Organic Chemistry I

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7. Further Reactions of Haloalkanes

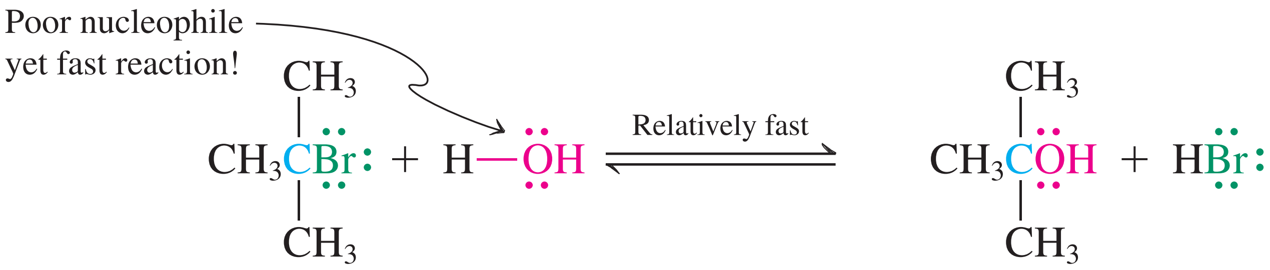
7.1 SOLVOLYSIS OF TERTIARY AND SECONDARY HALOALKANES

The rate of the S_N2 reaction diminishes drastically when the reacting center changes from primary to secondary to tertiary.

Secondary and tertiary halides do undergo substitution, but by another mechanism. In fact, these substrates transform readily, even in the presence of weak nucleophiles, to give substitution products.

Such a transformation, in which a substrate undergoes substitution by *solvent* molecules, is called **solvolysis** (e.g. methanolysis, ethanolysis, etc.). When the solvent is water, the term **hydrolysis** is applied.

An Example of Solvolysis: Hydrolysis

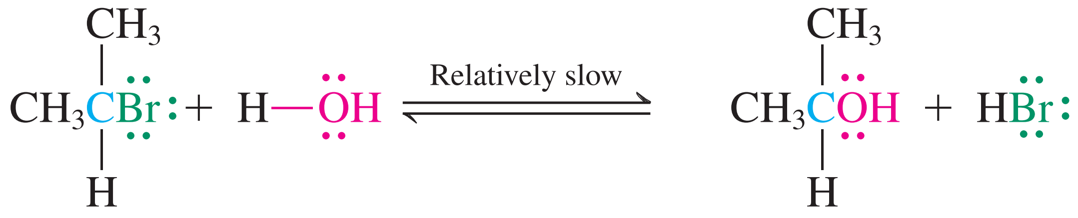


2-Bromo-2-methylpropane
(*tert*-Butyl bromide)

2-Methyl-2-propanol
(*tert*-Butyl alcohol)

2-Bromopropane is hydrolyzed similarly, albeit much more slowly, whereas 1-bromopropane, bromoethane, and bromomethane are *unchanged* under these conditions.

Hydrolysis of a Secondary Haloalkane



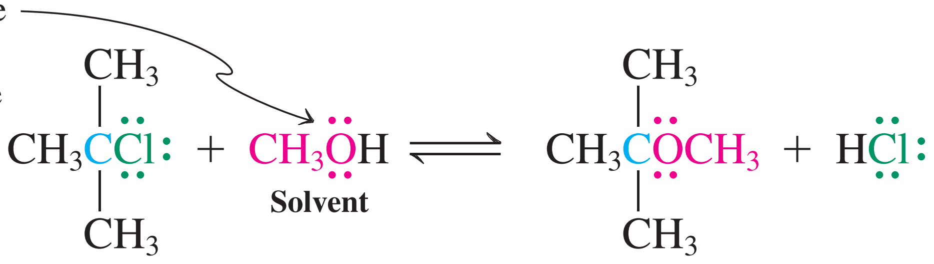
$$CH_3\overset{CH_3}{\underset{H}{C}}\ddot{\underset{..}{Br}}{:} + H{-}\ddot{\underset{..}{O}}H \xrightleftharpoons{\text{Relatively slow}} CH_3\overset{CH_3}{\underset{H}{C}}\ddot{\underset{..}{O}}H + H\ddot{\underset{..}{Br}}{:}$$

2-Bromopropane (Isopropyl bromide)

2-Propanol (Isopropyl alcohol)

Solvolysis also takes place in alcohol solvents.

Solvolysis of 2-Chloro-2-methylpropane in Methanol



Solvolysis—the solvent is also the nucleophile

$$CH_3\overset{CH_3}{\underset{CH_3}{C}}\ddot{\underset{..}{Cl}}{:} + CH_3\ddot{\underset{..}{O}}H \rightleftharpoons CH_3\overset{CH_3}{\underset{CH_3}{C}}\ddot{\underset{..}{O}}CH_3 + H\ddot{\underset{..}{Cl}}{:}$$

Solvent

2-Chloro-2-methylpropane

2-Methoxy-2-methylpropane

Although the process gives the products expected from an S_N2 reaction, the order of reactivity is *reversed* from that found under typical S_N2 conditions.

Primary halides are very slow in their reactions with water, secondary halides are more reactive, and tertiary halides are about *1 million times* as fast as primary ones.

To understand the details of this transformation, kinetics, stereochemistry, the effect of substrate structure, and solvent on reaction rates will be studied.

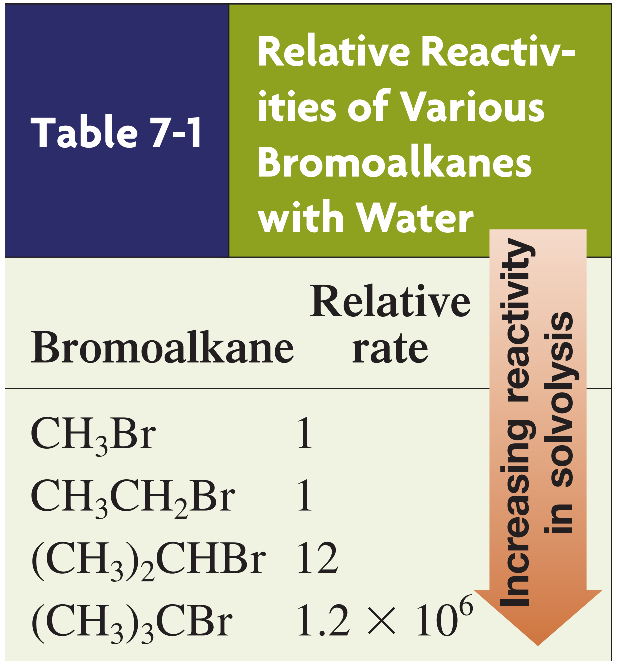


Table 7-1 **Relative Reactivities of Various Bromoalkanes with Water**

Bromoalkane	Relative rate
CH_3Br	1
CH_3CH_2Br	1
$(CH_3)_2CHBr$	12
$(CH_3)_3CBr$	1.2×10^6

Increasing reactivity in solvolysis

7.2 UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION

The S_N2 reaction:

- has second-order kinetics
- generates products stereospecifically with inversion of configuration
- is fastest with halomethanes and successively slower with primary and secondary halides
- takes place only extremely slowly with tertiary substrates

In contrast, solvolysis:

- follow a *first-order* rate law
- are *not* stereospecific
- are characterized by the *opposite* order of reactivity

Solvolysis follows first-order kinetics

By varying the concentrations of 2-bromo-2-methylpropane and water in formic acid (a polar solvent of very low nucleophilicity) and measuring the rates of solvolysis:

The results of these experiments show that *the rate of hydrolysis of the bromide is proportional to the concentration of only the starting halide, **not** the water.*

$$\text{Rate} = k[(\text{CH}_3)_3\text{CBr}]\ \text{mol L}^{-1}\ \text{s}^{-1}$$

The observed rate is that of the slowest step in the sequence: the **rate-determining step.**

The mechanism of solvolysis includes carbocation formation

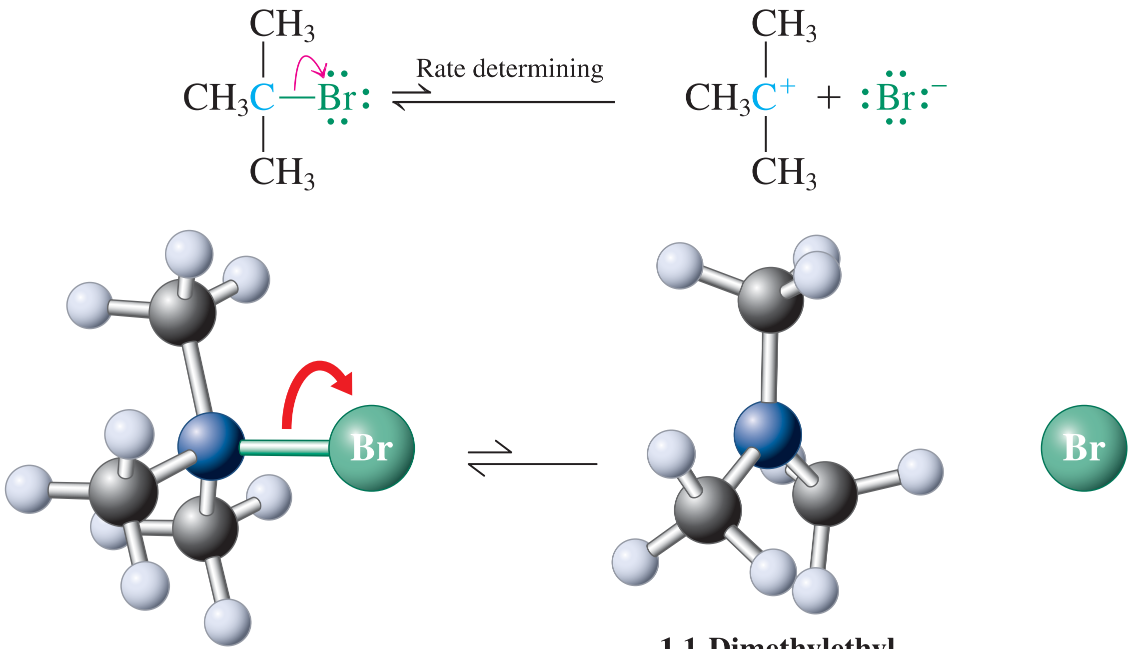
The hydrolysis of 2-bromo-2-methylpropane is said to proceed by **unimolecular nucleophilic substitution,** abbreviated **S_N1.** The number 1 indicates that only one molecule participates in the rate-determining step: The rate of the reaction does *not* depend on the concentration of the nucleophile.

The mechanism consists of three steps.

Step 1. The rate-determining step is the dissociation of the haloalkane to an alkyl cation and bromide. This conversion is an example of heterolytic cleavage.

The hydrocarbon product contains a positively charged central carbon atom attached to three other groups and bearing only an electron sextet. Such a structure is called a **carbocation.**

Dissociation of Halide to Form a Carbocation

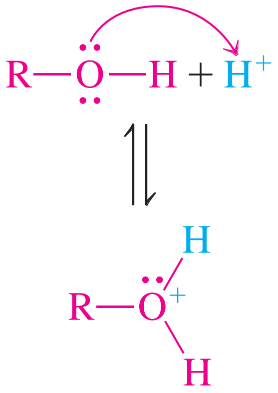


$$\mathrm{CH_3}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}{-}\ddot{\underset{..}{\mathrm{Br}}}: \xrightleftharpoons{\text{Rate determining}} \mathrm{CH_3}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}^{+}}} + :\ddot{\underset{..}{\mathrm{Br}}}:^{-}$$

1,1-Dimethylethyl cation (*tert*-Butyl cation)

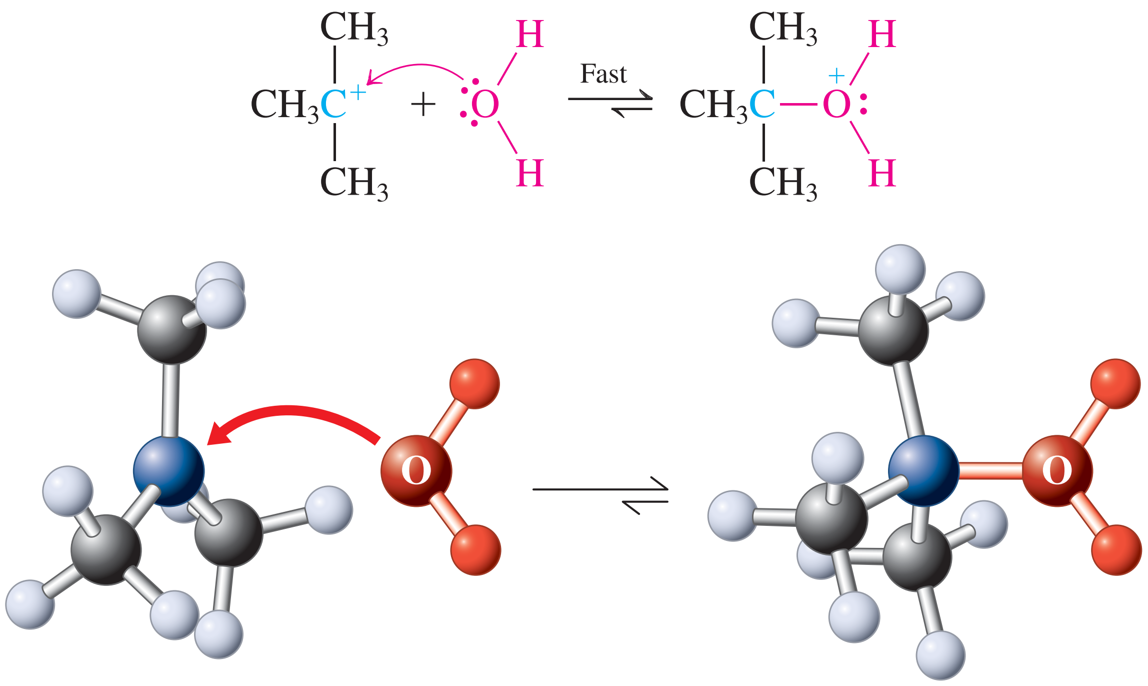
Step 2. The 1,1-dimethylethyl (*tert*-butyl) cation formed in step 1 is a powerful electrophile that is immediately trapped by the surrounding water. This process can be viewed as a nucleophilic attack by the solvent on the electron-deficient carbon.

The resulting species is an example of an **alkyloxonium ion,** the conjugate acid of an alcohol—in this case 2-methyl-2-propanol, the eventual product of the sequence.



Alkyloxonium ion

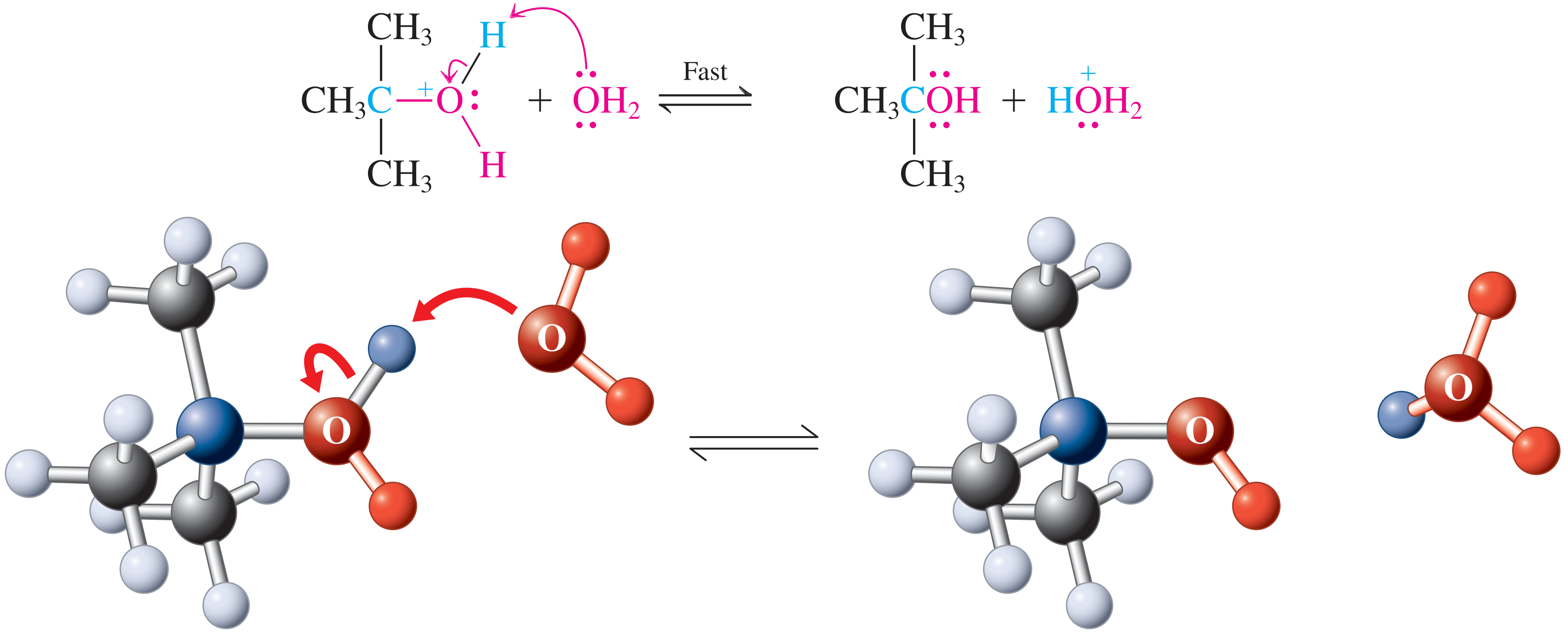
Nucleophilic Attack by Water



An alkyloxonium ion

Step 3. Like the hydronium ion, H_3O^+, the first member of the series of oxonium ions, all alkyloxonium ions are strong acids. They are therefore readily deprotonated by the water in the reaction medium to furnish the final alcohol.

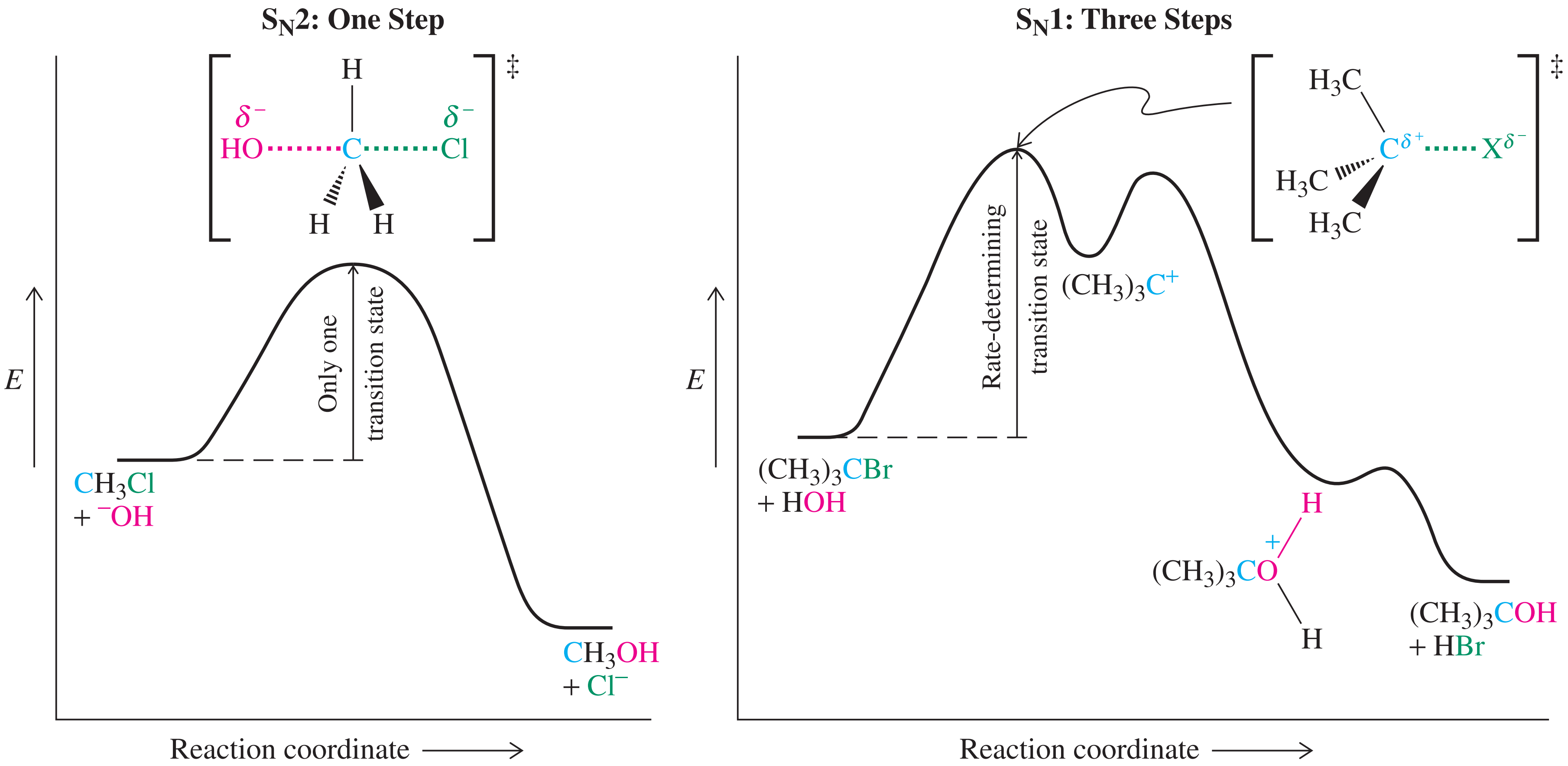
Deprotonation



Alkyloxonium ion
(Strongly acidic)

2-Methyl-2-propanol

The S_N1 diagram exhibits three transition states, one for each step in the mechanism. The first has the highest energy—and thus is rate determining—because it requires the separation of opposite charges.

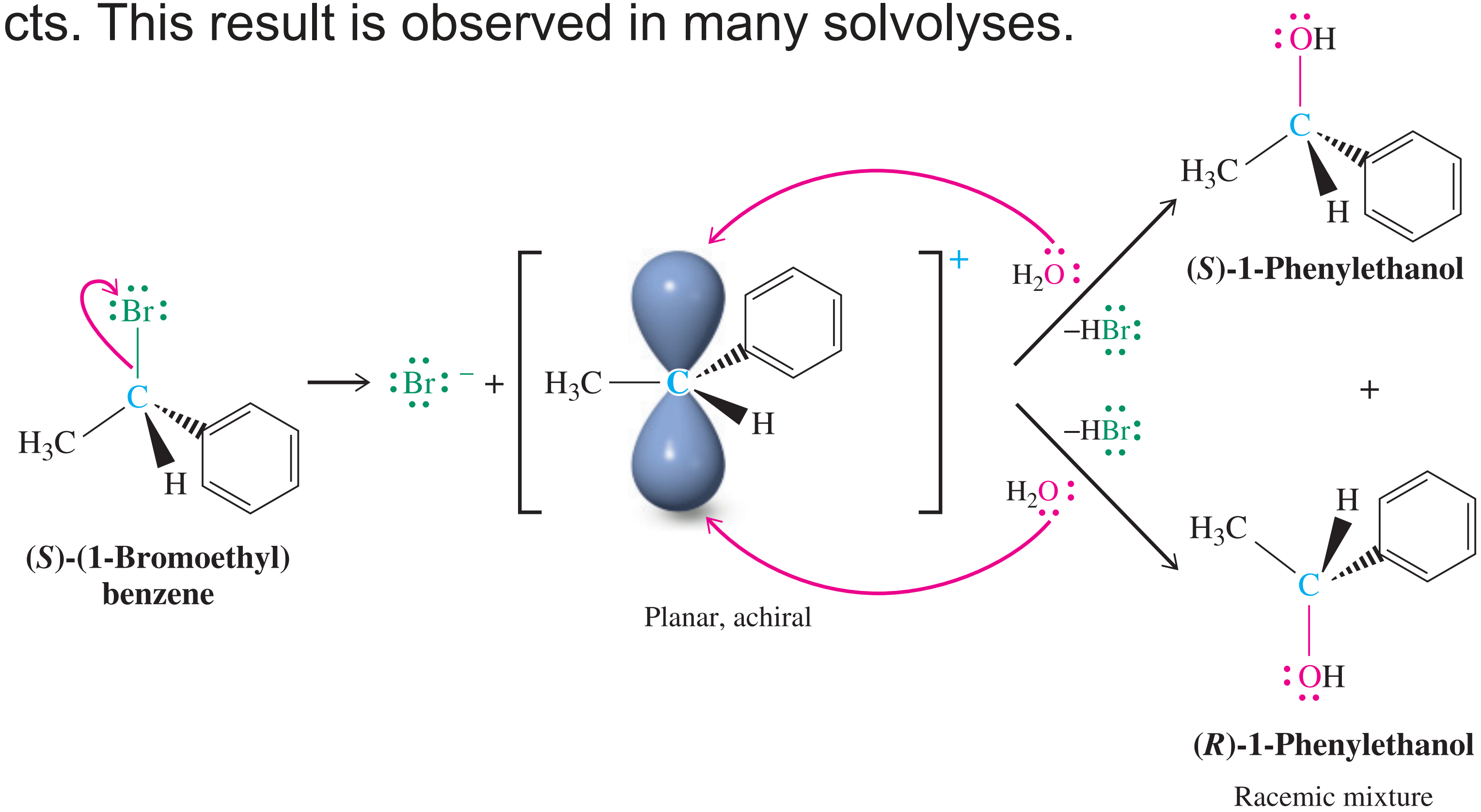


All three steps of the mechanism of solvolysis are **reversible**. The overall equilibrium can be driven in either direction by the suitable choice of reaction conditions. Thus, a large excess of nucleophilic solvent ensures complete solvolysis.

7.3 STEREOCHEMICAL CONSEQUENCES OF S_N1 REACTIONS

To minimize electron repulsion, the positively charged carbon assumes trigonal planar geometry, the result of *sp*^{2} hybridization. Such an intermediate is therefore achiral.

Starting with an optically active secondary or tertiary haloalkane in which the stereocenter bears the departing halogen, under conditions favorable for S_N1 reaction we should obtain racemic products. This result is observed in many solvolyses.



7.4 EFFECTS OF SOLVENT, LEAVING GROUP, AND NUCLEOPHILE ON UNIMOLECULAR SUBSTITUTION

As in S_N2 reactions, varying the solvent, the leaving group, and the nucleophile greatly affects unimolecular substitution.

Polar solvents accelerate the S_N1 reaction

Heterolytic cleavage of the C–X bond in the rate-determining step of the S_N1 reaction entails a transition-state structure that is highly polarized, leading eventually to two fully charged ions.

In contrast, in a typical S_N2 transition state, charges are not created; rather, they are dispersed.

Because of this polar transition state, the rate of an S_N1 reaction increases as solvent polarity is increased.

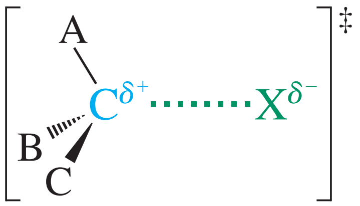
The effect is particularly striking when the solvent is changed from aprotic to protic. For example, hydrolysis of 2-bromo-2-methylpropane is much faster in pure water than in a 9:1 mixture of acetone and water.

Effect of Solvent on the Rate of an S_N1 Reaction

	Relative rate
$(CH_3)_3CBr \xrightarrow[\text{More polar solvent}]{100\%\ H_2O} (CH_3)_3COH + HBr$	400,000
$(CH_3)_3CBr \xrightarrow[\text{Less polar solvent}]{90\%\text{ acetone, }10\%\ H_2O} (CH_3)_3COH + HBr$	1

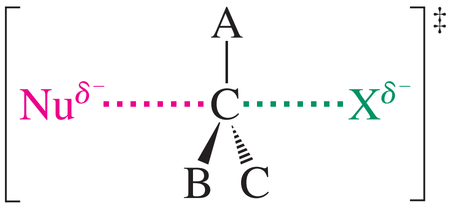
The protic solvent accelerates the S_N1 reaction because it stabilizes the transition state by hydrogen bonding with the leaving group.

In contrast, the S_N2 reaction is accelerated in polar *aprotic* solvents, mainly because of a solvent effect on the reactivity of the *nucleophile*.



S_N1

Opposite charges
are separated



S_N2

Negative charge
is dispersed

The S_N1 reaction speeds up with better leaving groups

Because the leaving group departs in the rate-determining step of the S_N1 reaction, it is not surprising that the rate of the reaction increases as the leaving-group ability of the departing group improves.

Tertiary iodoalkanes more readily undergo solvolysis than do the corresponding bromides, and bromides are more reactive than chlorides. Sulfonates are particularly prone to departure.

Relative Rate of Solvolysis of RX (R = Tertiary Alkyl)

$$X = -OSO_2R' > -I > -Br > -Cl$$

Increasing rate

The strength of the nucleophile affects the product distribution but not the reaction rate

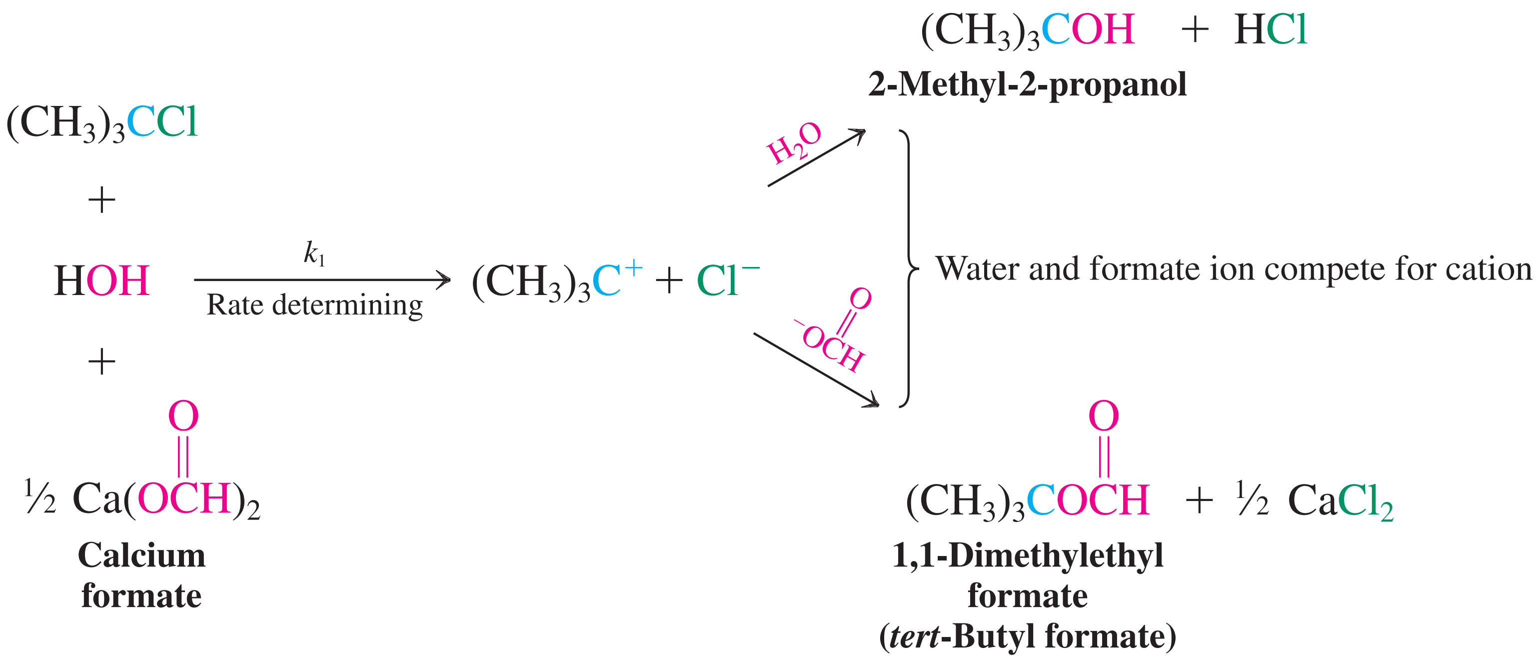
Because the rate-determining step of unimolecular substitution does *not* include the nucleophile, changing its structure (or concentration) does *not* alter the rate of disappearance of the haloalkane.

When two or more nucleophiles compete for capture of the intermediate carbocation, their relative strengths and concentrations may greatly affect the *product distribution.*

For example, hydrolysis of a solution of 2-chloro-2-methylpropane gives the expected 2-methyl-2-propanol (*tert*-butyl alcohol), with a rate constant k_1. Quite a different result is obtained when the same experiment is carried out in the presence of the soluble salt calcium formate.

Formate ion, a better nucleophile than water, wins out in competition for bonding to the intermediate carbocation. The rate of disappearance of the starting material is determined by k_1, but the relative yields of the *products* depend on the relative reactivities and concentrations of the competing nucleophiles.

Competing Nucleophiles in the S_N1 Reaction



$(CH_3)_3CCl$ + HOH + $\frac{1}{2}\,Ca(OCH)_2$ (with C=O)

Calcium formate

$\xrightarrow[\text{Rate determining}]{k_1}$ $(CH_3)_3C^+ + Cl^-$

$\xrightarrow{H_2O}$ $(CH_3)_3COH + HCl$

2-Methyl-2-propanol

$\xrightarrow{^-OCH(=O)}$ $(CH_3)_3COCH(=O) + \frac{1}{2}\,CaCl_2$

1,1-Dimethylethyl formate (*tert*-Butyl formate)

Water and formate ion compete for cation

7.5 EFFECT OF THE ALKYL GROUP ON THE S_N1 REACTION: CARBOCATION STABILITY

Carbocation stability increases from primary to secondary to tertiary

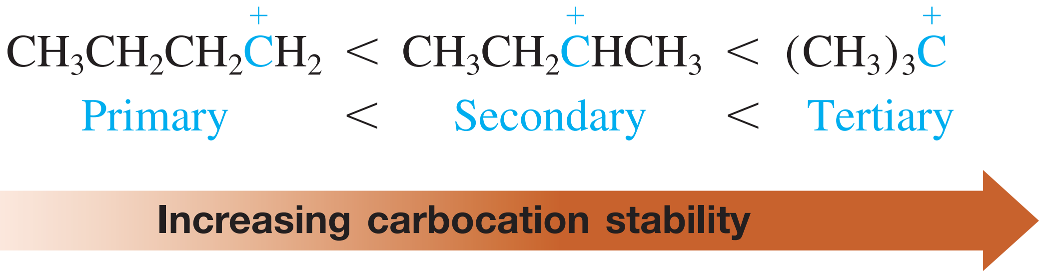
Primary haloalkanes undergo *only* bimolecular nucleophilic substitution. In contrast, secondary and tertiary systems often transform through carbocation intermediates.

The reasons for this difference: (1) steric hindrance increases along the series, thereby slowing down S_N2 and (2) increasing alkyl substitution stabilizes carbocation centers.

Only secondary and tertiary cations are energetically feasible under the conditions of the S_N1 reaction.

Tertiary haloalkanes undergo solvolysis so readily, because tertiary carbocations are more stable than their less substituted relatives, which form more easily.

Relative Stability of Carbocations



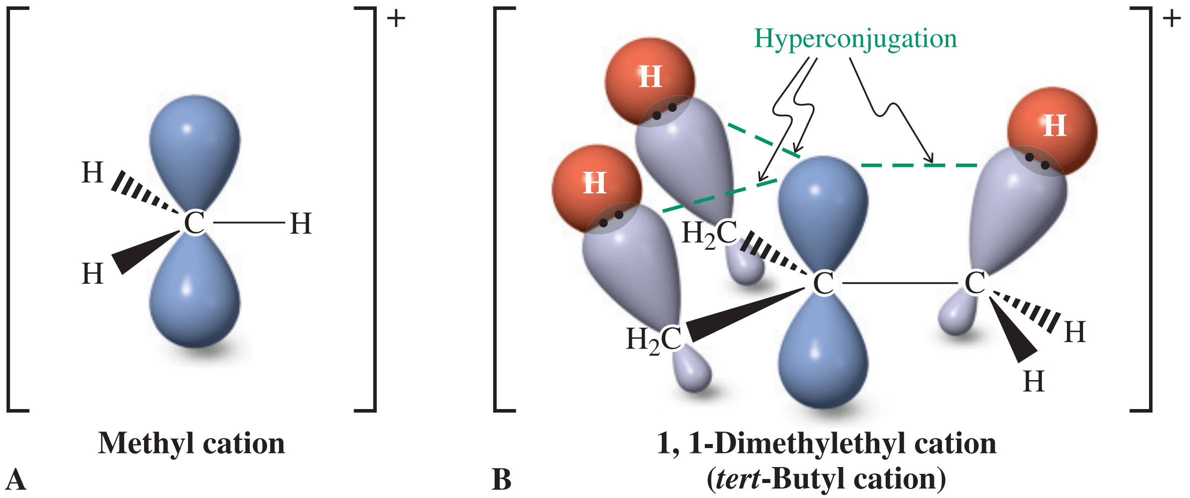
$$CH_3CH_2CH_2\overset{+}{C}H_2 < CH_3CH_2\overset{+}{C}HCH_3 < (CH_3)_3\overset{+}{C}$$

Primary < Secondary < Tertiary

Hyperconjugation stabilizes positive charge

Carbocation stability parallels that of the corresponding radicals. Hyperconjugation is the result of overlap of a *p* orbital with a neighboring bonding molecular orbital, such as that of a C–H or a C–C bond.

In a carbocation, the *p* orbital is empty. The alkyl group donates electron density to the electron-deficient center and thus stabilizes it.



Methyl cation

1, 1-Dimethylethyl cation
(*tert*-Butyl cation)

Secondary systems undergo both S_N1 and S_N2 reactions depending on conditions

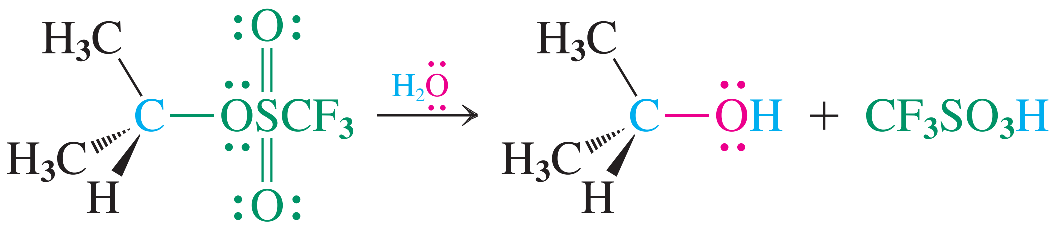
Both S_N2 and S_N1 reactions are possible: Steric hindrance slows but does not preclude bimolecular nucleophilic attack. At the same time, unimolecular dissociation becomes competitive because of the relative stability of secondary carbocations.

The pathway chosen depends on the **reaction conditions**: the solvent, the leaving group, and the nucleophile.

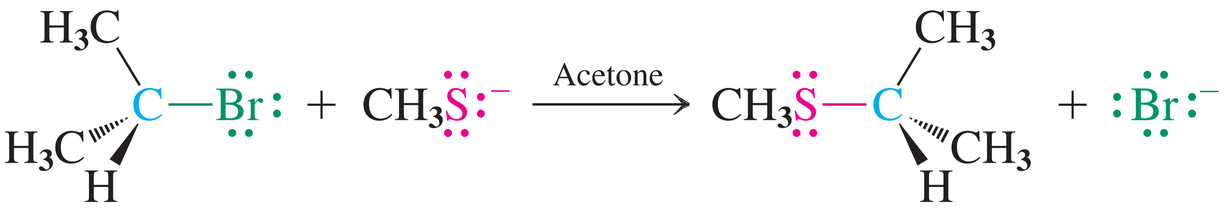
If we use a substrate carrying a very good leaving group, a poor nucleophile, and a polar protic solvent (S_N1 conditions), then *unimolecular* substitution is favored.

If we employ a high concentration of a good nucleophile, a polar aprotic solvent, and a haloalkane bearing a reasonable leaving group (S_N2 conditions), then *bimolecular* substitution predominates.

Substitution of a Secondary Substrate Under S_N1 Conditions



Substitution of a Secondary Haloalkane Under S_N2 Conditions



Two conditions must be satisfied before dissociation of a carbon–halogen bond into ions can occur:

(1) the carbon atom must be secondary or tertiary so that the carbocation has sufficient thermodynamic stability to form

(2) the reaction must take place in a polar solvent capable of interacting with and stabilizing *both* positive and negative ions.

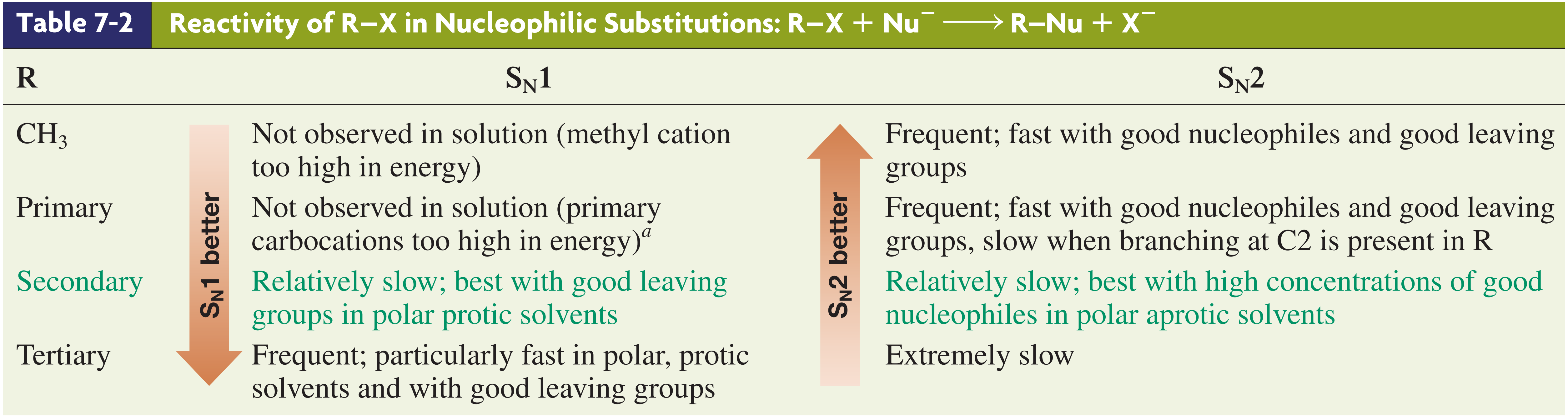


Table 7-2 **Reactivity of R–X in Nucleophilic Substitutions: $R{-}X + Nu^- \longrightarrow R{-}Nu + X^-$**

R		S_N1		S_N2
CH_3	↓ S_N1 better	Not observed in solution (methyl cation too high in energy)	↑ S_N2 better	Frequent; fast with good nucleophiles and good leaving groups
Primary		Not observed in solution (primary carbocations too high in energy)[a]		Frequent; fast with good nucleophiles and good leaving groups, slow when branching at C2 is present in R
Secondary		Relatively slow; best with good leaving groups in polar protic solvents		Relatively slow; best with high concentrations of good nucleophiles in polar aprotic solvents
Tertiary		Frequent; particularly fast in polar, protic solvents and with good leaving groups		Extremely slow

Which is "greener": S_N1 or S_N2?

The contrast between the stereochemical outcomes of the S_N1 and S_N2 mechanisms directly affects the comparative utility of the two processes in synthesis. The S_N2 process is *stereospecific:* reaction of a single stereoisomeric substrate gives a single stereoisomeric product. In contrast, virtually all reactions that proceed via the S_N1 mechanism at a stereocenter give mixtures of stereoisomers.

And it gets worse: The chemistry of carbocations, in all S_N1 reactions, is complex. These species are prone to rearrangements, frequently resulting in complicated collections of products. In addition, carbocations undergo another important transformation: *loss of a proton* to furnish a double bond.

S_N1 reactions, unlike S_N2 processes, are of limited use in synthesis because they fail the first two criteria of "green" reactions: They are poor in atom efficiency and wasteful overall, because they tend to lead to mixtures of stereoisomeric substitution products and other organic compounds. S_N2 is "greener."