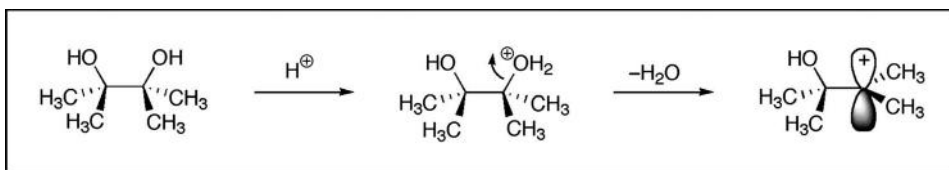
Scheme 5.9 *Rearrangements via 1,2-hydride shifts generate more stable carbocations from less stable carbocations.*
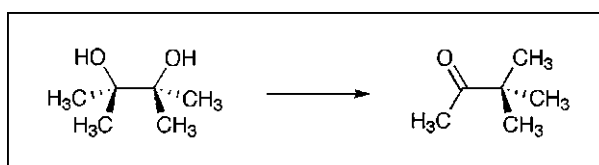

Scheme 5.10 *Pinacol rearrangement.*

Mechanistically, the pinacol rearrangement is explained by initial carbocation formation through solvolysis. This step, illustrated in Scheme 5.11, involves protonation of an alcohol followed by water leaving and generating a tertiary carbocation. In looking at this cation, one may imagine that a 1,2-hydride shift is possible. However, the only sources of hydrogens for such a shift are the methyl groups adjacent to the cationic center. If a hydride migrates from one of these methyl groups, as illustrated in Scheme 5.12, the result would be generation of a primary carbocation. Since primary carbocations are less stable than tertiary carbocations, this migration will not occur.

While the hydride shift illustrated in Scheme 5.12 cannot occur as a part of the pinacol rearrangement, the intermediate carbocation is subject to **alkyl migrations**. As shown in Scheme 5.13, a 1,2-alkyl shift results in transfer of the cation from a **tertiary center** to a center adjacent to a heteroatom. As the oxygen heteroatom possesses lone electron pairs, these lone pairs serve to stabilize the cation. Thus, the illustrated 1,2-alkyl shift transforms a carbocation into a more stable carbocation.
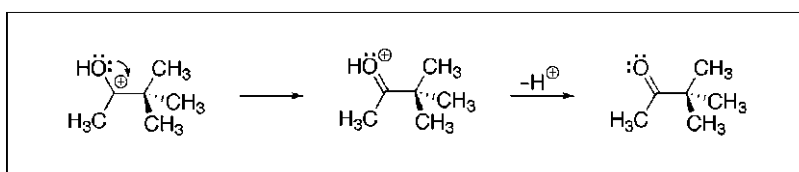

Scheme 5.11 *Pinacol rearrangement proceeds through solvolysis-mediated cation formation.*
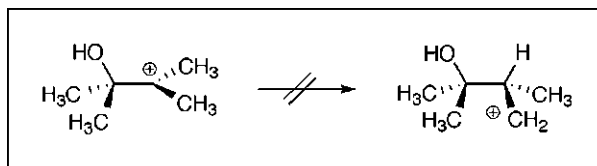
Scheme 5.12 *1,2-Hydride shifts will not occur when the product cation is less stable than the starting cation.*
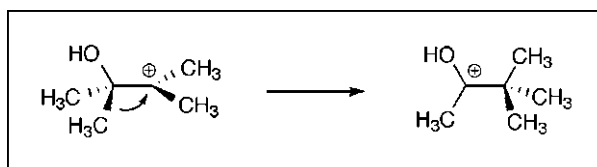
Scheme 5.13 *Alkyl migrations occur when the resulting carbocation is more stable than the starting carbocation.*

Scheme 5.14 *Conclusion of the pinacol rearrangement involves migration of the positive charge to the adjacent oxygen atom followed by deprotonation.*

Mechanistic conclusion of the pinacol rearrangement is illustrated in Scheme 5.14 and involves initial donation of an oxygen lone pair to the cation, thus migrating the charge to the oxygen atom. The resulting oxygen cation then releases a proton, liberating the illustrated neutral ketone.

As the mechanistic steps discussed for the pinacol rearrangement have been illustrated using arrow pushing, it is important to recognize that in all cases, the arrows have been drawn pushing electrons toward positive charges. This point has been previously discussed and will continue to be emphasized.

5.4.3 Preventing Side Reactions

Because of 1,2-hydride and alkyl shifts, it is possible to obtain **multiple products** from S_N1 reactions. Thus, to induce one product to predominate, we must find a way to stabilize the carbocation. This is done by using highly **polar solvents** such as **acetic acid**, **dimethyl formamide**, and **dimethyl sulfoxide**. In using this strategy, the lifetime of a carbocation can be extended, allowing the most stable product more time to form. As a result,
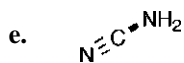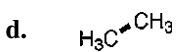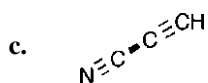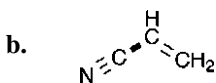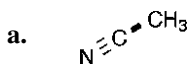
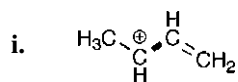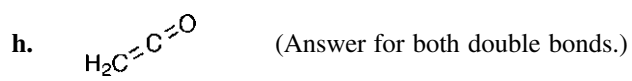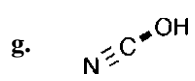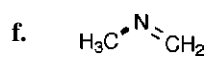**control** over formation of desired products in reasonable yields from S$_N$1 reactions can be achieved.

5.5 SUMMARY

In this chapter, S$_N$1 reactions were introduced, compared to S$_N$2 reactions and discussed mechanistically. Through these discussions, the involvement of electron orbitals, and their various **hybrids**, was addressed. Furthermore, complicating side reactions such as **hydride** and **alkyl migrations** were presented. As discussions move into more advanced mechanistic types, it is important to maintain awareness of the involvement and orientation of orbitals, the steric environment at reactive centers, and the overall reactivity of nucleophiles and electrophilic centers.

PROBLEMS

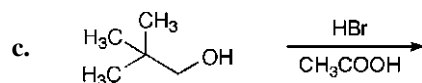**1.** For the following molecules, state the hybridization (sp, sp^2, sp^3) of the orbitals associated with the highlighted bond. Also, state the geometry of the bound atomic centers (linear, bent, trigonal planar, tetrahedral).

a. $N \equiv C - CH_3$

b. $N \equiv C - \overset{\overset{\textstyle H}{|}}{C} = CH_2$

c. $N \equiv C - C \equiv CH$

d. $H_3C - CH_3$

e. $N \equiv C - NH_2$

f. $H_3C\overset{\bullet}{-}N\overset{\cdot}{=}CH_2$

g. $N\overset{\cdot}{\equiv}C\overset{\bullet}{-}OH$

h. $H_2C{=}C\overset{\cdot}{=}O$ (Answer for both double bonds.)

i. $H_3C{-}\overset{\oplus}{C}H{-}\overset{H}{C}{=}CH_2$

j. $H_3C{-}\underset{CH_3}{\overset{\oplus}{C}}{-}C{\equiv}CH$
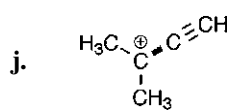
2. Predict all of the products of the following reactions:

a.

$$\underset{H_3C}{\overset{Br}{\bigwedge}}\ CH_3 \quad \xrightarrow[\text{DMSO}]{\text{AgCN}}$$

b.

$$\bigwedge\bigwedge\text{OH} \quad \xrightarrow{\text{CH}_3\text{COOH}} \quad \xrightarrow{\text{NaOH}}$$

c.

$$\underset{H_3C}{\overset{H_3C}{\bigwedge}}\overset{CH_3}{\underset{}{\bigwedge}}\text{OH} \quad \xrightarrow[\text{CH}_3\text{COOH}]{\text{HBr}}$$

d.

$$\underset{H_3C}{\overset{H_3C}{\bigwedge}}\overset{CH_3}{\bigwedge}\overset{CH_3}{\underset{\text{OH}}{\bigwedge}}CH_3 \quad \xrightarrow[\text{CH}_3\text{COOH}]{\text{HBr}}$$
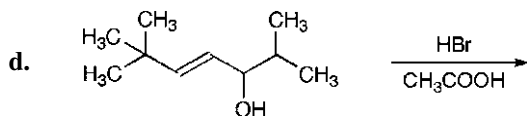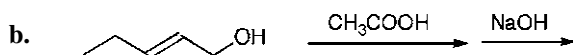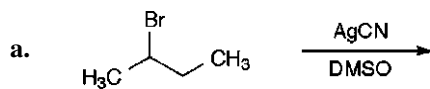
3. For each of the following reactions, determine which will proceed via an S_N1 or an S_N2 mechanism. In cases where both may be applicable, list appropriate reaction conditions (e.g., solvents, reagents) that would favor S_N1 over S_N2 and vice versa. Explain your answers.

a.

b.

c.
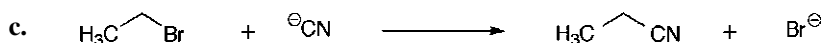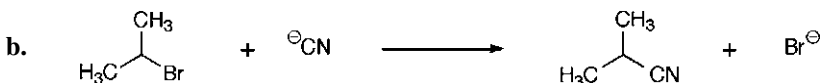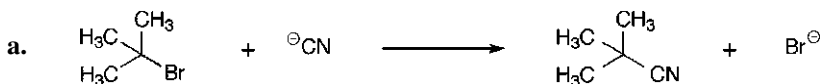
4. In studying 1,2-alkyl and hydride shifts, we explored the observation that shifts will not occur unless the newly formed carbocation is more stable than the starting carbocation. Additionally, as illustrated in Figure 5.12, these shifts were explained using hyperconjugation, thus requiring that the orbital containing the positive charge and the bond containing the shifting group lie within the same plane. This is necessary in order to allow sufficient orbital overlap for the shift to take place.

In addition to 1,2-shifts, which occur between adjacent bonds, other shifts are possible where the migrating group apparently moves across space. As with 1,2-shifts, these additional shifts can only occur when the positively charged empty p orbital lies within the same plane as the bond containing the migrating group, thus allowing sufficient orbital overlap. With this in mind, explain the following 1,5-hydride shift. (*Hint*: Consider different structural conformations. You may want to use models.) Asterisk (*) marks enrichment with ^{13}C.