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Nucleophilic Substitution Reactions

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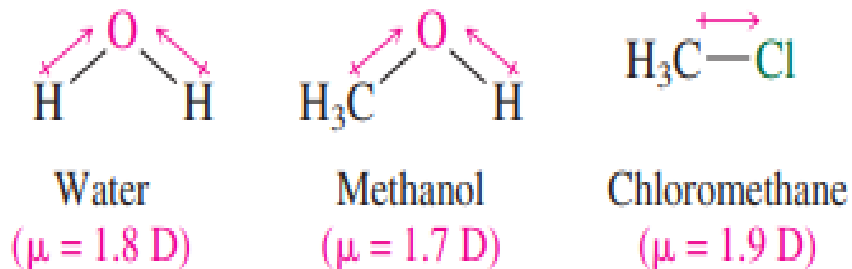
Organic compounds are grouped into families according to the functional groups they contain. Two of the most important families are **alcohols** and **alkyl halides**; both of which are versatile starting materials for preparing numerous other families. The major portion of the present chapter concerns the conversion of alcohols to alkyl halides by reaction with hydrogen halides:



It is convenient in equations such as this to represent generic alcohols and alkyl halides as **ROH** and **RX**, respectively, where “R” stands for an alkyl group. In addition to convenience, this notation lets us focus more clearly on the functional group transformation; the OH functional group of an alcohol is replaced by a halogen, such as chlorine (X = Cl) or bromine (X = Br).

The carbon that bears the functional group is **sp³-hybridized** in alcohols and alkyl halides. Carbon–halogen bond distances in alkyl halides increase in the order **C-F (140 pm) < C-Cl (179 pm) < C-Br (197 pm) < C-I (216 pm)**. **Carbon–oxygen and carbon–halogen bonds are polar covalent bonds**, and carbon bears a partial positive charge in alcohols ($\delta^+\text{C}-\text{O}^{\delta-}$) and in alkyl halides ($\delta^+\text{C}-\text{X}^{\delta-}$).

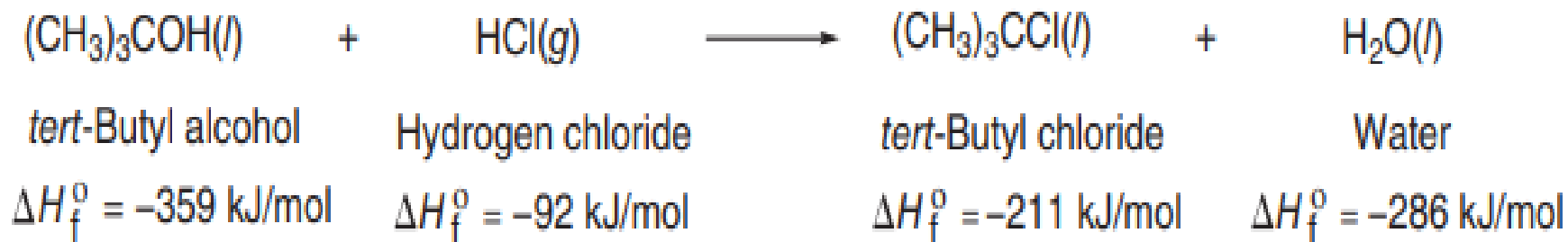
Alcohols and alkyl halides are polar molecules. The dipole moments of methanol and chloromethane are very similar to each other and to water



Reaction of Alcohols with Hydrogen Halides: The S_N1 Mechanism

The reaction of an alcohol with a hydrogen halide is a **substitution**.

A halogen, usually chlorine or bromine, replaces a hydroxyl group as a substituent on carbon. In addition to knowing what the reactants and products of a chemical reaction are, it is useful to evaluate the energy relationships between them (thermodynamics) and the pathway by which reactants become products (mechanism



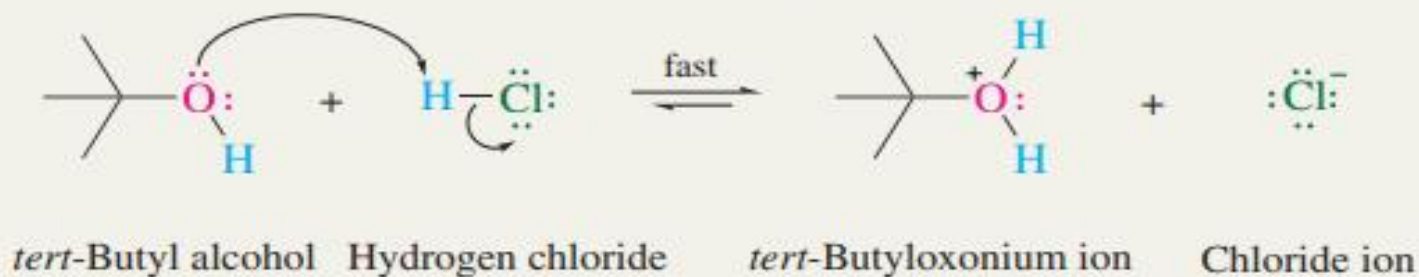
Formation of *tert*-Butyl Chloride from *tert*-Butyl Alcohol and Hydrogen Chloride

THE OVERALL REACTION:

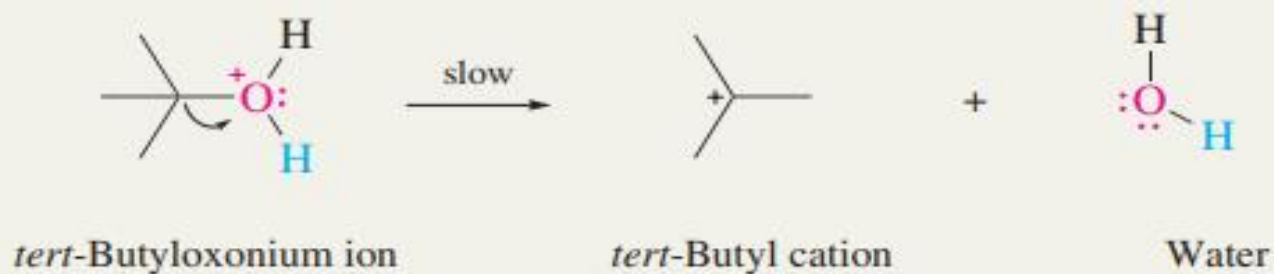


THE MECHANISM:

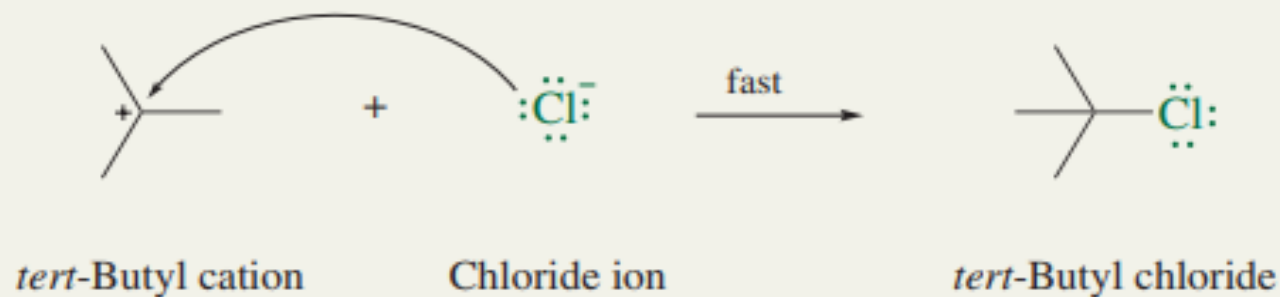
Step 1: Protonation of *tert*-butyl alcohol to give an alkyloxonium ion:



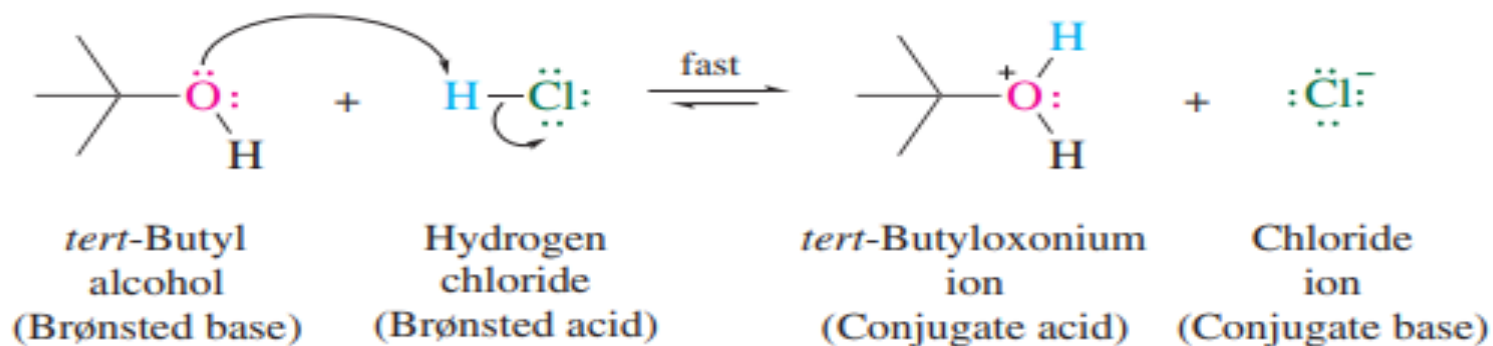
Step 2: Dissociation of *tert*-butyloxonium ion to give a carbocation:



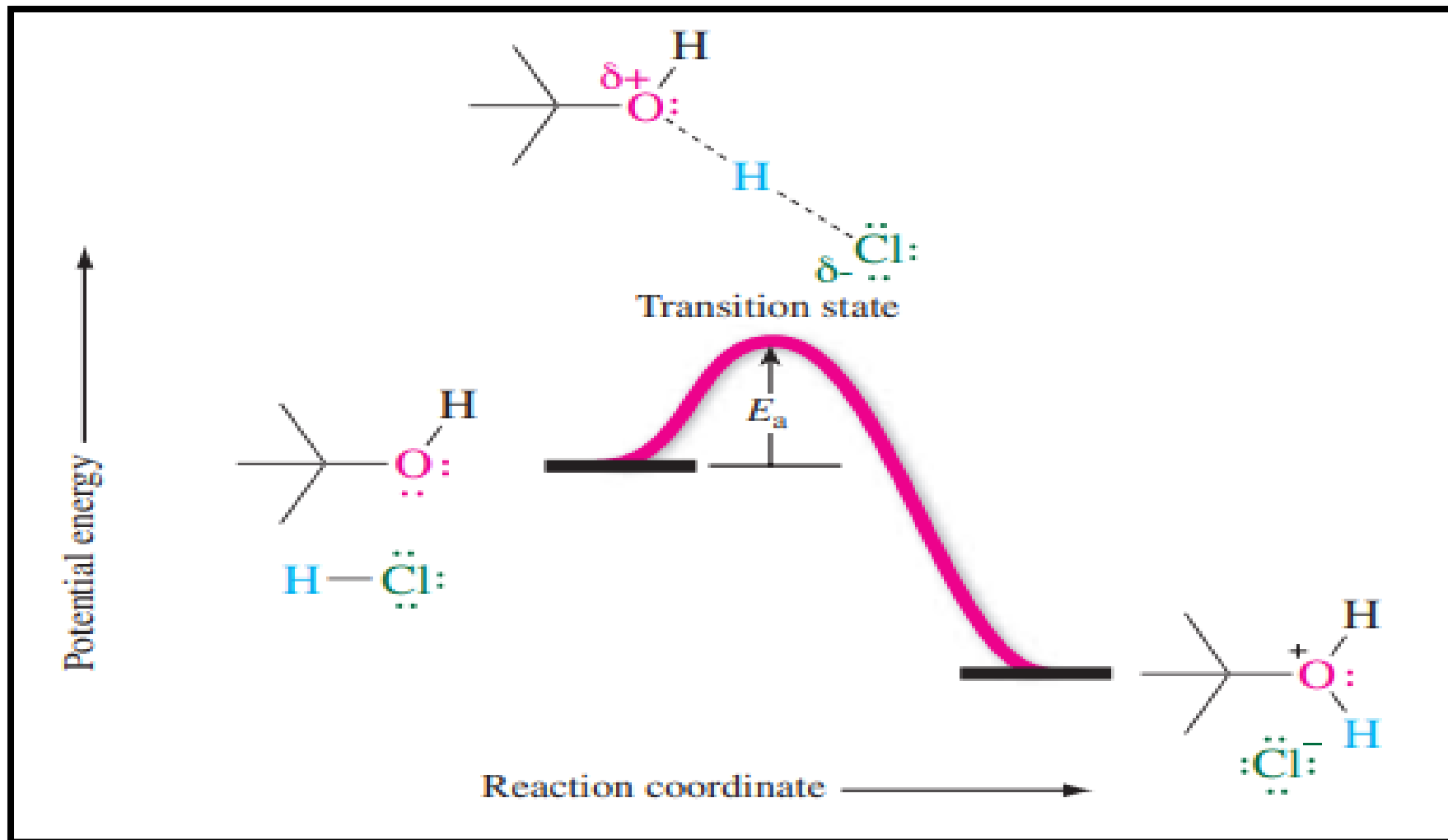
Step 3: Capture of *tert*-butyl cation by chloride ion:



Step 1: Proton Transfer, that alcohols resemble water in respect to their Brønsted acidity (ability to donate a proton from oxygen). They also resemble water in their Brønsted basicity (ability to accept a proton on oxygen). Just as proton transfer to a water molecule gives oxonium ion (hydronium ion, H_3O^+), proton transfer to an alcohol gives an alkyloxonium ion (ROH_2^+).

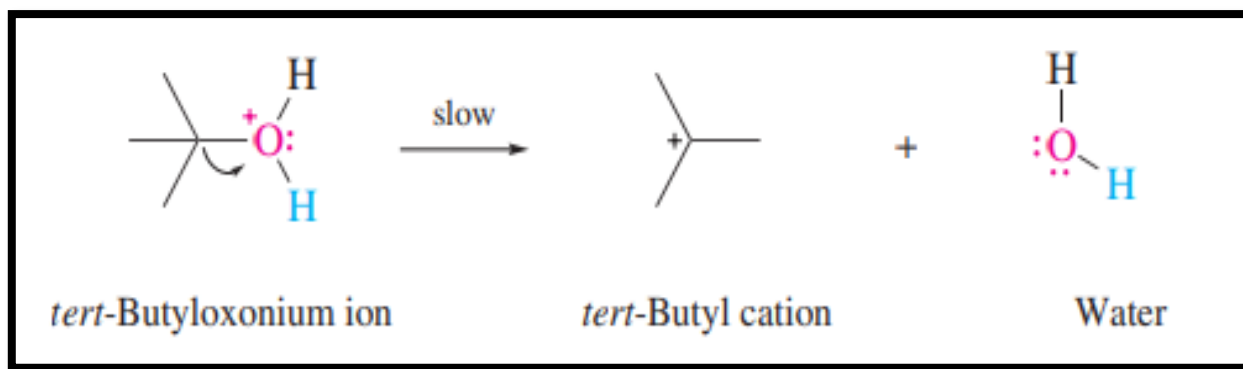


Transfer of a proton from hydrogen chloride to tert-butyl alcohol is bimolecular because two molecules [HCl and (CH₃)₃COH] undergo chemical change.



Step 2: Carbocation Formation

In the second elementary step of Mechanism 5.1, the alkyloxonium ion dissociates to a molecule of water and a carbocation, an ion that contains a positively charged carbon.

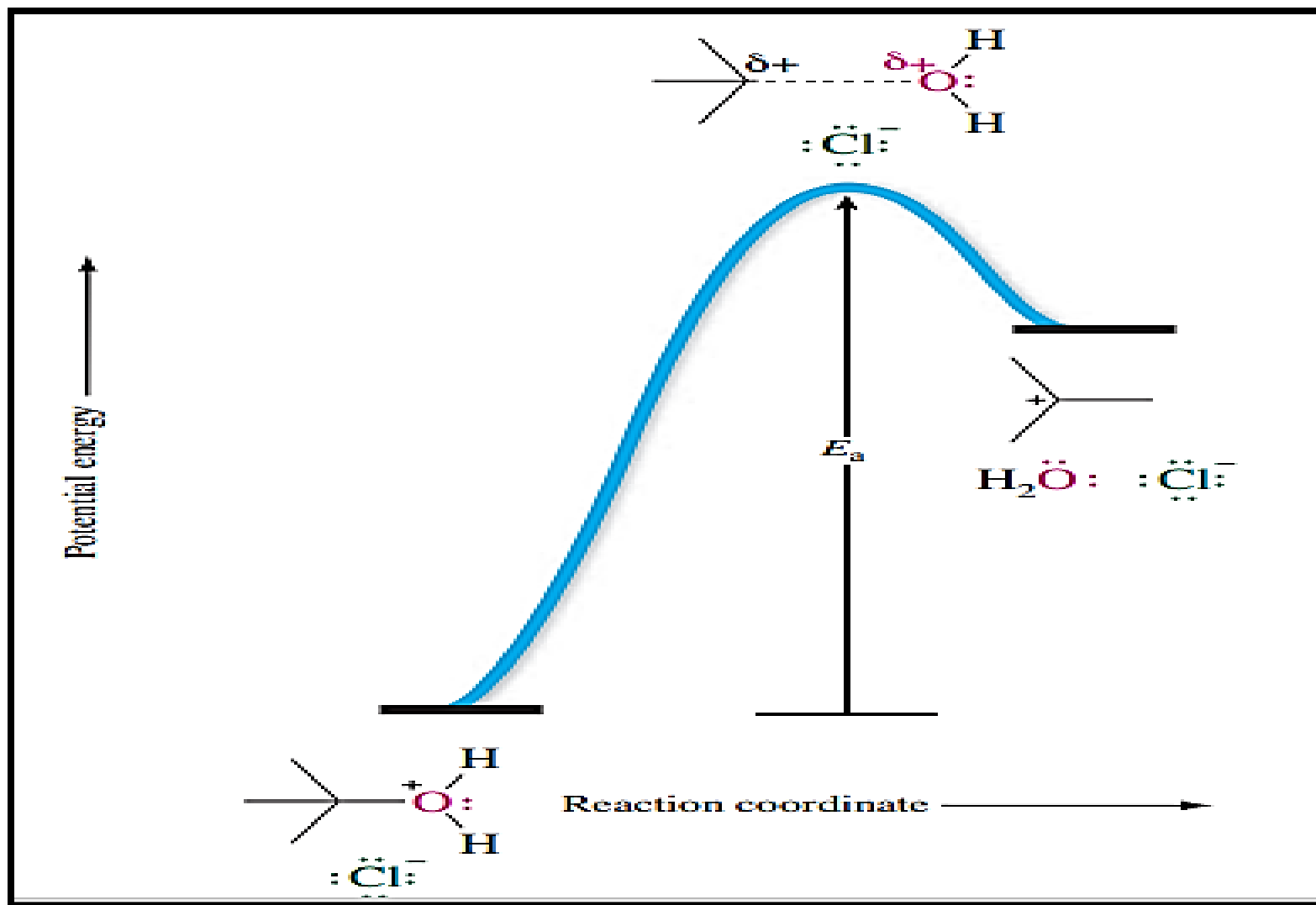


Only one species, tert-butyloxonium ion, undergoes a chemical change in this step.

Therefore, the step is **unimolecular**. It is, however, a relatively unstable species and

its formation by dissociation of the alkyloxonium ion is **endothermic**.

Step 2 : is the slowest step in the mechanism and has the highest activation energy. Because this step is endothermic, the products of it are placed higher in energy than the reactants.



Potential energy diagram for dissociation of tert-butyloxonium ion to tert-butyl cation

Step 3: Reaction of tert-Butyl Cation with Chloride Ion

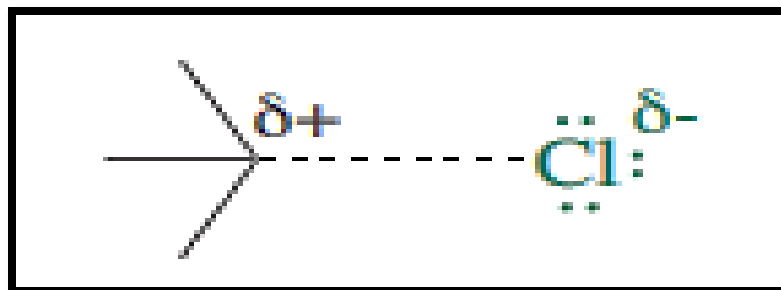
, which follows and completes the mechanism, is a **Lewis acid/Lewis base reaction**.

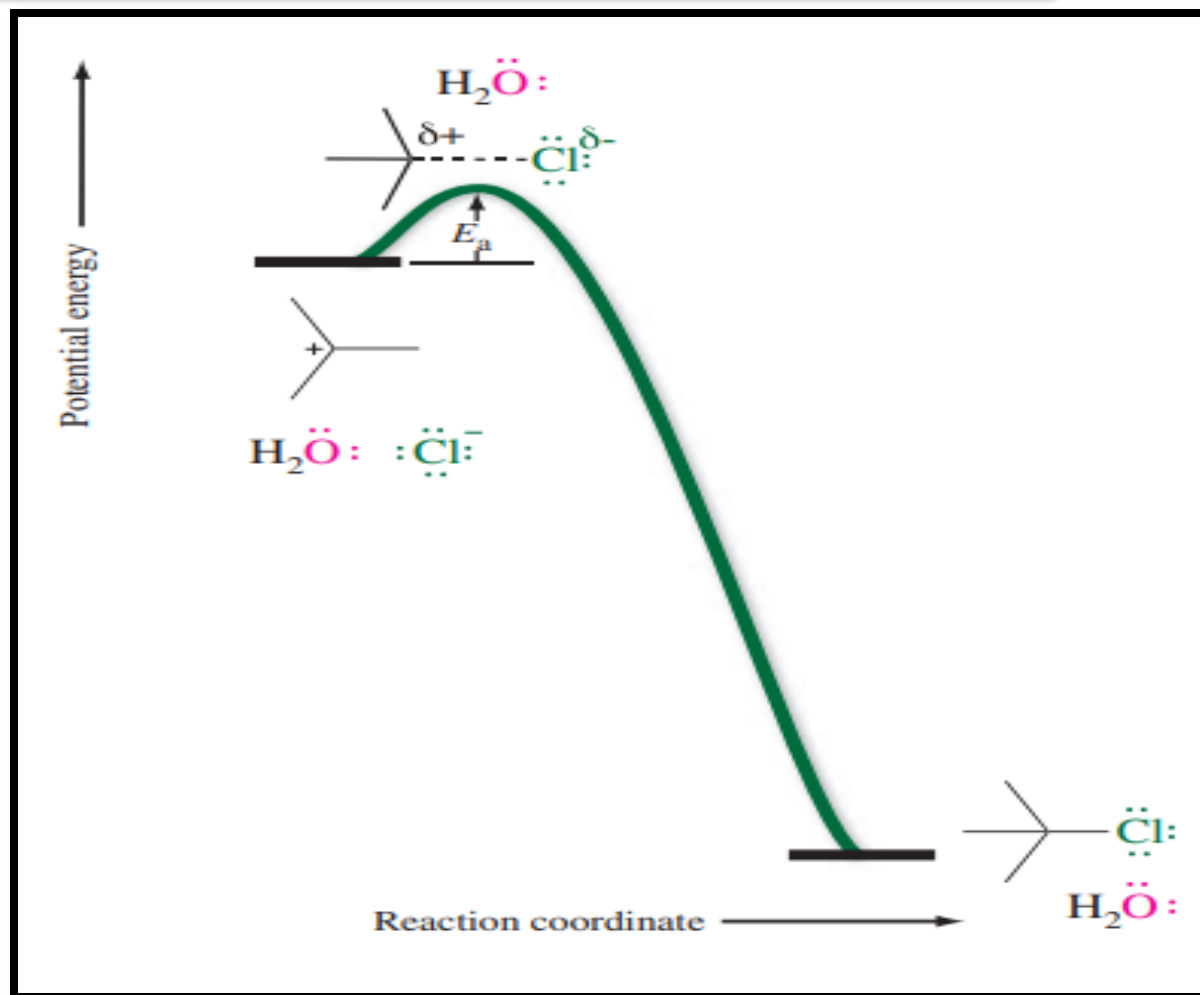
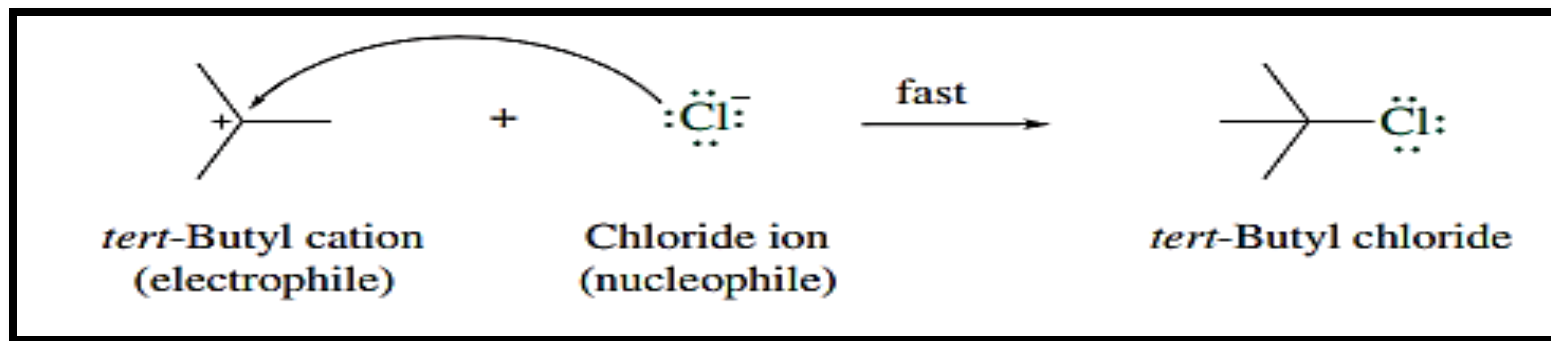
Reaction of tert-Butyl Cation with Chloride Ion . The Lewis bases that react with **electrophiles** are called **nucleophiles** . They have an unshared electron pair that they can use in covalent bond formation. **The nucleophile in step 3 is chloro**

Step 3 is bimolecular because two species, the carbocation and chloride ion, react together.

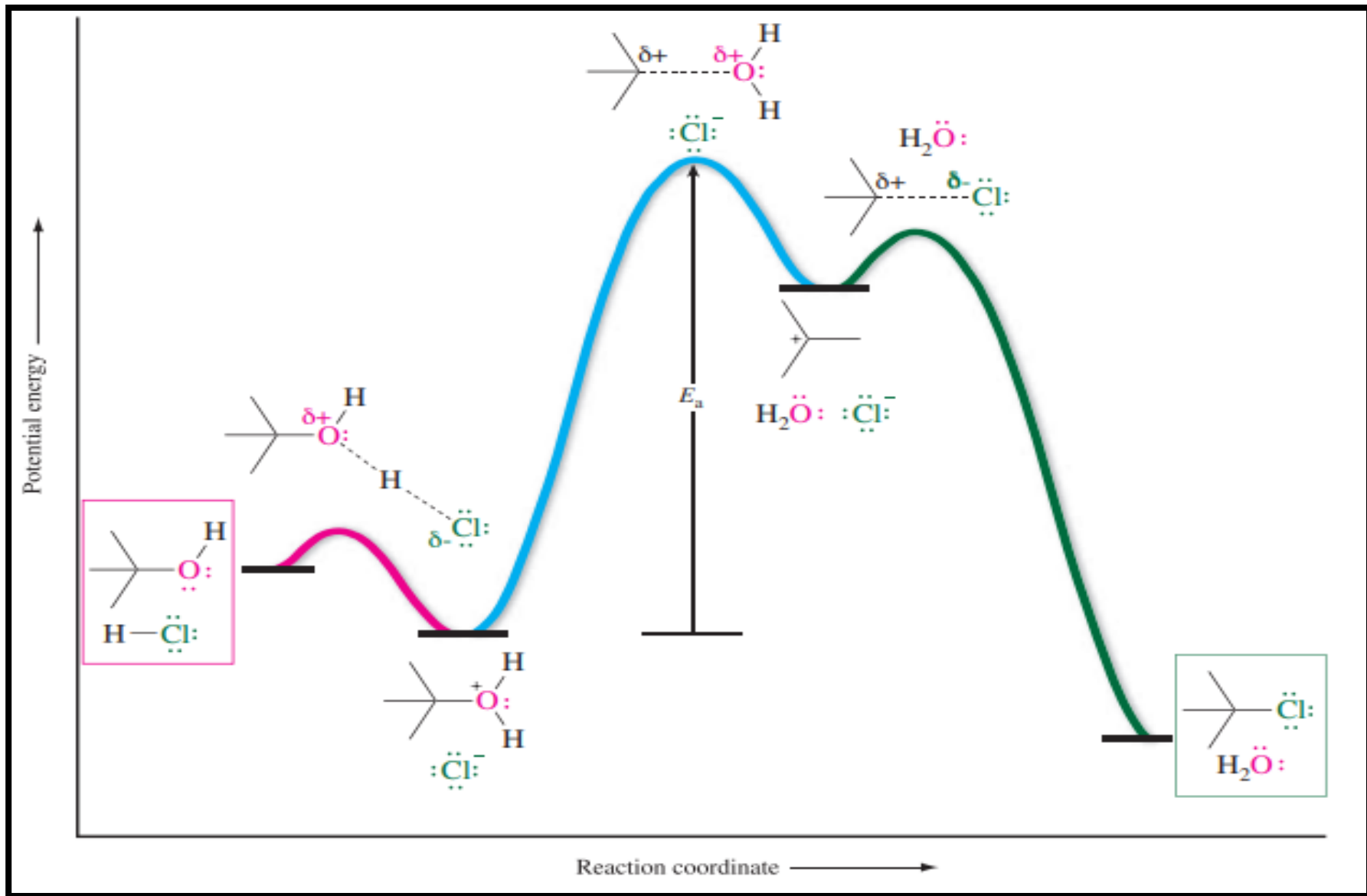
The step is exothermic; it leads from the carbocation intermediate to the stable isolated products of the reaction.

- **The activation energy for this step is small, and bond formation between a positive ion and a negative ion occurs rapidly.**
- **The transition state for this step involves partial bond formation between tert-butyl cation and chloride ion .**

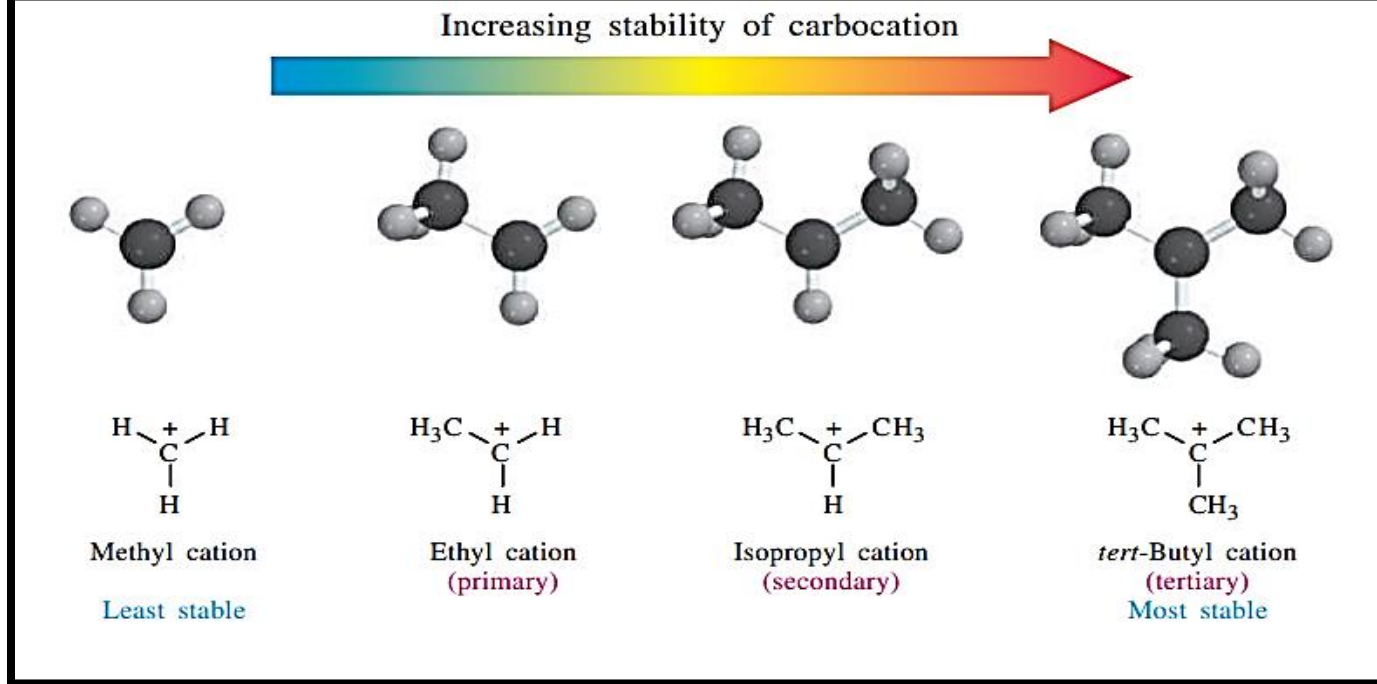




Potential energy diagram for reaction of tert-butyl cation with chloride anion



Potential energy diagram for the reaction of tert-butyl alcohol and hydrogen chloride according to the S_N1 mechanism

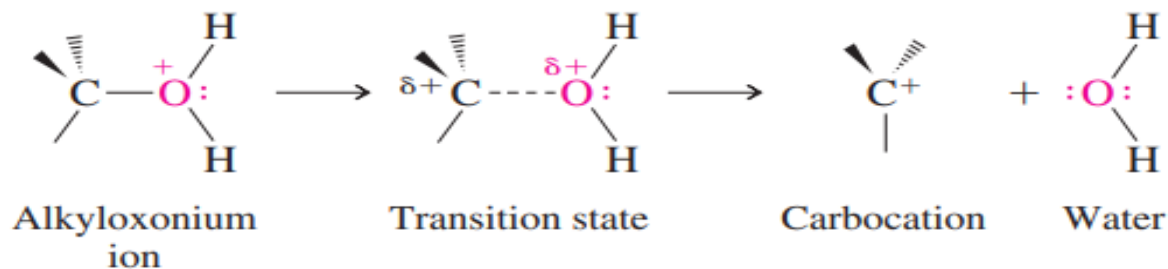


The order of carbocation stability is **methyl < primary < secondary < tertiary**.

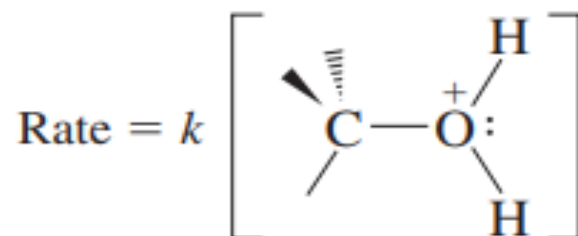
Alkyl groups that are directly attached to the positively charged carbon stabilize carbocations

Effect of Alcohol Structure on Reaction Rate

One important experimental fact is that the rate of reaction of alcohols with hydrogen halides increases in the order primary < secondary < tertiary. This reactivity order parallels the carbocation stability order and is readily accommodated by the mechanism we have outlined. The rate-determining step in the $\text{S}_{\text{N}}1$ mechanism is **dissociation of the alkyloxonium ion to the carbocation.**

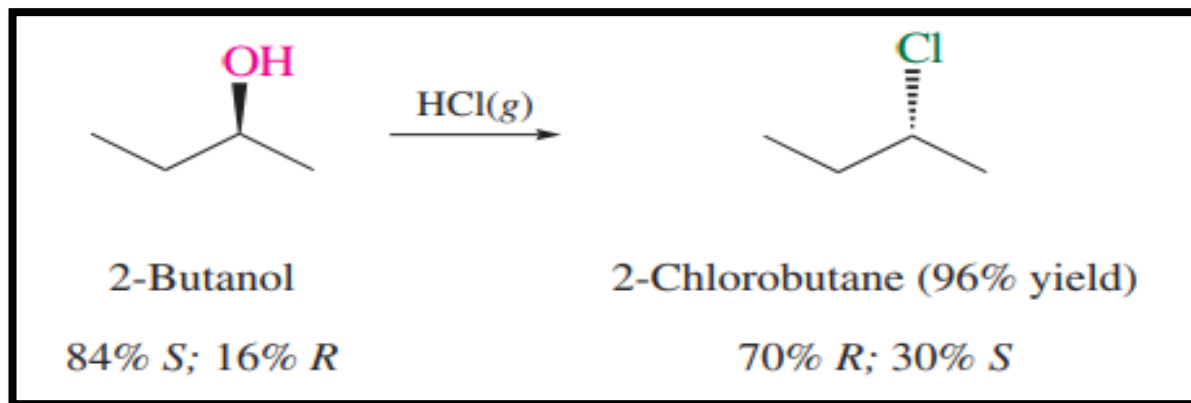


The rate of this step is proportional to the concentration of the alkyloxonium ion



Stereochemistry and the S_N1 Mechanism

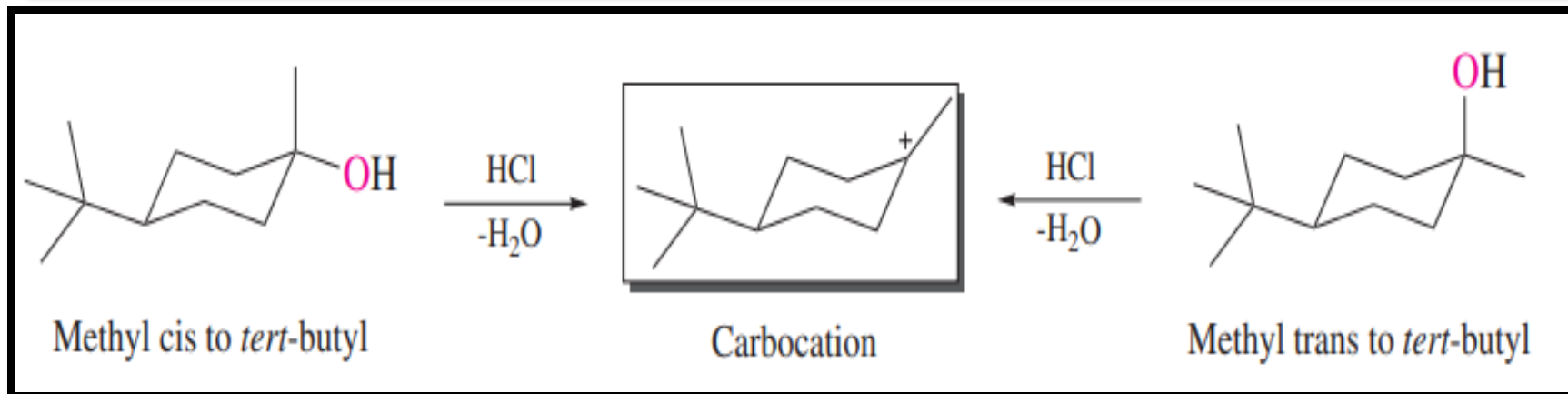
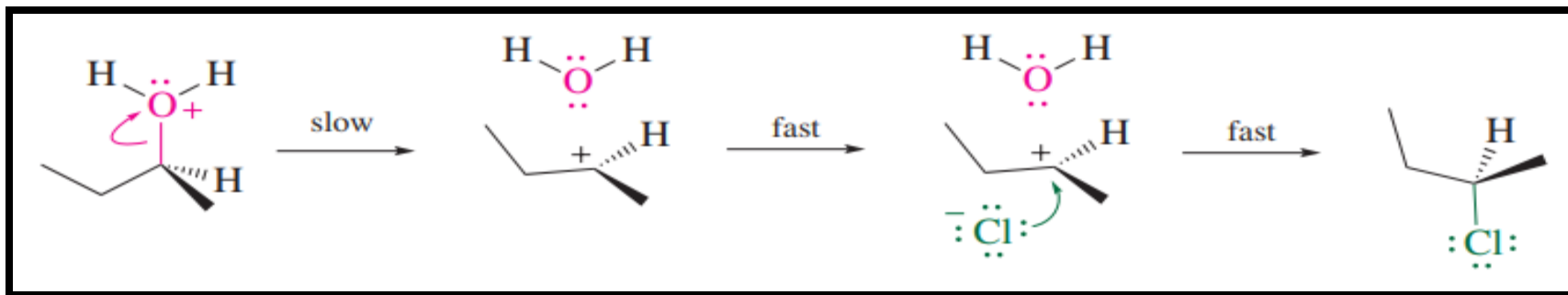
When studying reactions that are believed to involve carbocations as intermediates, it is common to test this proposal by assessing the **stereo chemical** relationship between the organic reactant and its product. **Almost all the studies of the reactions of hydrogen halides with optically active alcohols have involved secondary alcohols, the case of 2-butanol being typical.**



The change in configuration at the chirality center from 84% *S* in the alcohol to 70% *R* in the product is an example of a reaction that proceeds with predominant **inversion of configuration at the chirality center**.

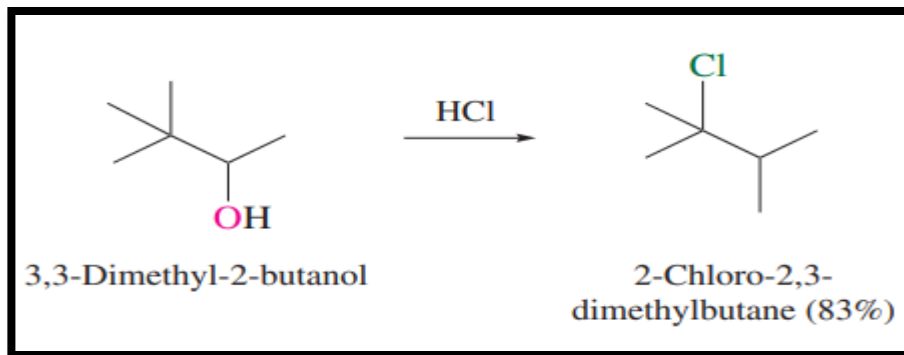
A modified version of the $\text{S}_{\text{N}}1$ mechanism is generally accepted to account for the observed stereochemistry. According to this model, dissociation of the oxonium ion intermediate to a carbocation and water remains the rate-determining step. The two of them, however, retain a close spatial orientation that favors approach of chloride from the side opposite the original

C--O bond



Carbocation Rearrangements

A reaction is said to have proceeded with *rearrangement* when an atom or group in the reactant migrates from the atom to which it is attached and becomes bonded to another. In the example shown .

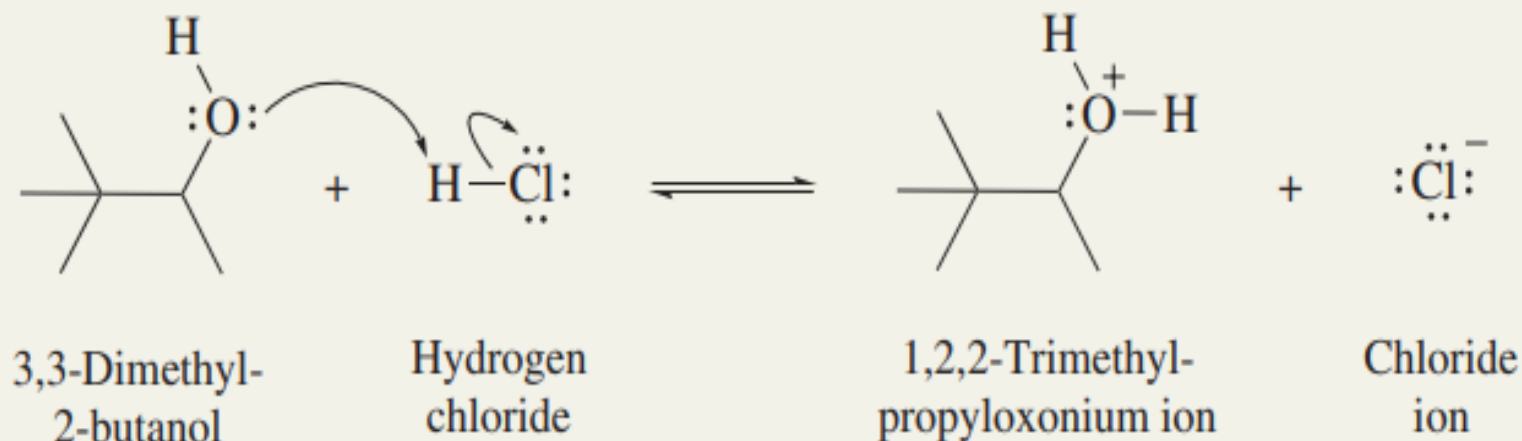


instead of chlorine simply replacing the hydroxyl group at C-2, one of the methyl groups at C-3 has moved to C-2 and its original place at C-3 is taken by the incoming chlorine. The generally accepted explanation for this rearrangement is outlined in Mechanism 5.2.

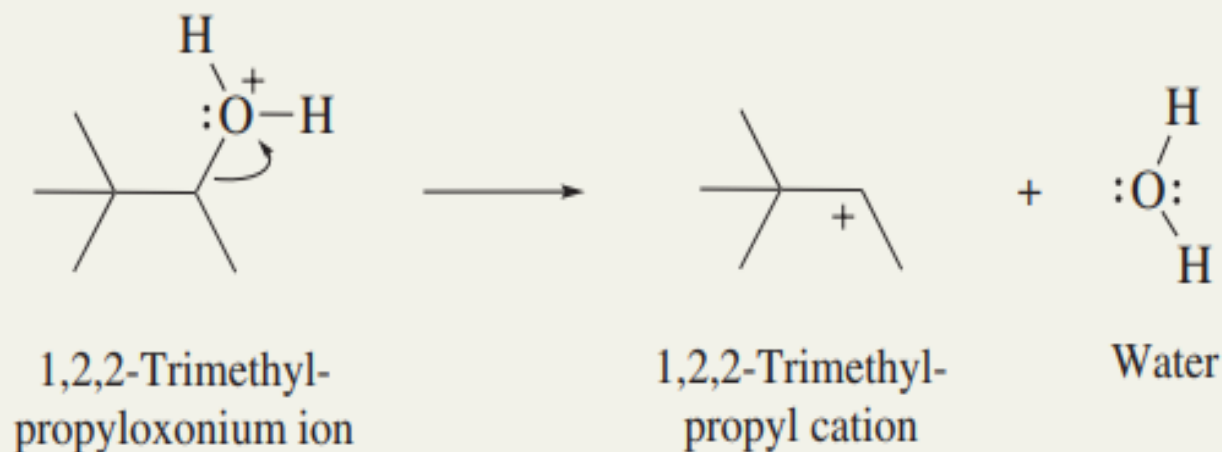
It extends the SN1 mechanism of Section 5.8 by introducing a new reaction path for carbocations. Not only can a carbocation react with a halide ion, it can also rearrange to a more stable carbocation prior to capture by the nucleophile.

THE MECHANISM:

Step 1: This is a proton-transfer reaction. Hydrogen chloride is the proton donor (Brønsted acid) and the alcohol is the proton acceptor (Brønsted base).



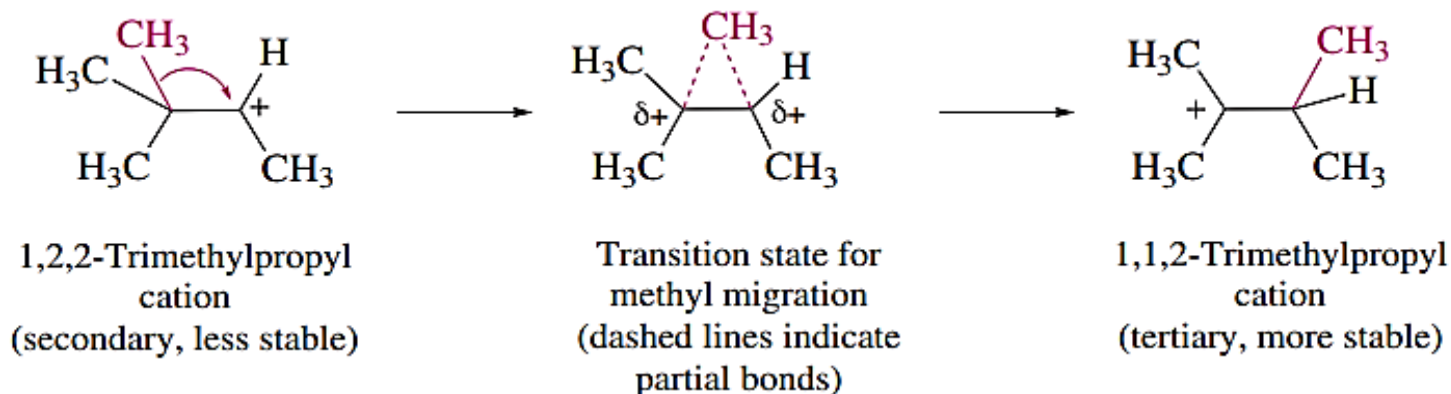
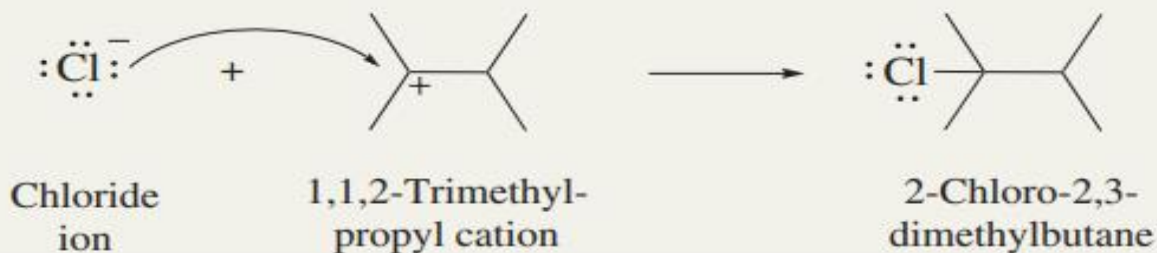
Step 2: The oxonium ion dissociates to a carbocation and water.



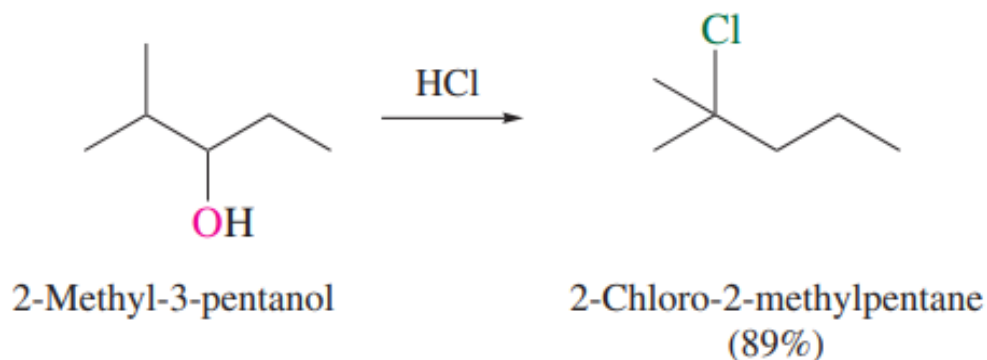
Step 3: The secondary carbocation formed in step 2 rearranges to a more stable tertiary carbocation. One of the methyl groups at C-3 migrates with its electron pair to C-2.



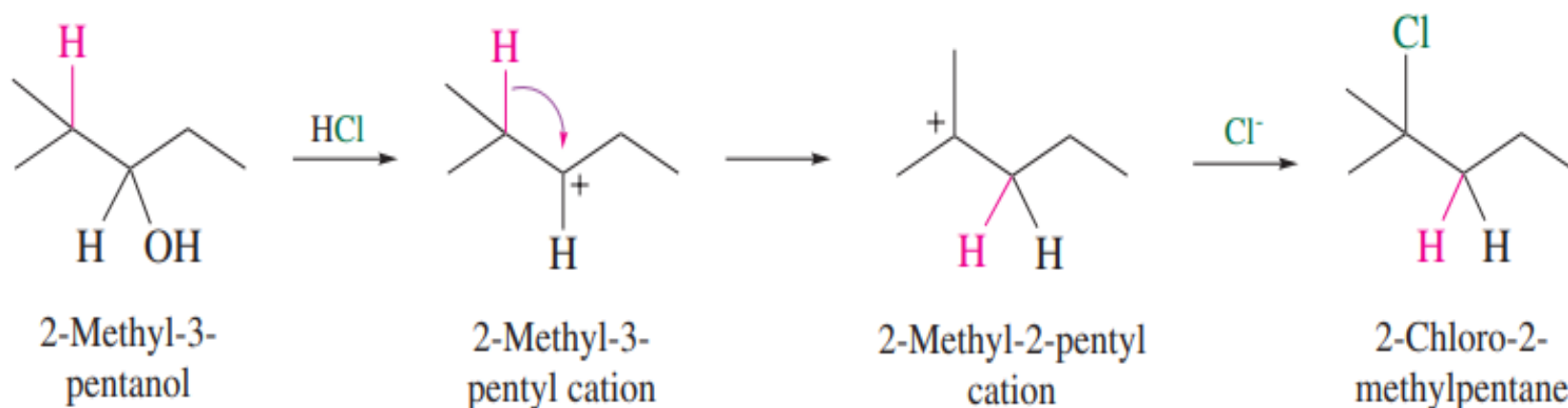
Step 4: Chloride ion acts as a nucleophile and bonds to the positively charged carbon.



Many carbocation rearrangements involve migration of a hydrogen and are called hydride shifts.



In this example, a secondary carbocation is formed initially then converted to a more stable tertiary one by migration of a hydrogen with its pair of electrons



Reaction of Methyl and Primary Alcohols with Hydrogen Halides: The S_N2 Mechanism

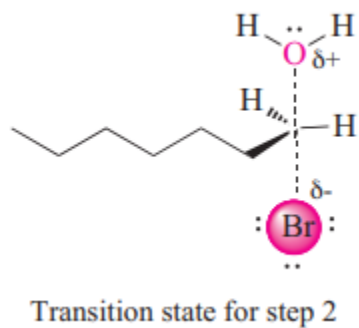
Unlike tertiary and secondary carbocations, methyl and primary carbocations are too high in energy to be intermediates in chemical reactions. However, methyl and primary alcohols are converted, albeit rather slowly, to alkyl halides on treatment with hydrogen halides.

Therefore, they must follow a different mechanism, one that avoids carbocation intermediates. This alternative process is outlined in Mechanism 5.3 for the reaction of 1-heptanol with hydrogen bromide

The first step of this new mechanism is exactly the same as that seen earlier for the reaction of tert-butyl alcohol with hydrogen chloride—formation of an alkyloxonium ion by proton transfer from the hydrogen halide to the alcohol. Like the earlier example, this is a rapid, reversible Brønsted acid–base reaction

The major difference between the two mechanisms is the second step. The second step in the reaction of tert-butyl alcohol with hydrogen chloride is the unimolecular dissociation of tert-butyloxonium ion to tert-butyl cation and water. Heptyloxonium ion, however, instead of dissociating to an unstable primary carbocation, reacts differently

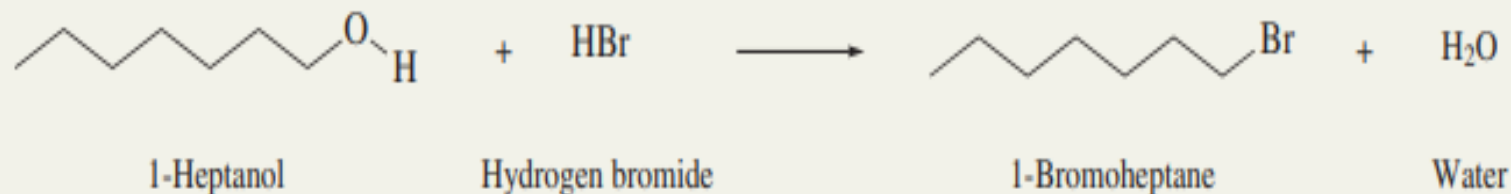
. It reacts with bromide ion, which acts as a nucleophile. We can represent the transition state of this displacement as:



Bromide ion forms a bond to the primary carbon by “pushing off” a water molecule. This step is bimolecular because it involves both bromide and heptyloxonium ion. Step 2 is slower than the proton transfer in step 1, so it is rate-determining. Using Ingold’s terminology, we classify nucleophilic substitutions that have a bimolecular rate-determining step by the mechanistic symbol SN2. In the present case, the SN2 mechanism is favored because the reaction site, being a primary carbon, is less crowded than that of a secondary or tertiary carbon. Further, because primary carbocations are much less stable than secondary and tertiary ones, an SN1 mechanism is too slow to compete with SN2

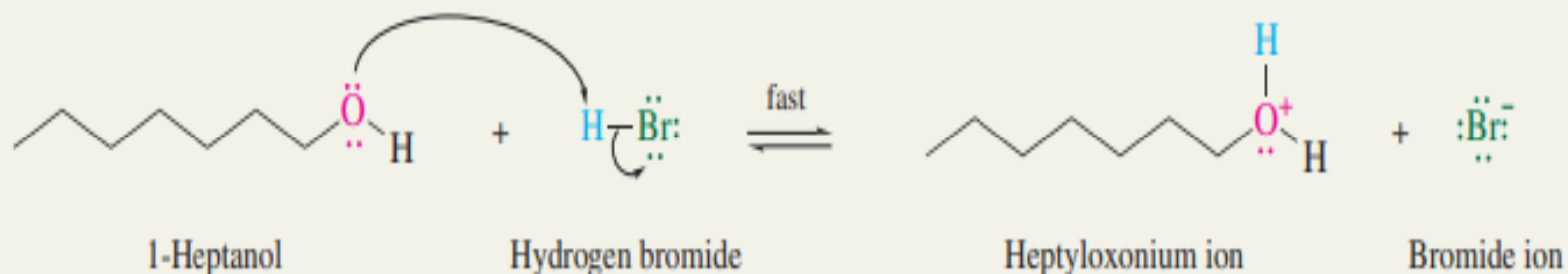
Formation of 1-Bromoheptane from 1-Heptanol and Hydrogen Bromide

THE OVERALL REACTION:

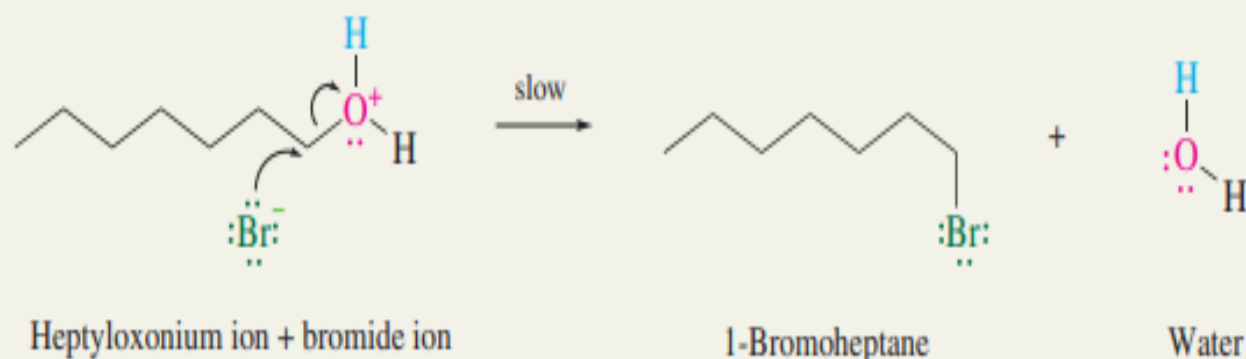


THE MECHANISM:

Step 1: Proton transfer from hydrogen bromide to 1-heptanol to give the corresponding alkyloxonium ion:

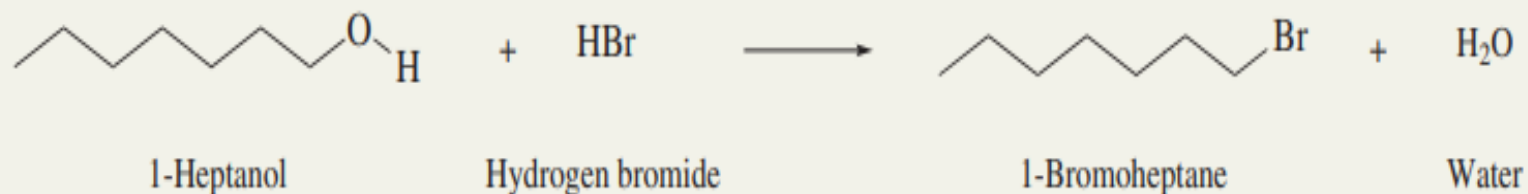


Step 2: Displacement of water from the alkyloxonium ion by bromide:



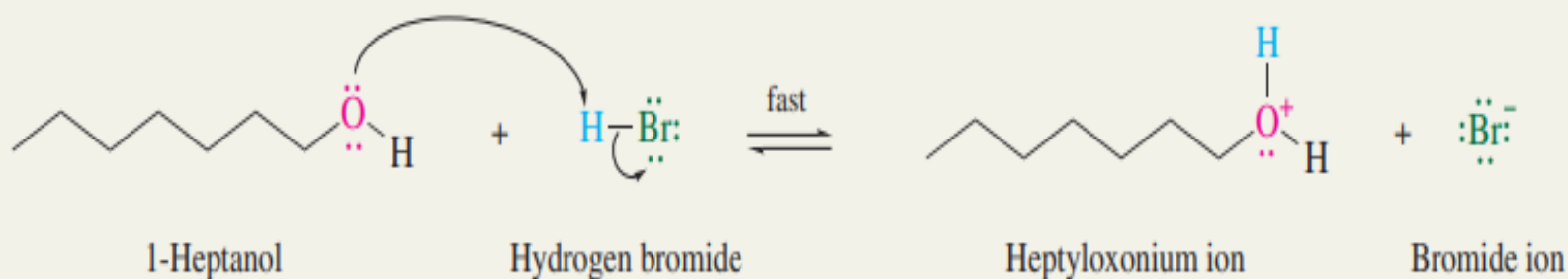
Formation of 1-Bromoheptane from 1-Heptanol and Hydrogen Bromide

THE OVERALL REACTION:

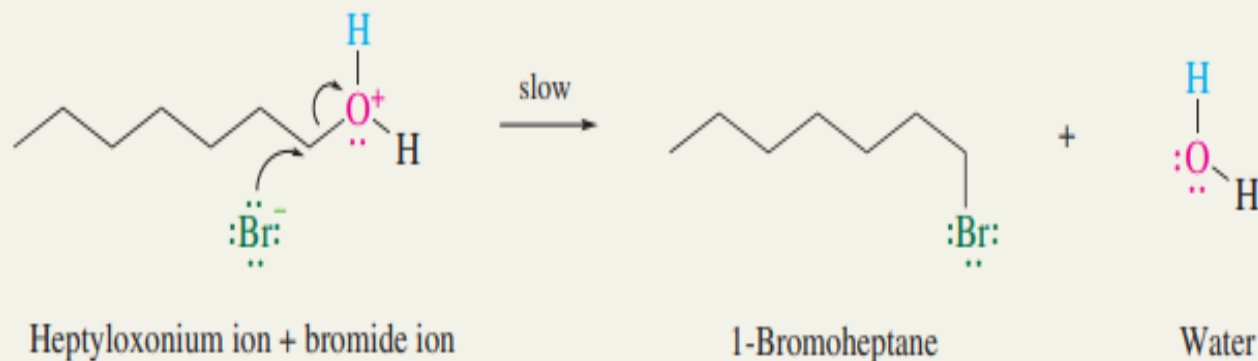


THE MECHANISM:

Step 1: Proton transfer from hydrogen bromide to 1-heptanol to give the corresponding alkyloxonium ion:

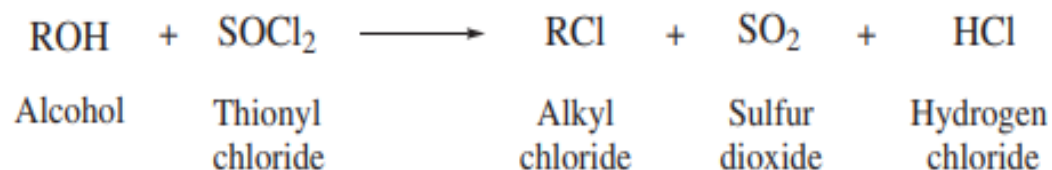


Step 2: Displacement of water from the alkyloxonium ion by bromide:

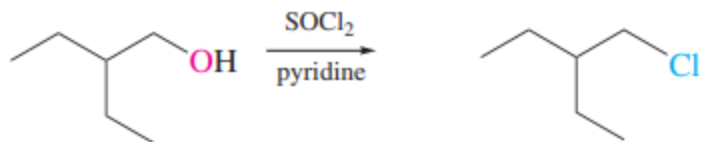
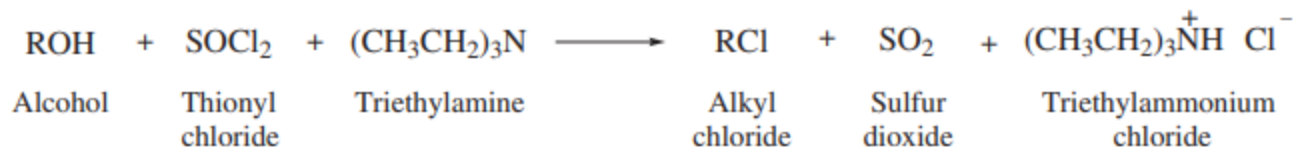


Other Methods for Converting Alcohols to Alkyl Halides

Alkyl halides are such useful starting materials for preparing other functional-group types that chemists have developed several alternative methods for converting alcohols to them. Of these, those based on thionyl chloride (SOCl_2) and the phosphorus trihalides PCl_3 and PBr_3 , bear special mention. Thionyl chloride reacts with alcohols to give alkyl chlorides



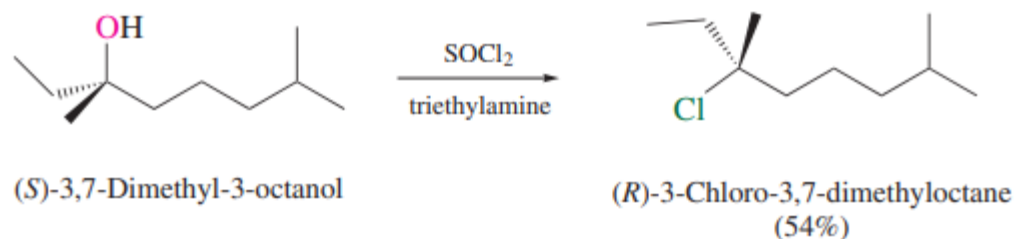
The reactions are typically carried out in the presence of an amine such as pyridine or triethylamine. In such cases, the amine acts as both a Brønsted base and a catalyst.



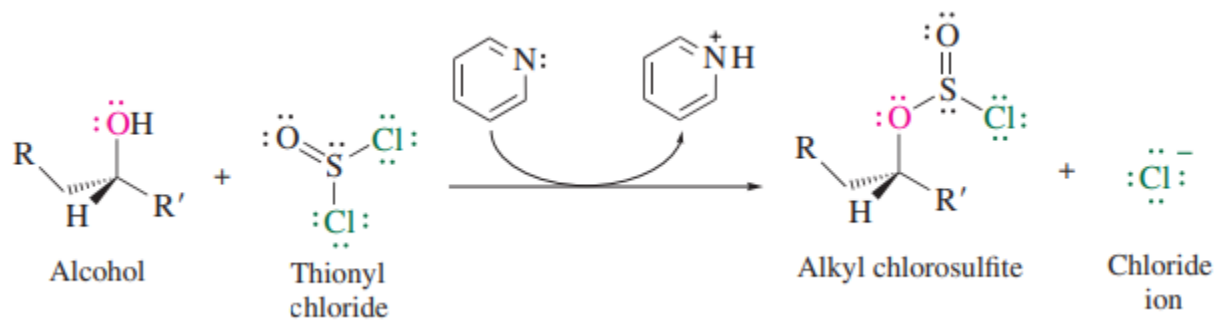
2-Ethyl-1-butanol

1-Chloro-2-ethylbutane (82%)

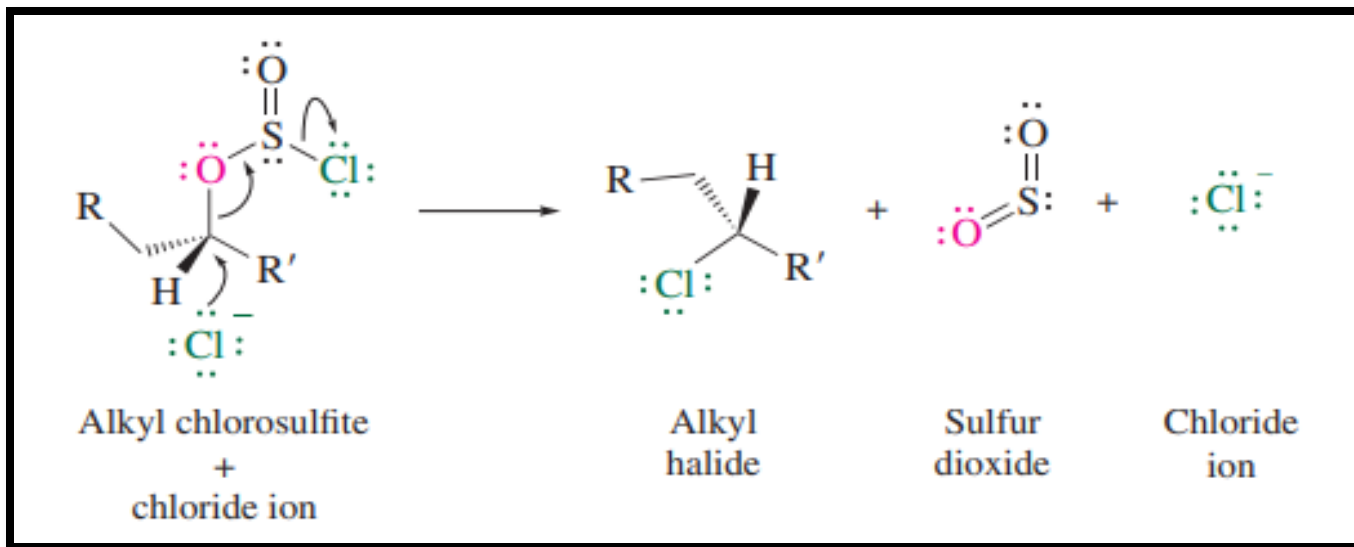
Inversion of configuration is normally observed when optically active alcohols are used.



In the first stage, reaction with thionyl chloride converts alcohol to a chlorosulfite. **Pyridine**, shown above the arrow in the equation, acts as a catalyst in one reaction and as a weak base in another. Triethylamine can serve the same function



In the second stage, the alkyl halide is formed by reaction of the chlorosulfite with chloride ion. In the presence of pyridine or trimethylamine as a catalyst, two separate reactions characterize this stage

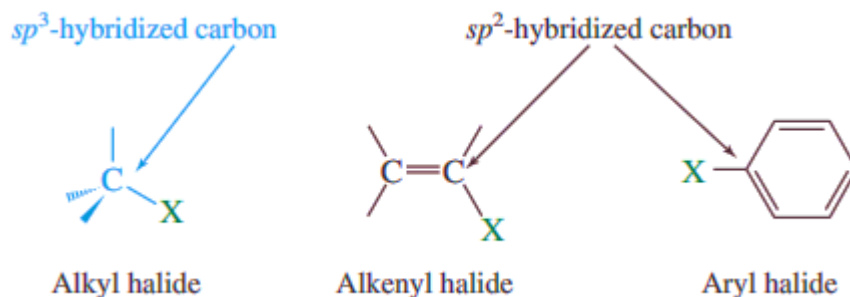


If the starting alcohol is primary, carbon–chlorine bond formation and carbon–oxygen bond-breaking occur in the same step by an SN2 process. If the starting alcohol is secondary or tertiary, an SN1 process in which a carbon–oxygen bond-breaking step precedes carbon–chlorine bond-making is involved

Alcohols react with hydrogen halides to yield alkyl halides. The reaction is useful as a synthesis of alkyl halides. The reactivity of hydrogen halides decreases in the order $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$. Alcohol reactivity decreases in the order tertiary > secondary > primary.

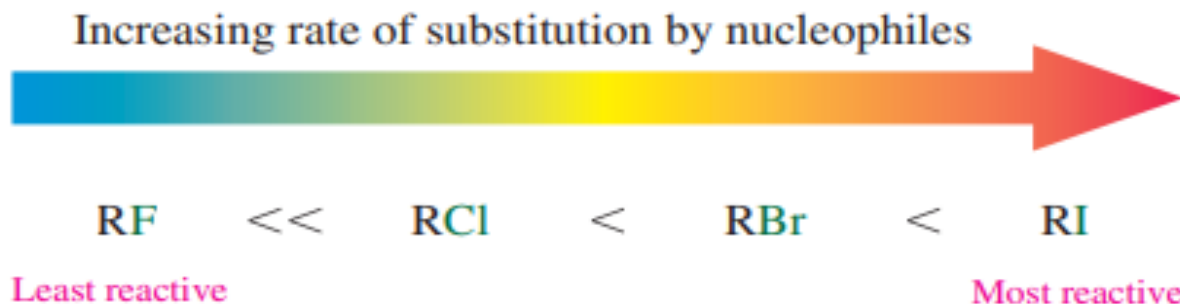
Alkyl halides

Alkyl halides, that is, compounds in which the halogen is attached to an sp^3 -hybridized carbon. Alkenyl halides and aryl halides, compounds in which the halogen is attached to sp^2 -hybridized carbons, are essentially unreactive under these conditions, and the principles to be developed in this chapter do not apply to them.



Relative Reactivity of Halide Leaving Groups

Among alkyl halides, alkyl iodides undergo Nucleophilic substitution at the fastest rate, alkyl fluorides the slowest



Alkyl chlorides are rarely used in Nucleophilic substitutions. These reactivity differences can be related to (1) **the carbon–halogen bond strength** and (2) **the basicity of the halide anion**.

Alkyl iodides have the weakest carbon–halogen bond and require the lowest activation energy to break;

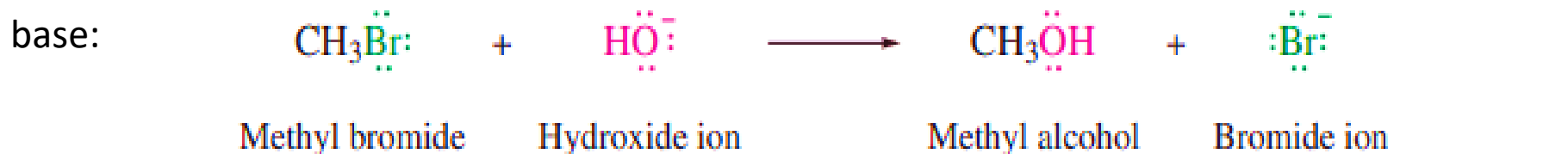
Alkyl fluorides have the strongest carbon–halogen bond and require the highest activation energy. Regarding basicity of the halide leaving group, iodide is the **weakest base**, fluoride the strongest.

It is generally true that the less basic the leaving group, the smaller the energy requirement for cleaving its bond to carbon and the faster the rate.

Alkyl iodides are several times more reactive than alkyl bromides and from 50 to 100 times more reactive than alkyl chlorides. Alkyl fluorides are several thousand times less reactive than sodium benzoate)

The S_N2 Mechanism of Nucleophilic Substitution

Kinetics: Because the rate of Nucleophilic substitution of an alkyl halide be it methyl, primary, secondary, or tertiary—depends on the leaving group (**I > Br > Cl > F**), the carbon–halogen bond must break in the slow (**rate-determining**) step, and the concentration of the alkyl halide must appear in the rate law. What about the nucleophile? Hughes and Ingold



obey a second-order rate law, first order in the alkyl halide and first order in the nucleophile

$$\text{Rate} = k[\text{CH}_3\text{Br}][\text{HO}^-]$$

They concluded that the rate-determining step is bimolecular and proposed the substitution Nucleophilic bimolecular (S_N2) mechanism shown as an equation .

The Hughes–Ingold S_N2 mechanism is a **one-step concerted process in which both the alkyl halide and the nucleophile are involved at the transition state**. Cleavage of the bond between carbon and the leaving group is assisted by formation of a bond between carbon and the nucleophile

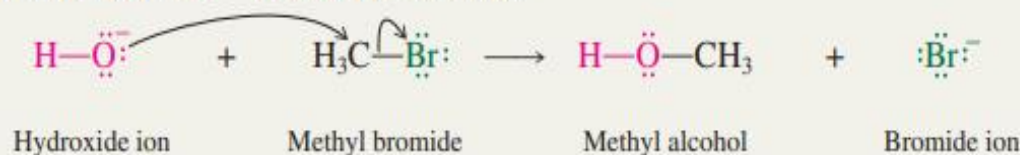
Carbon is partially bonded to both the incoming nucleophile and the departing halide at the transition state. Progress is made toward the transition state as the nucleophile begins to share a pair of its electrons with carbon and the halide ion leaves, taking with it the pair of electrons in its bond to carbon

The S_N2 Mechanism of Nucleophilic Substitution

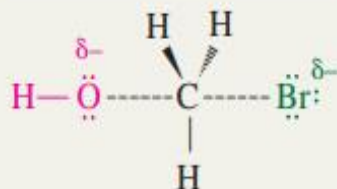
THE OVERALL REACTION:



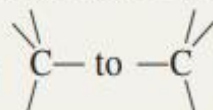
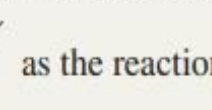
THE MECHANISM: The reaction proceeds in a single step. Hydroxide ion acts as a nucleophile. While the C—Br bond is breaking, the C—O bond is forming.



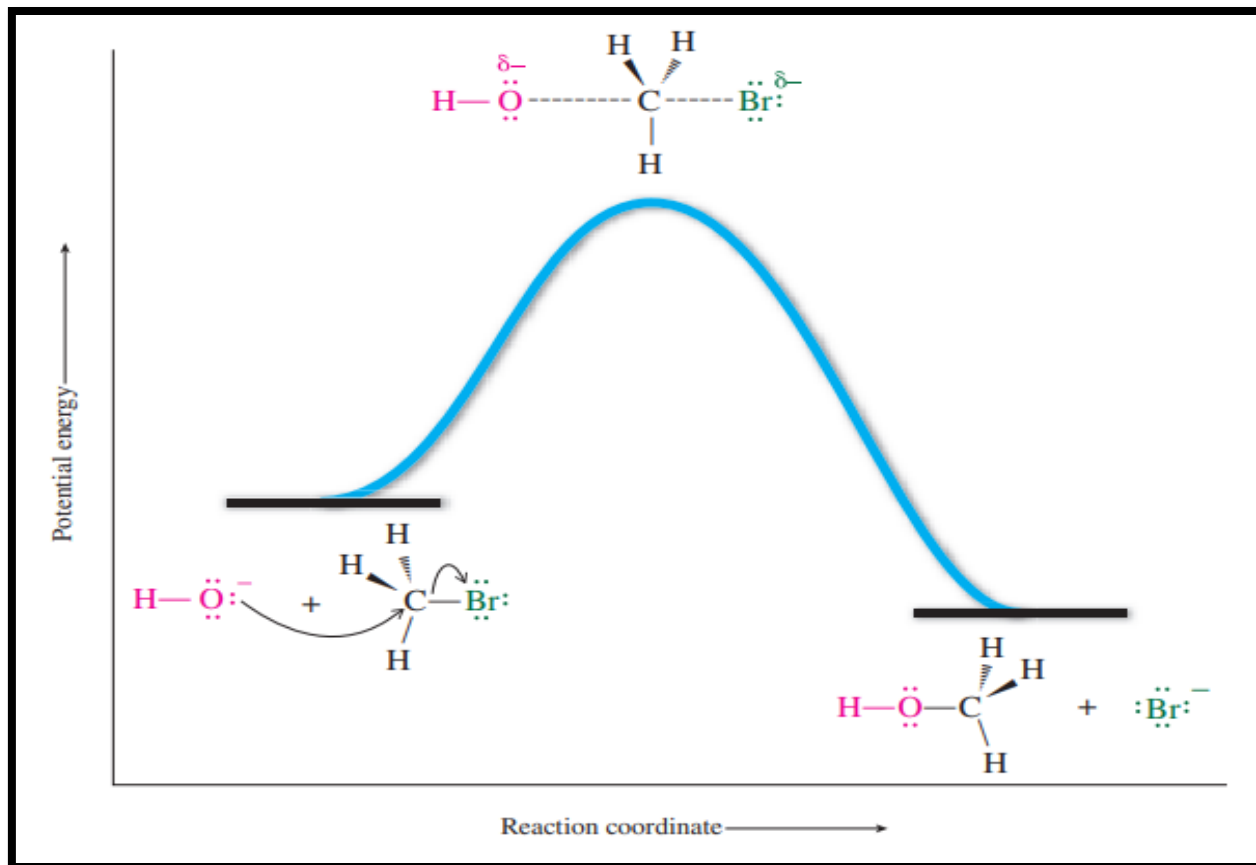
THE TRANSITION STATE: Hydroxide ion attacks carbon from the side opposite the C—Br bond.



Carbon is partially bonded to both hydroxide and bromide. The arrangement of bonds

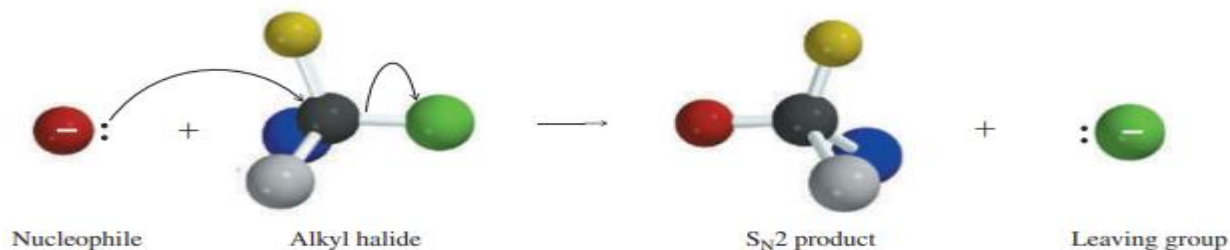
undergoes tetrahedral inversion from  to  as the reaction progresses.

Potential energy diagram for the reaction of methyl bromide with hydroxide ion by the SN2 mechanism.

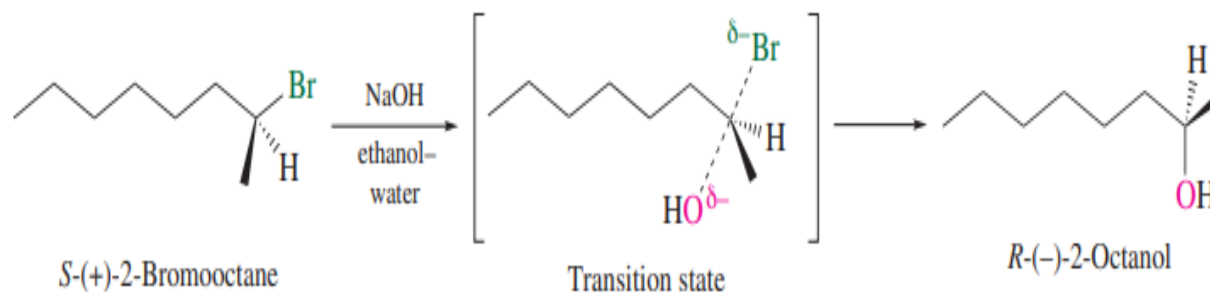


Stereochemistry. The nucleophile attacks carbon from the **side opposite the bond to the leaving group**. Another way of expressing the same point, especially when substitution occurs at a chirality center, is that SN2 reactions proceed with **inversion of configuration at the carbon that bears the leaving group**.

The tetrahedral arrangement of bonds in the reactant is converted to an inverted tetrahedral arrangement in the product



This generalization comes **from studies of Nucleophilic substitutions of optically active alkyl halides** such as that shown in the equation:



Countless experiments have confirmed that substitution by the SN2 mechanism is **stereospecific** and suggest that there exists a stereoelectronic requirement for the nucleophile to approach carbon from the side opposite the bond to the leaving group.

The SN2 mechanism is believed to describe most substitutions in which simple **primary and secondary alkyl halides react with negatively charged nucleophiles**.

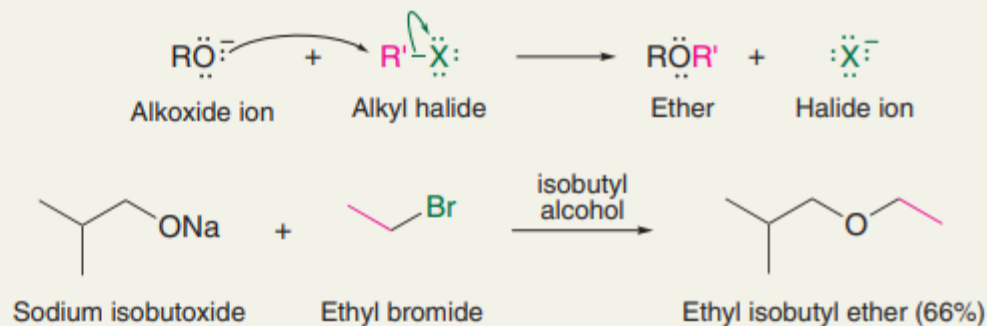
All the examples that introduced Nucleophilic substitution in Table 6.1 proceed by the SN2 mechanism (or a mechanism very much like SN2 remember .

TABLE 6.1 Functional-Group Transformation via Nucleophilic Substitution

Nucleophile and comments

Alkoxide ion: The oxygen atom of a metal alkoxide is nucleophilic and replaces the halogen of an alkyl halide. The product is an *ether*.

General equation and specific example



Continued

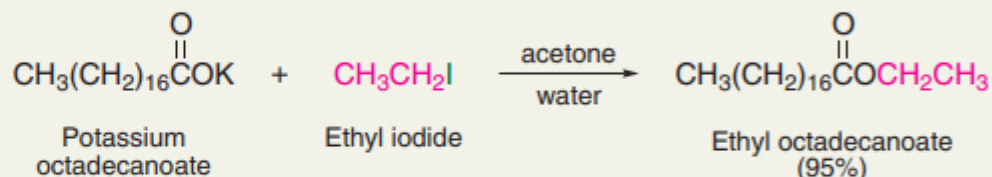
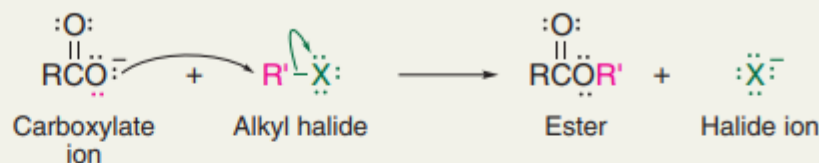
TABLE 6.1

Functional-Group Transformation via Nucleophilic Substitution (Continued)

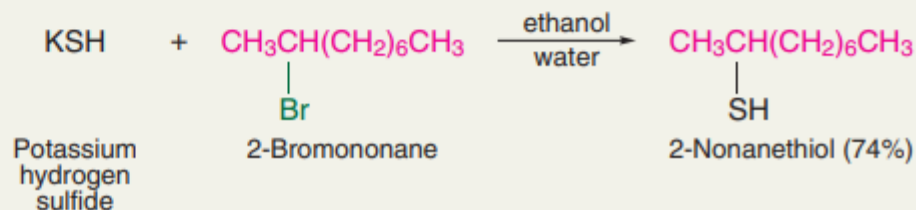
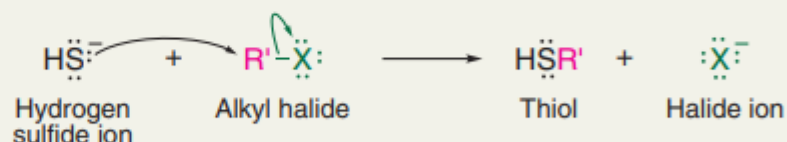
Nucleophile and comments

General equation and specific example

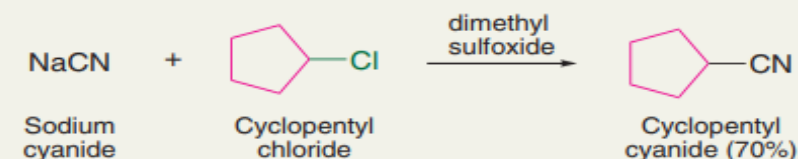
Carboxylate ion: An ester is formed when the negatively charged oxygen of a carboxylate replaces the halogen of an alkyl halide.



Hydrogen sulfide ion: Using hydrogen sulfide as a nucleophile permits the conversion of alkyl halides to *thiols*.



Cyanide ion: The negatively charged carbon of cyanide is the site of its nucleophilic character. Cyanide reacts with alkyl halides to extend a carbon chain by forming an *alkyl cyanide* or *nitrile*.

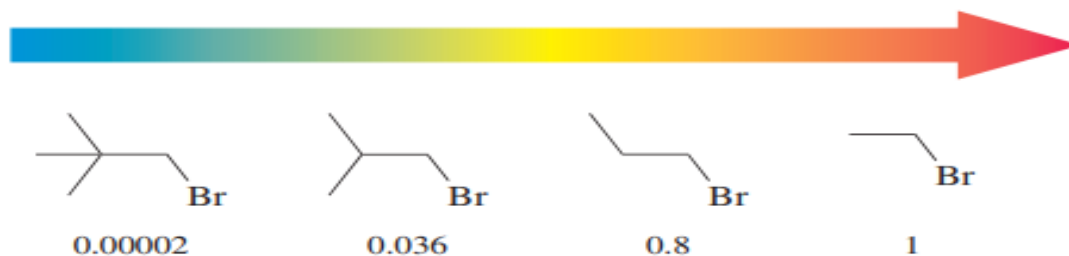


The very large rate differences between methyl, ethyl, isopropyl, and tert-butyl bromides reflect the **steric hindrance each offers to Nucleophilic attack**. The nucleophile must approach the alkyl halide from the side opposite the bond to the leaving group, and, as

This approach is **hindered by alkyl substituents on the carbon that is being attacked**.

The three hydrogens of methyl bromide offer little **resistance to approach of the nucleophile, and a rapid reaction occurs**. Replacing one of the hydrogens by a methyl group somewhat **shields the carbon from approach of the nucleophile and causes ethyl bromide to be less reactive than methyl bromide**. Replacing all three hydrogens by methyl groups almost completely blocks approach to the tertiary carbon of $(\text{CH}_3)_3\text{CBr}$ and shuts down bimolecular nucleophilic substitution.

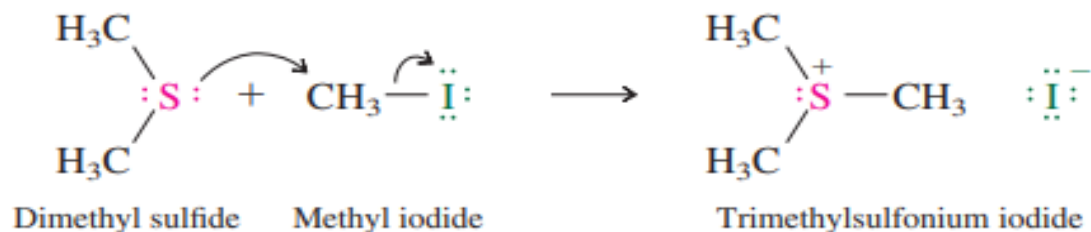
In general, $\text{S}_\text{N}2$ reactions of alkyl halides show the following dependence of rate on structure: **$\text{CH}_3\text{X} > \text{primary} > \text{secondary} > \text{tertiary}$** .



Nucleophiles and Nucleophilicity

The Lewis base that acts as the nucleophile often is, but need not always be, an anion.

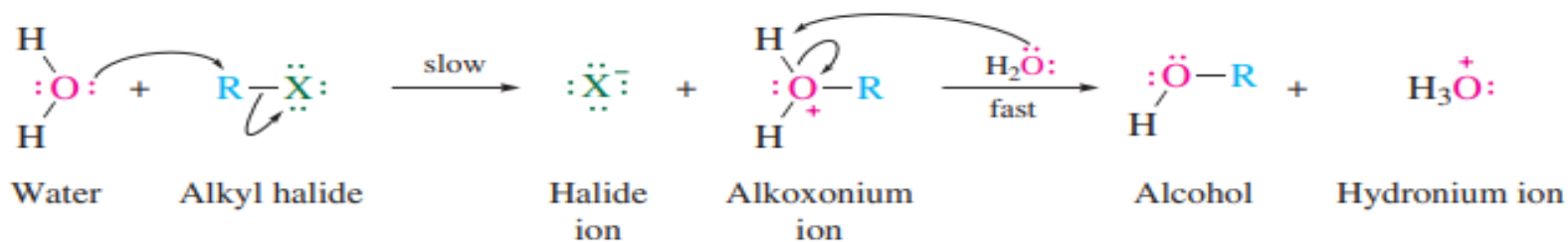
Neutral Lewis bases such as amines ($R_3N:$), phosphines ($R_3P:$), and sulfides ($R_2S:$) can also serve as nucleophiles.



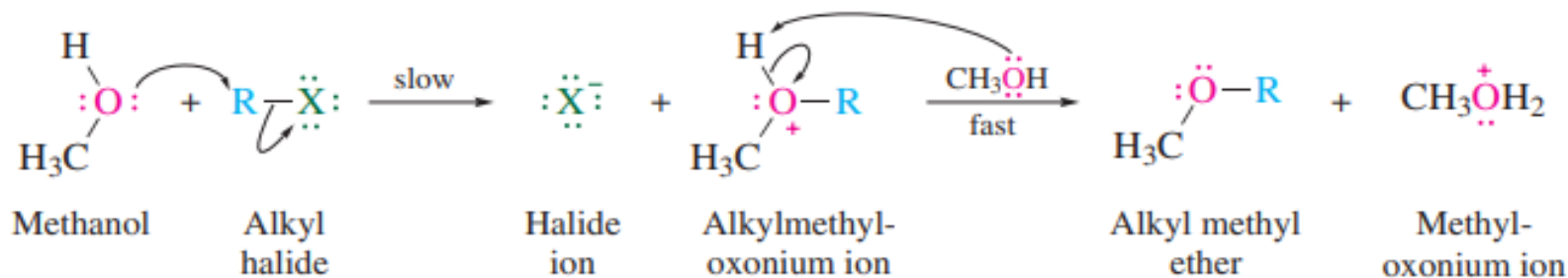
Other common examples of substitutions involving neutral nucleophiles include solvolysis reactions—substitutions where the nucleophile is the solvent in which the reaction is carried out. Solvolysis in water (hydrolysis) converts an alkyl halide to an alcohol.



The reaction occurs in two steps. The first yields an alkyloxonium ion by nucleophilic substitution and is rate-determining. The second gives the alcohol by proton transfer—a rapid Brønsted acid–base reaction.

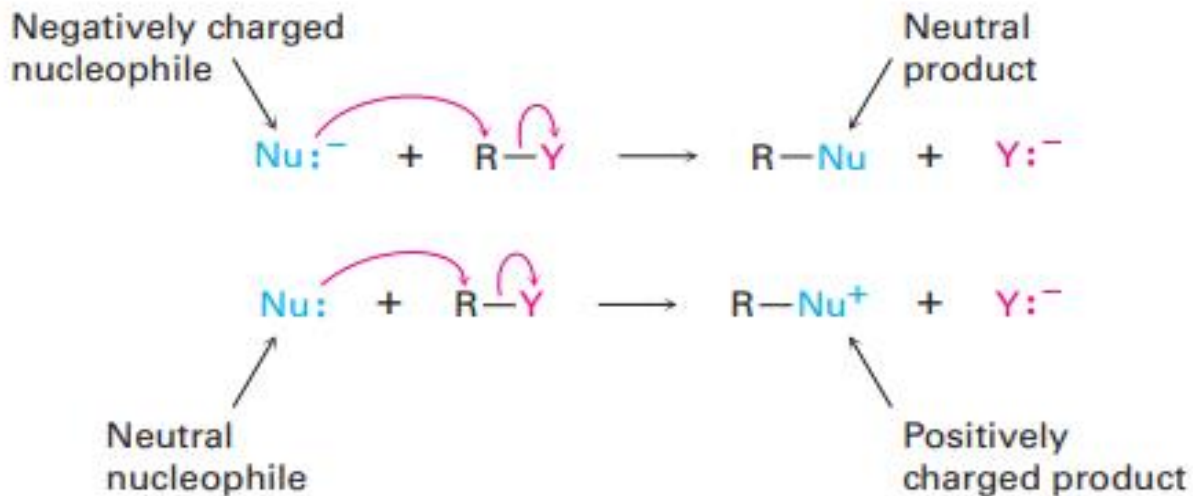


Analogous reactions take place in other solvents that, like water, contain an OH group. Solvolysis in methanol (methanolysis) gives a methyl ether.



Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^- , HS^- , RS^-	$>10^5$
Good nucleophiles	Br^- , HO^- , RO^- , CN^- , N_3^-	10^4
Fair nucleophiles	NH_3 , Cl^- , F^- , RCO_2^-	10^3
Weak nucleophiles	H_2O , ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

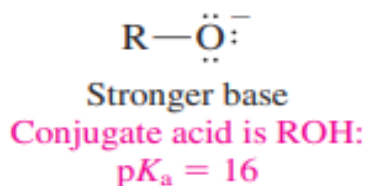


Nucleophilicity usually increases going down a column of the periodic table

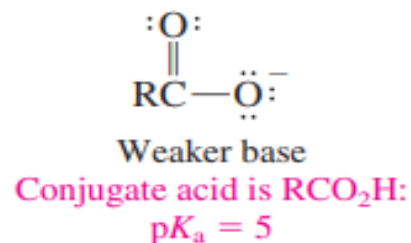
Negatively charged nucleophiles are usually more reactive than neutral ones

OH^- is both more basic and more Nucleophilic than acetate ion, CH_3CO_2^- , which in turn is more basic and more Nucleophilic than H_2O

Because attack by the nucleophile is the rate-determining step of the SN2 mechanism, the rate of substitution varies from nucleophile to nucleophile. Nucleophilic strength, or nucleophilicity, is a measure of how fast a Lewis base displaces a leaving group from a suitable substrate. Table 6.2 compares the rate at which various Lewis bases react with methyl iodide in methanol, relative to methanol as the standard nucleophile. As long as the Nucleophilic atom is the same, the more basic the nucleophile, the more reactive it is. An alkoxide ion (RO⁻) is more basic and more Nucleophilic than a carboxylate ion (RCO₂⁻).



is more nucleophilic than



The connection between **basicity** and **nucleophilicity** holds when comparing atoms in the **same row of the periodic table**.

Thus, **HO⁻** is more basic and more Nucleophilic than **F⁻**, and **NH₃** is more basic and more Nucleophilic than **H₂O**.

It does not hold when proceeding down a column in the periodic table. In that case, polarizability involving the distortion of the electron density surrounding an atom or ion comes into play.

The more easily distorted the electron distribution, the more nucleophilic the atom or ion.

Among the halide ions, for example, **I⁻** is the least basic but the most nucleophilic, **F⁻** the most basic but the least nucleophilic.

In the same vein, **phosphines (R₃P)** are more nucleophilic than amines (**R₃N**), and **thioethers (R₂S)** more nucleophilic than their oxygen counterparts (**R₂O**)

Another factor, likely the one most responsible for the **inverse relationship between basicity and nucleophilicity among the halide ions**, is the degree to which the ions are solvated by ion-dipole forces of the type illustrated

in Figure 6.3. Smaller anions, because of their **high charge-to-size ratio**, are more strongly solvated than larger ones.

In order to act as a nucleophile, the halide must shed some of the solvent molecules that surround it.

Among the halide anions, ion-dipole forces are strongest for F^- and weakest for I^- . Thus, the nucleophilicity of F^- is suppressed more than that of Cl^- , Cl^- more than Br^- , and Br^- more than I^- .

Similarly, HO^- is smaller, more solvated, and less nucleophilic than HS^- .


The importance of solvation in reducing the nucleophilicity of small anions more than larger ones can be seen in the fact that, when measured in the gas phase where solvation forces don't exist, the order of halide nucleophilicity reverses and does track **basicity: $F^- > Cl^- > Br^- > I^-$** . When comparing species that have the same nucleophilic atom, a **negatively charged nucleophile is more reactive than a neutral one**

The Leaving Group

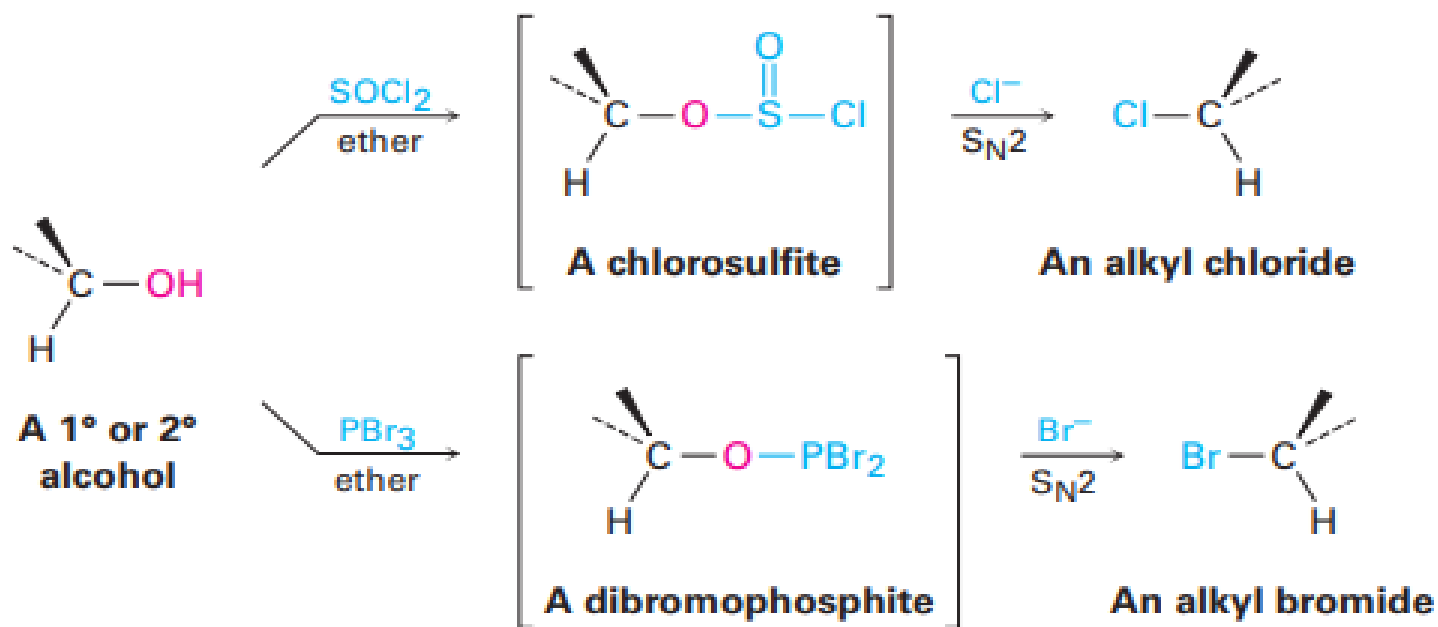
Still another variable that can affect the SN2 reaction is the nature of the group displaced by the incoming nucleophile. Because the leaving group is expelled with a negative charge in most SN2 reactions, the best leaving groups are those that best stabilize the negative charge in the transition state. The greater the extent of charge stabilization by the leaving group.

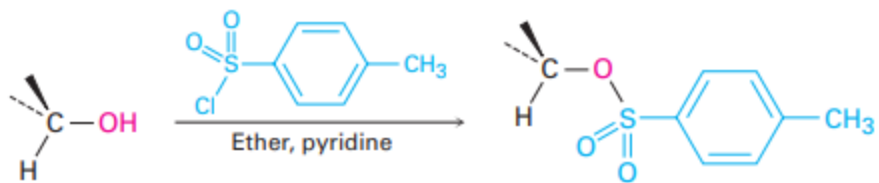
the groups that best stabilize a negative charge are also the weakest bases. Thus, weak bases such as Cl⁻, Br⁻, and tosylate ion make good leaving groups, while strong bases such as ⁻OH and ⁻NH₂ make poor leaving groups.

Relative reactivity	$\text{OH}^-, \text{NH}_2^-, \text{OR}^-$	F ⁻	Cl ⁻	Br ⁻	I ⁻	TosO ⁻
	<<1	1	200	10,000	30,000	60,000

 Leaving group reactivity

It's just as important to know which are **poor leaving groups** as to know which are **good**, and the preceding data clearly indicate that **F⁻, HO⁻, RO⁻, and H₂N⁻** are not displaced by nucleophiles. In other words, **alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions**. To carry out an S_N2 reaction with an alcohol, it's necessary to convert the **-OH into a better leaving group**. This, in fact, is just what happens when a primary or secondary alcohol is converted into either an alkyl chloride by reaction with SOCl₂ or an alkyl bromide by reaction with PBr₃





A 1° or 2°
alcohol

A tosylate

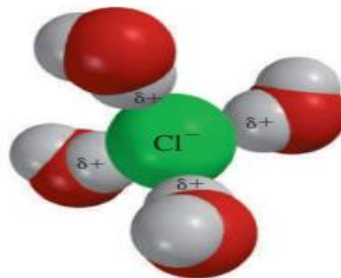
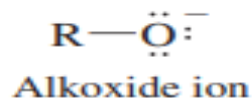
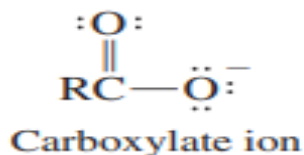
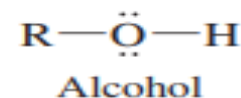


Figure 6.3

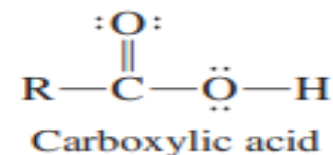
Solvation of a chloride ion by water.



is more nucleophilic than

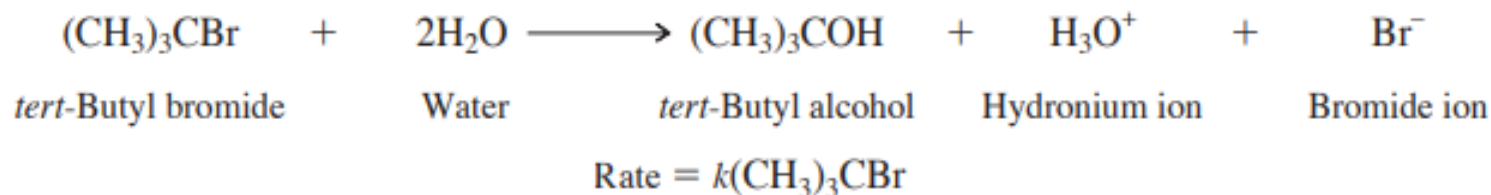


is more nucleophilic than



The S_N1 Mechanism of Nucleophilic Substitution

In their studies of reaction kinetics, Hughes and Ingold observed that the hydrolysis of tert-butyl bromide follows a first-order rate law:



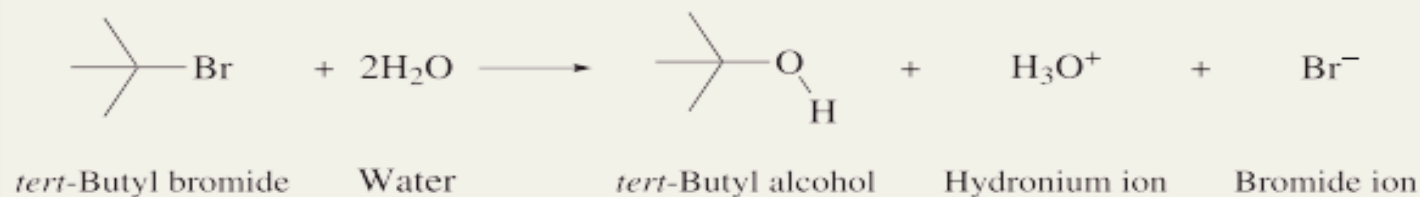
The reaction rate depends only on the concentration of tert-butyl bromide. Just as they interpreted a second-order rate law in terms of a bimolecular rate-determining step

, Hughes and Ingold saw first-order kinetics as evidence for a **unimolecular rate-determining step involving only the alkyl halide while independent of both the concentration and identity of the nucleophile**. Like the SN1 mechanism for the reaction of alcohols with hydrogen halides (Section 5.8), this pathway is characterized by the formation of a carbocation in the rate determining step

Mechanism 6.2

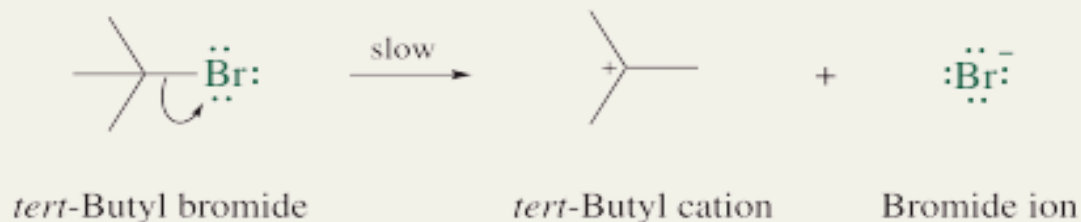
The S_N1 Mechanism of Nucleophilic Substitution

THE OVERALL REACTION:

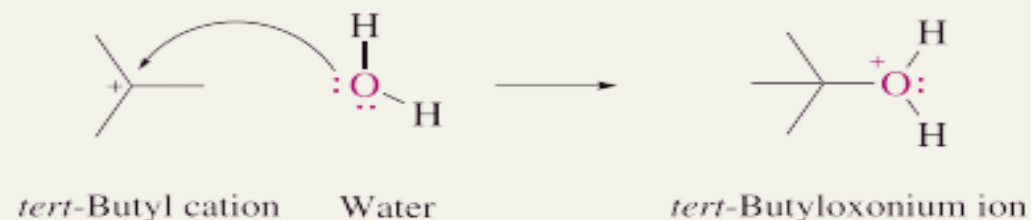


THE MECHANISM:

Step 1: The alkyl halide dissociates to a carbocation and a halide ion.

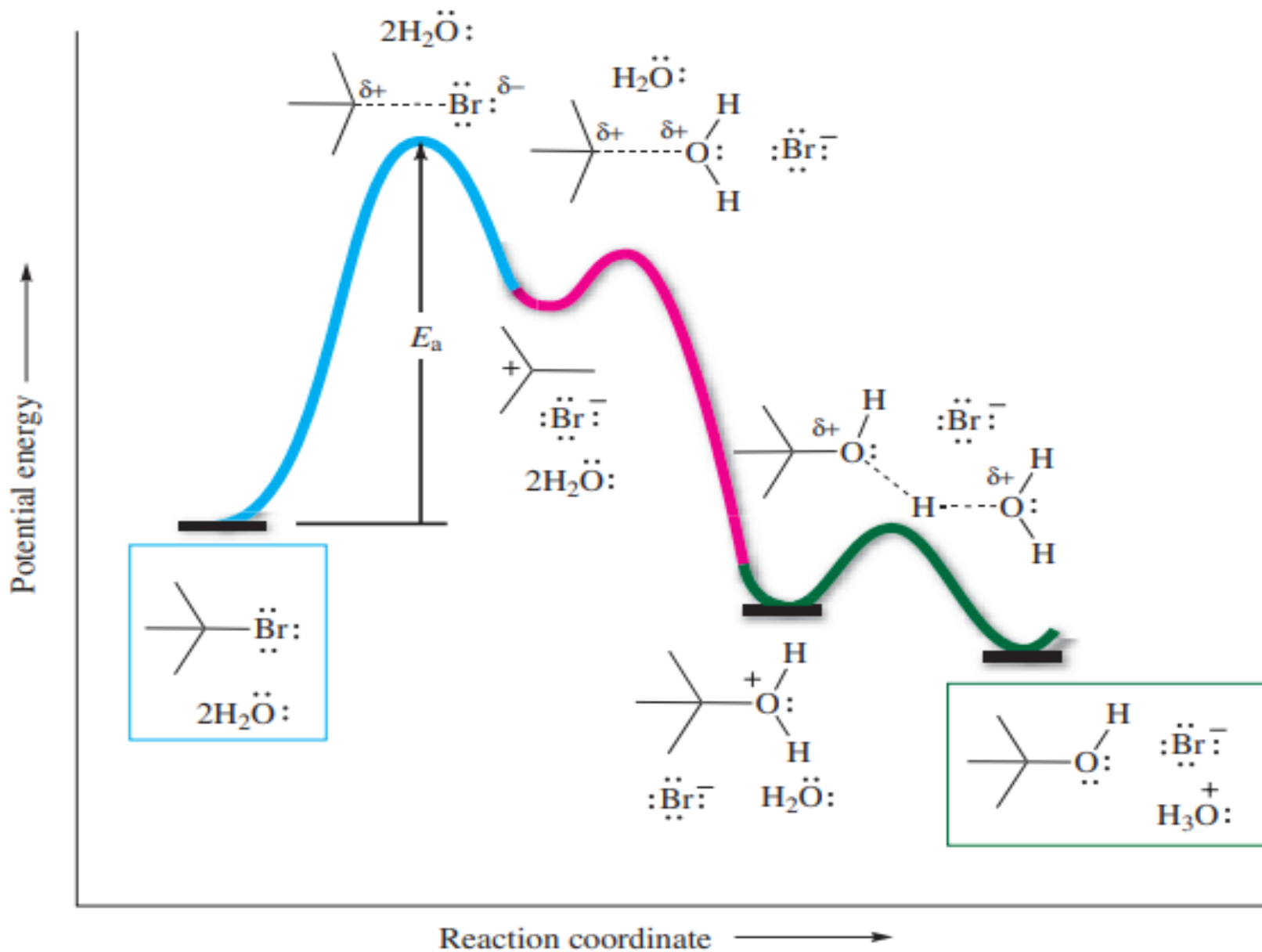


Step 2: The carbocation formed in step 1 reacts rapidly with water, which acts as a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an alkyloxonium ion.



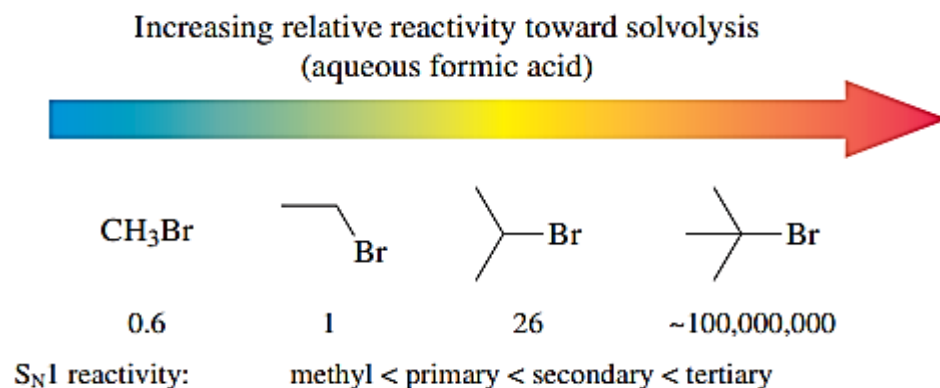
Step 3: This step is a fast acid–base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.





Energy diagram illustrating the SN1 mechanism for hydrolysis of tert-butyl bromide

competition from SN2. Under these conditions, the structure/reactivity trend among alkyl halides is exactly opposite to the SN2 profile.



We have seen a similar trend in the reaction of alcohols with hydrogen halides, the more stable the carbocation, the faster it is formed, and the faster the reaction rate.

Methyl and primary carbocations are so high in energy that they are unlikely intermediates in Nucleophilic substitutions.

Although methyl and ethyl bromide undergo hydrolysis under the conditions just described, substitution probably takes place by an SN2 process in which water is the nucleophile..

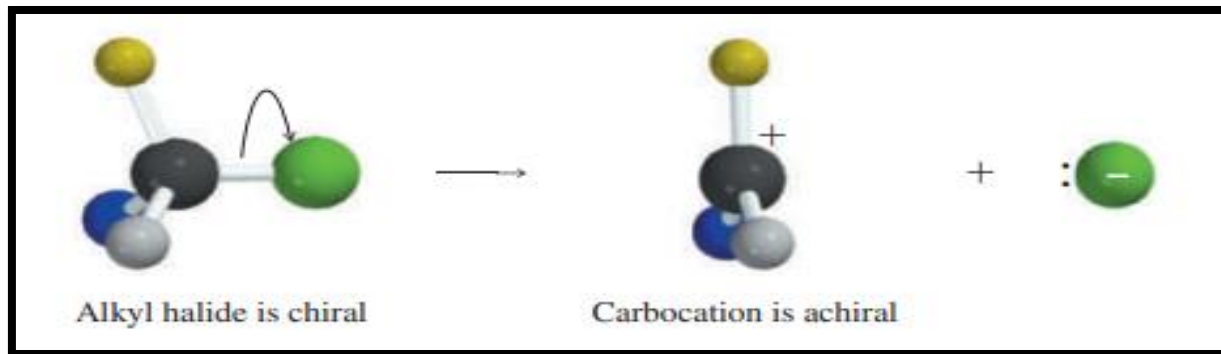
In general, methyl and primary alkyl halides never react by the SN1 mechanism; tertiary alkyl halides never react by SN2.

Secondary alkyl halides occupy a borderline region in which the nature of the nucleophile is the main determining factor in respect to the mechanism.

Secondary alkyl halides usually react with good nucleophiles by the SN2 mechanism, and with weak nucleophiles by SN1

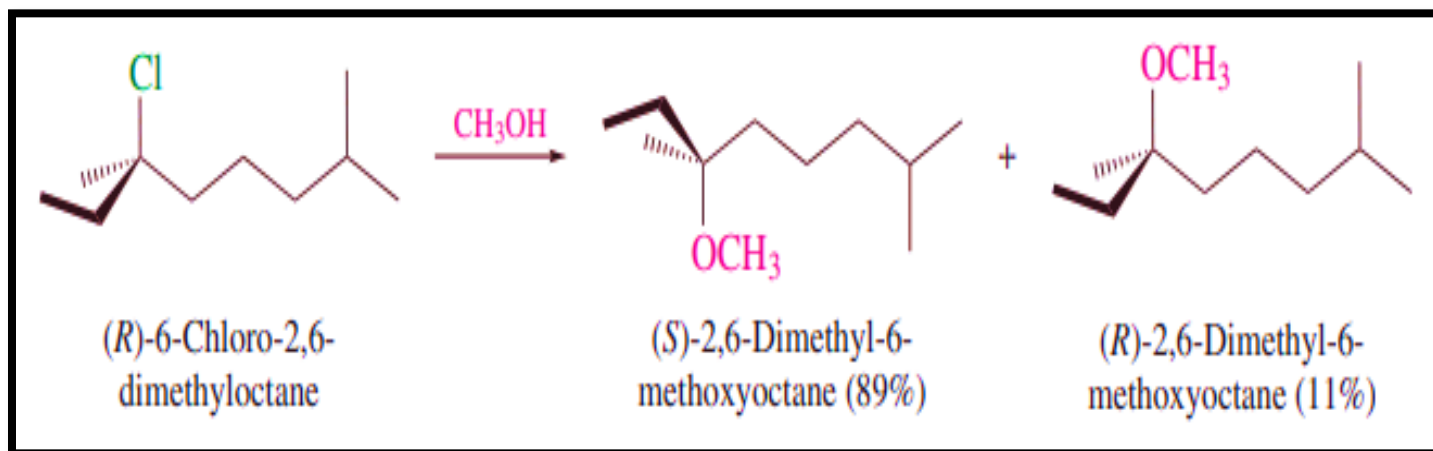
Stereochemistry of S_N1 Reactions

Although SN2 reactions are stereospecific and proceed with **inversion of configuration at carbon**, the situation is not as clear-cut for SN1. When the leaving group departs from a chirality center of an optically active halide, the positively charged carbon that results is sp²-hybridized and cannot be a chirality center. The three bonds to that carbon define a plane of symmetry.

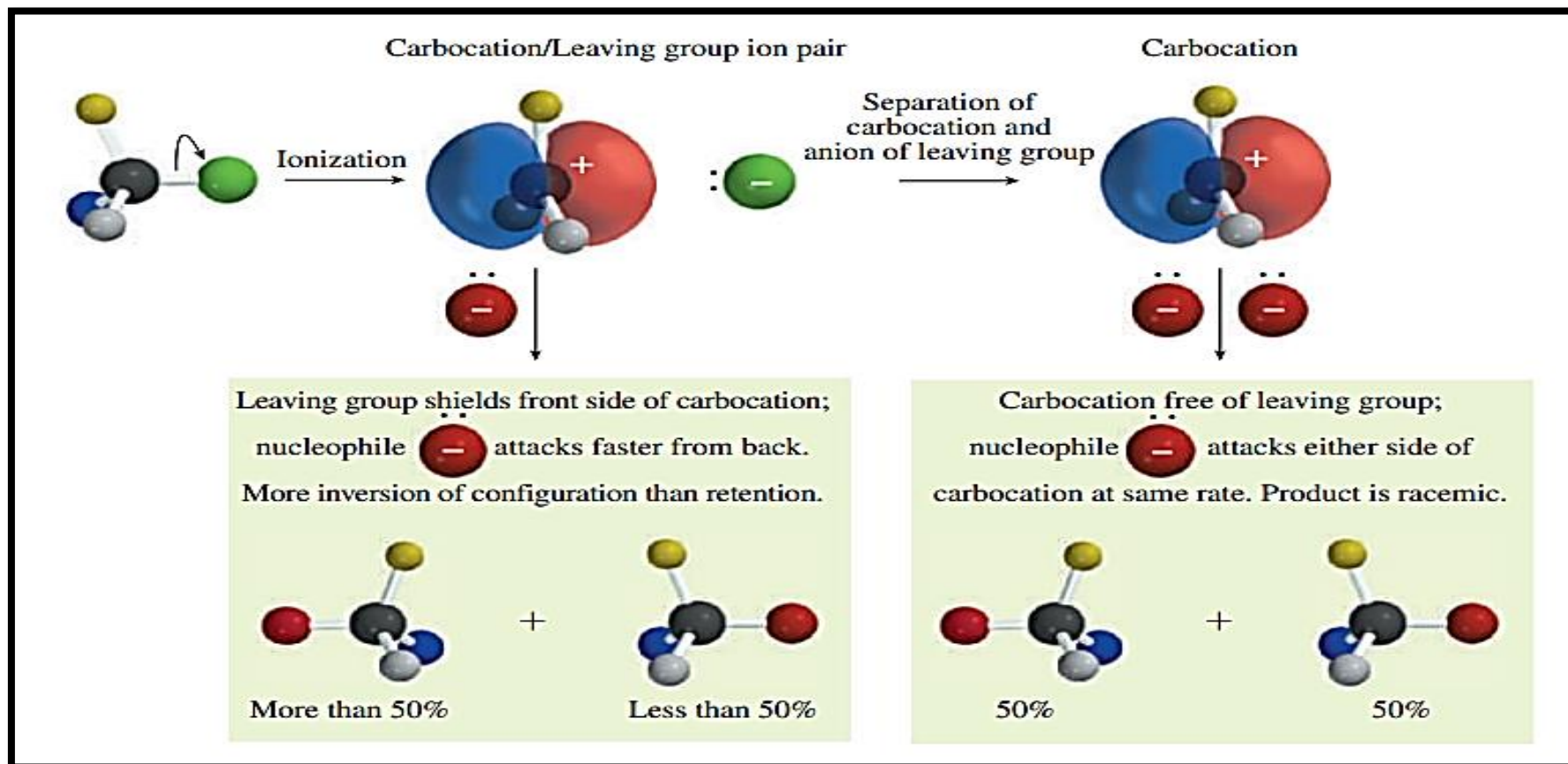
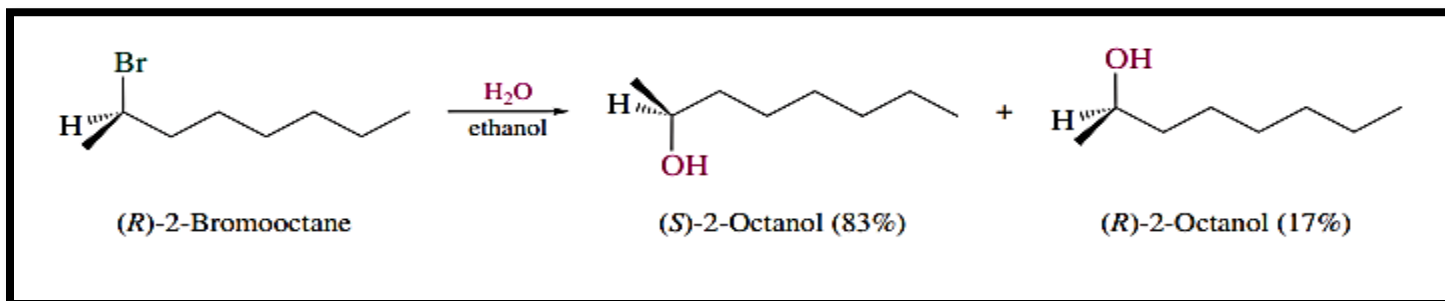


If a nucleophile can approach each face of the carbocation equally well, substitution by the SN1 mechanism should give a 1:1 mixture of enantiomers irrespective **of whether the starting alkyl halide is R, S, or racemic**. SN1 reactions should give racemic products from optically active starting materials. But they rarely do.

Methanolysis of the tertiary alkyl halide (*R*)-3-chloro-3,7-dimethyloctane, which almost certainly proceeds by an SN1 mechanism, takes place with a high degree of inversion of configuration.



Similarly, hydrolysis of (R)-2-bromooctane follows a first-order rate law and yields 2-octanol with 66% net inversion of configuration.



SN1 stereochemistry

The carbocation formed by ionization of an alkyl halide is shielded on its “front” side by the leaving group. The nucleophile attacks this carbocation–halide ion pair faster from the less shielded “back” side and the product is formed with net inversion of configuration. In a process that competes with Nucleophilic attack on the ion pair, the leaving group diffuses away from the carbocation. **The nucleophile attacks the carbocation at the same rate from either side to give equal amounts of enantiomers.**

Carbocation Rearrangements in S_N1 Reactions

Additional evidence for carbocation intermediates in certain Nucleophilic substitutions comes **from observing rearrangements of the kind** described in Section 5.12. For example, hydrolysis of the secondary alkyl bromide 2-bromo-3-methylbutane yields the rearranged tertiary alcohol 2-methyl-2-butanol as the only substitution product.

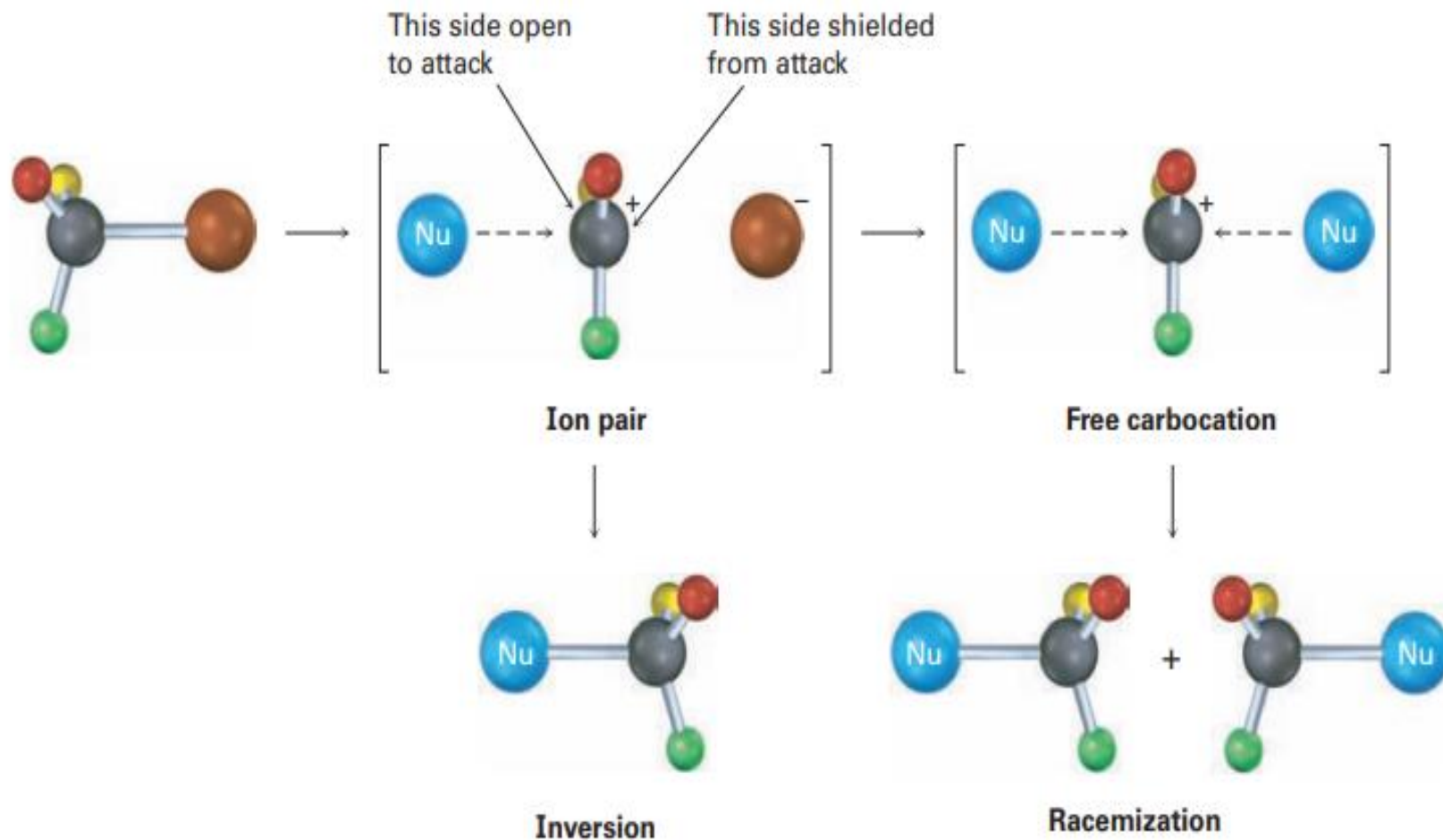
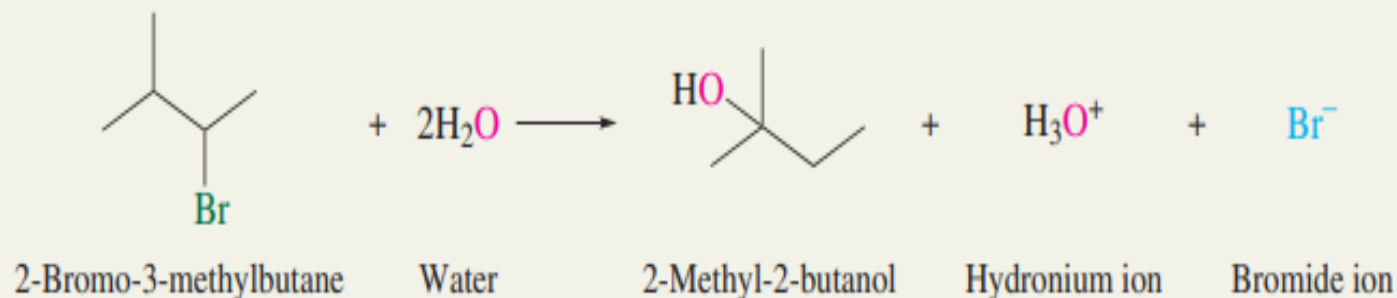


FIGURE 11-11 Ion pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.

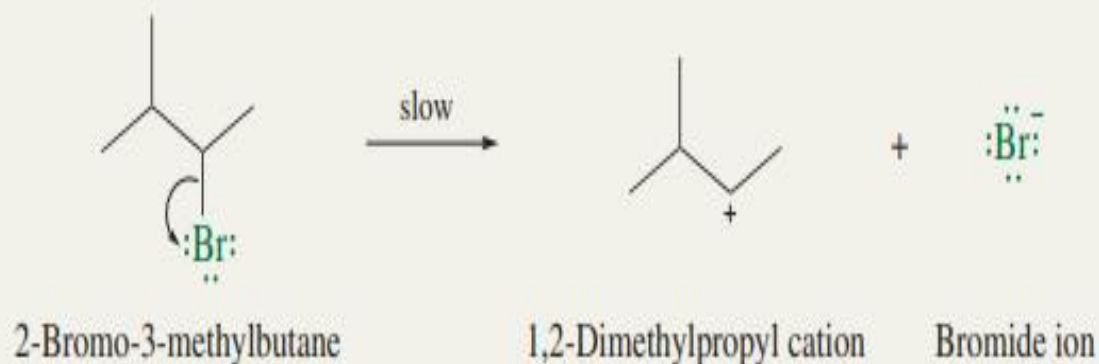
Carbocation Rearrangement in the S_N1 Hydrolysis of 2-Bromo-3-methylbutane

THE OVERALL REACTION:

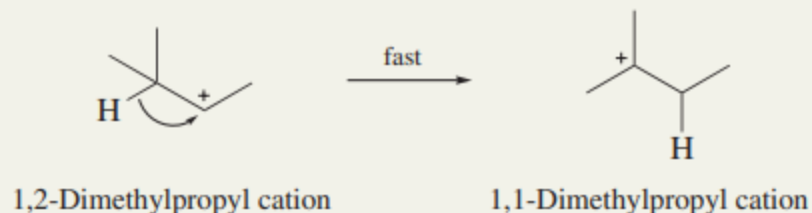


THE MECHANISM:

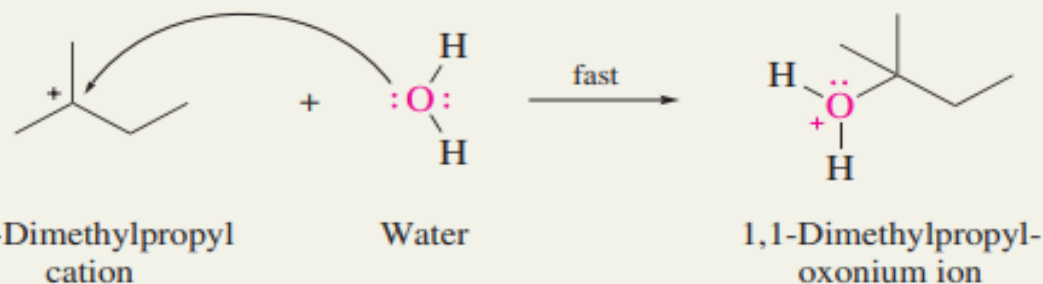
Step 1: The alkyl halide ionizes to give a carbocation and bromide ion. This is the rate-determining step.



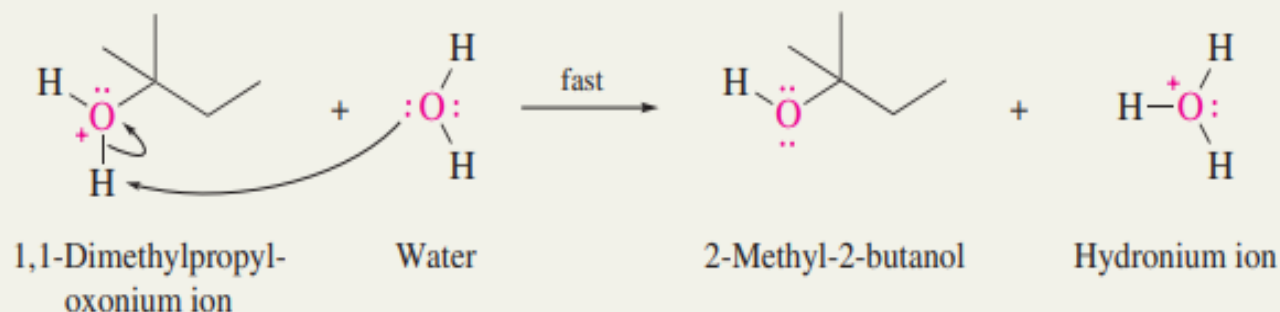
Step 2: The carbocation formed in step 1 is secondary; it rearranges by a hydride shift to form a more stable tertiary carbocation.



Step 3: The tertiary carbocation is attacked by water acting as a nucleophile.



Step 4: Proton transfer from the alkyloxonium ion to water completes the process.



Rearrangements, when they do occur, are taken as evidence for carbocation intermediates and point to the $\text{S}_{\text{N}}1$ mechanism as the reaction pathway.

Rearrangements are never observed in $\text{S}_{\text{N}}2$ reactions of alkyl halides