Alkyl Halides: Properties and Reactions

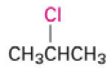
Vollhardt: Chapters 6 & 7; sections 8.7 & 8.8
McMurry: Chapters 10 & 11

Naming alkylhalides:

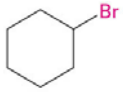
Simple compounds (common names):

	CH_3X halide	as suffix		as prefix
X = F:	methylfluoride		*or*	fluoromethane
Cl:	-chloride			chloro-
Br:	-bromide			bromo-
I:	-iodide			iodo-

CH_2Cl_2	$CHCl_3$	CCl_4
methylene chloride	chloroform	carbontetrachloride
or	*or*	*or*
dichloromethane	trichloromethane	tetrachloromethane



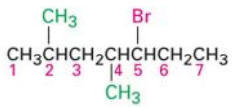
2-Chloropropane
(or isopropyl chloride)

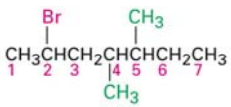


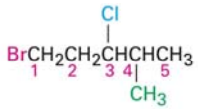
Bromocyclohexane
(or cyclohexyl bromide)

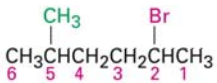
Systematic Naming of Haloalkanes

1. Find the longest chain, name it as the parent chain
2. Number the carbons beginning at the end nearer the first substituent (alkyl or halogen)
3. If by rule 2, the parent chain can be numbered from either end, begin with the end nearer to the substituent whose name comes first in the alphabet









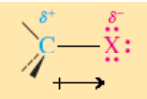
Physical Properties of Methyl Halides

Halo-methane	Bond length (Å)	Bond strength [kcal mol^{-1} (kJ mol^{-1})]
CH_3F	1.385	110 (460)
CH_3Cl	1.784	85 (356)
CH_3Br	1.929	70 (293)
CH_3I	2.139	57 (238)

	Boiling point (°C)				
R	X = H	F	Cl	Br	I
CH_3	-161.7	-78.4	-24.2	3.6	42.4
CH_3CH_2	-88.6	-37.7	12.3	38.4	72.3
$CH_3(CH_2)_2$	-42.1	-2.5	46.6	71.0	102.5
$CH_3(CH_2)_3$	-0.5	32.5	78.4	101.6	130.5
$CH_3(CH_2)_4$	36.1	62.8	107.8	129.6	157.0
$CH_3(CH_2)_7$	125.7	142.0	182.0	200.3	225.5

C-X bond strength decreases with the increasing size of X and bond length.

Polar C-X bond

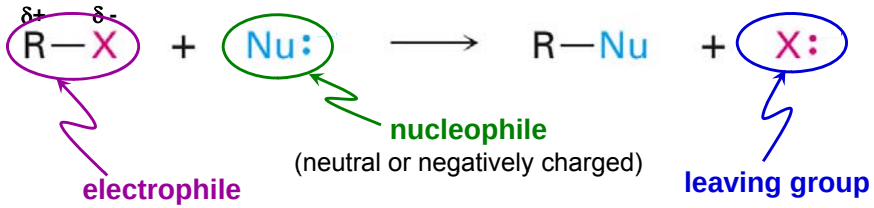


Boiling points increase with the size of X and are higher than those of corresponding alkanes, due to increased strength of dipole-dipole and dispersion interactions.

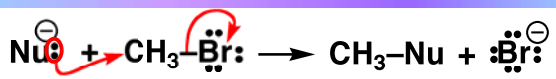
Reactions of Alkyl Halides: Nucleophilic Substitution

Our study of organic reactions will be organized around mechanistic similarities. This method of organization allows organic chemistry to be understood - not just memorized - based on unifying principles of reactivity. It allows you to reason by analogy to rationalize reactions that you may never have previously seen.

Nucleophiles attack electrophillic centers:



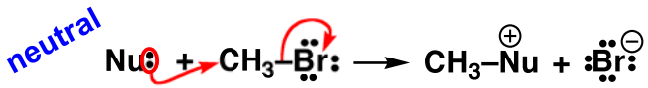
The Nucleophile Introduces a Wide Variety of New Functional Groups



nucleophile	product	compound class
$HO^{\ominus}$	$CH_3–OH$	alcohol
$RO^{\ominus}$	$CH_3–OR$	ether
$HS^{\ominus}$	$CH_3–SH$	thiol
$RS^{\ominus}$	$CH_3–SR$	sulfide

nucleophile	product	compound class
$HC{\equiv}C^{\ominus}$	$CH_3–C{\equiv}CH$	alkyne
$:N{\equiv}C^{\ominus}$	$CH_3–C{\equiv}N:$	nitrile
$:I^{\ominus}$	$CH_3–I:$	alkyl iodide
$^{\ominus}:N{=}N^{\oplus}{=}N:^{\ominus}$	$CH_3–N{=}N^{\oplus}{=}N:^{\ominus}$	alkyl azide

The Nucleophile Introduces a Wide Variety of New Functional Groups



nucleophile	product	compound class
$:NH_3$	$CH_3–NH_3^{\oplus}$	alkyl ammonium ion
$H_2O:$	$CH_3–O^{\oplus}(H)(H)$	an alcohol (after proton transfer)
$RO{H}$	$CH_3–O^{\oplus}(H)(R)$	an ether (after proton transfer)

$CH_3OH_2^+$ $pK_a = -2.4$

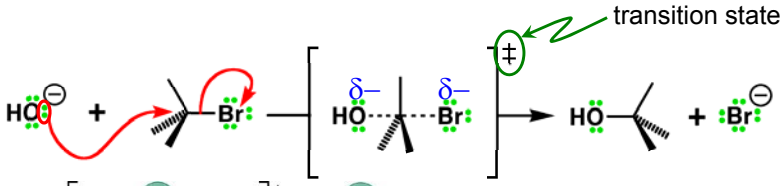
An S_N2 reaction proceeds in the direction that allows the stronger base to displace the weaker base

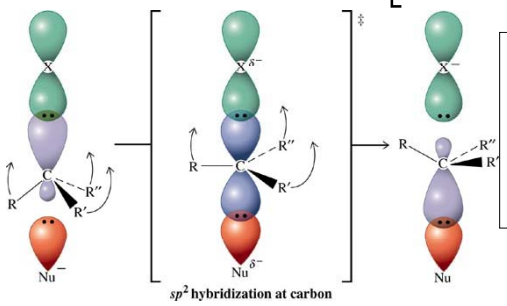
What's the stronger base? Br^- or CH_3OH?

H-Br $pK_a = -9$

Nucleophilic Substitution Mechanism (I): the S_N2 Reaction

The S_N2 pathway (**S**ubstitution, **N**ucleophilic, **Bi**molecular)

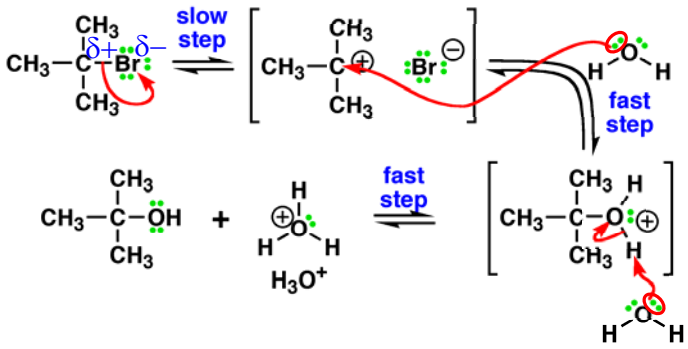




- Simutaneous bond making and bond breaking
- The TS≠ involves the association of two molecules (bimolecular)
- reaction rate = k [substrate] × [nucleophile] mol L^{-1} s^{-1}

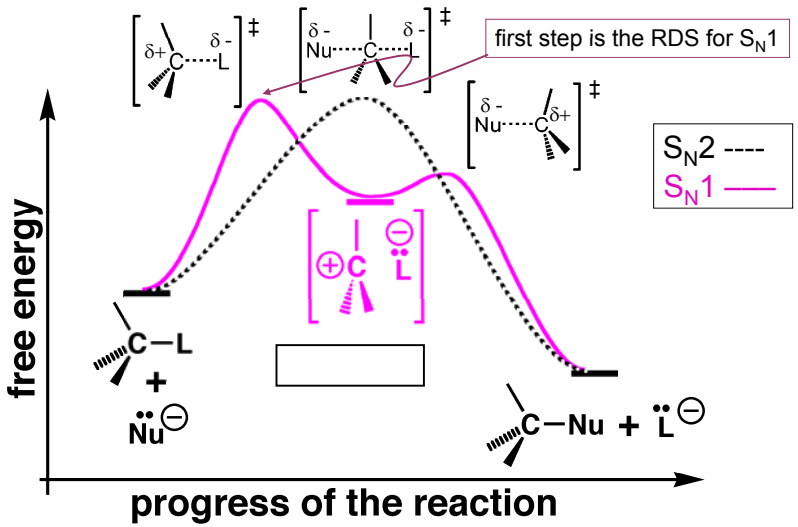
Nucleophilic Substitution Mechanism (II): the S_N1 Reaction

The S_N1 pathway (**S**ubstitution, **N**ucleophilic, **Uni**molecular)



- Bond breaking precedes bond making
- The TS≠ of the rate-determining step involves just one molecule (unimolecular); reaction rate = k [substrate] mol L^{-1} s^{-1}

Comparison of S_N1 and S_N2 Pathways



Recognizing Leaving Groups (LGs)

Leaving group reactivity correlates to basicity.
The _____ the base, the _____ its leaving ability.

				pK_a
H–F	⇌	$H^{\oplus}$ +	$F^{\ominus}$	3.2
H–Cl	⇌	$H^{\oplus}$ +	$Cl^{\ominus}$	-7
H–Br	⇌	$H^{\oplus}$ +	$Br^{\ominus}$	-9
H–I	⇌	$H^{\oplus}$ +	$I^{\ominus}$	-10

Increasing acidity H–X

Increasing basicity X^-

Increasing leaving ability

		relative rates of reaction
HO^- + RCH_2I	⟶ RCH_2OH + I^-	30,000
HO^- + RCH_2Br	⟶ RCH_2OH + Br^-	10,000
HO^- + RCH_2Cl	⟶ RCH_2OH + Cl^-	200
HO^- + RCH_2F	⟶ RCH_2OH + F^-	1

This general trend holds for S_N2, S_N1 and other reactions that we'll study

Why LG Ability Correlates to Basicity

In the TS≠ (RDS), the leaving group develops negative charge; thus, the ability of a group to function as a leaving group is related to the stability of the corresponding anion

TS≠ for S_N2

TS≠ for S_N1

reactive

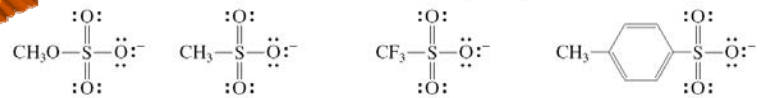
unreactive

RI > RBr > RCl >> RF ~ $R-O-\overset{O}{\overset{\|}{C}}-CH_3$ > R–OH, $R-OCH_3$, $R-NH_2$

Increasing reactivity

Good leaving groups!

Sulfate and Sulfonate Leaving Groups

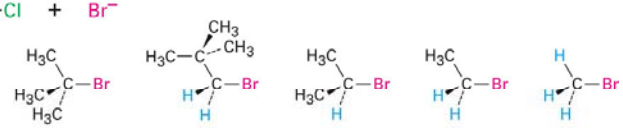


Methyl sulfate ion | Methanesulfonate ion (Mesylate ion) | Trifluoromethanesulfonate ion (Triflate ion) | 4-Methylbenzenesulfonate ion (*p*-Toluenesulfonate ion, tosylate ion)

The Substrate: Steric Effects in S_N2 Reactions

$R-Br + Cl^- \longrightarrow R-Cl + Br^-$

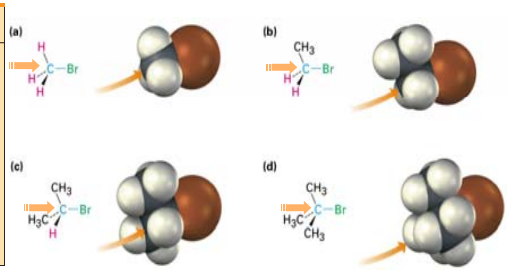
Bromoalkane	Relative rate
$H-CH_2Br$	1
CH_3CH_2Br	0.1
$CH_3CH(CH_3)Br$	0.03
$CH_3C(CH_3)_2Br$	1.3×10^{-5}



	Tertiary	Neopentyl	Secondary	Primary	Methyl
Relative reactivity	< 1	1	500	40,000	2,000,000

S_N2 reactivity

Bromoalkane	Rate
CH_3Br	145
CH_3CH_2Br	1
$CH_3CH(CH_3)Br$	0.0078
$CH_3C(CH_3)_2Br$	Negligible

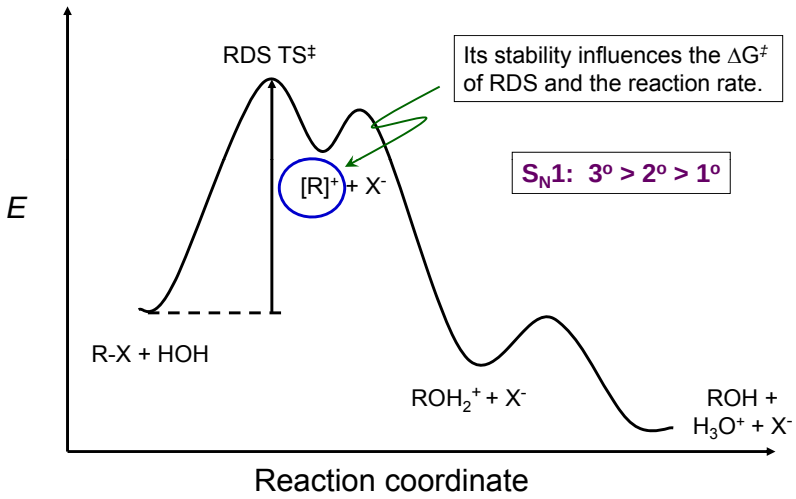


methyl > primary > secondary > tertiary
(fast) (slower) (very slow) (does not occur)

Bulky substituents hinder the attack of the nucleophile

Solvolysis: S_N1 Reaction

$$R\text{-}X + HOH\ (solvent) \longrightarrow ROH + H_3O^+ + HX$$



S_N1: $3^o > 2^o > 1^o$

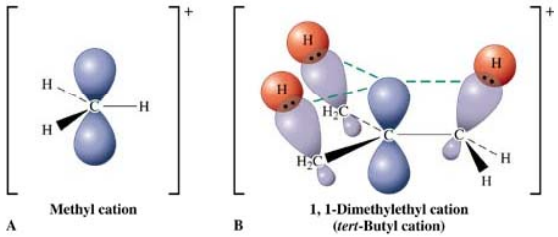
Substrates in S_N1 Reactions: Carbocation Stability

Governed by electronic factors ← Carbocation stability

favors S_N1	$R_3C–X$	$R_2CH–X$	$RCH_2–X$	$CH_3–X$	favors S_N2
	(3°)	(2°)	(1°)	(methyl)	
	S_N1	S_N2 & S_N1	S_N2	S_N2	

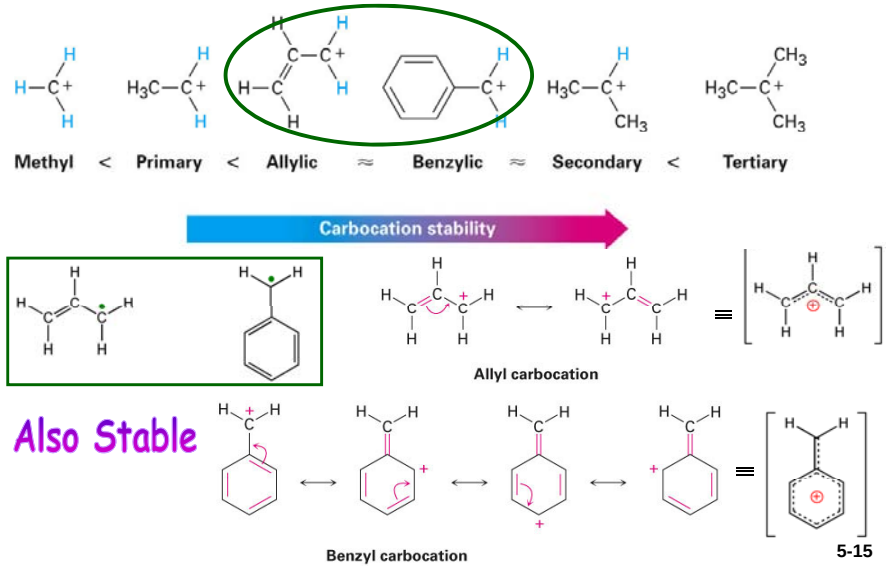
Access to the site of reaction → Governed by steric factors

Hyperconjugation stablizes positive charge.



Substrates in S_N1 Reactions: Carbocation Stability

Why are these 1° carbocations as stable as 2° carbocations?



The Nucleophiles

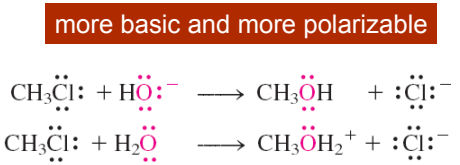
Nucleophilicity depends on:
basicity, **polarizability**, and **solvent properties**.

more basic, more nucleophilic
higher polarizability, better nucleophile

Basicity is the affinity of a base for a proton;
Nucleophilicity is the affinity of a Lewis base for a carbon atom.

- Comparing nucleophiles having the same reactive atom, the species with the negative charge is the more powerful nucleophile than their conjugated acid.

more basic and more polarizable



$H_2\ddot{O}: < H\ddot{O}:^{\ominus}$

$H_3\ddot{N} < H_2\ddot{N}:^{\ominus}$

$CH_3–\ddot{S}H < CH_3–\ddot{S}:^{\ominus}$

Generalizations about Nucleophilicity (II)

Increasing Nucleophilicity →

$H_2\ddot{O}$ < $\ddot{N}H_3$

Within a row, nucleophilicity increases from right to left and parallels with basicity

row 2 $:\ddot{F}^{\ominus}$ < $H\ddot{O}^{\ominus}$ < $H_2\ddot{N}^{\ominus}$ < $H_3C^{\ominus}$

basicity →

more basic and more polarizable

row 3 $:\ddot{Cl}^{\ominus}$ < $H\ddot{S}^{\ominus}$ < $H_2\ddot{P}^{\ominus}$

Increasing Nucleophilicity →

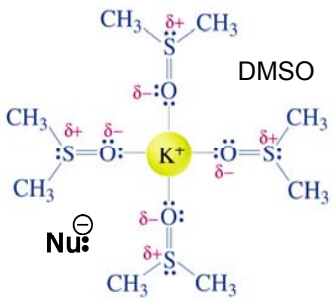
nucleophile	$CH_3C(=O)\ddot{O}^{\ominus}$ carboxylate ion	< $H\ddot{O}^{\ominus}$ hydroxide ion	< $CH_3\ddot{O}^{\ominus}$ alkoxide ion	
conjugate acid	$CH_3C(=O)\ddot{O}H$	$H\ddot{O}H$	$CH_3\ddot{O}H$	
pK_a	4-5	15.7	17	

In a series of nucleophiles with the same nucleophilic atom, the stronger the base, the greater the nucleophilicity.

Summary on Nucleophilicity of Nucleophiles

Increasing Nucleophilicity →

solvent				
Polar aprotic	$:\ddot{I}^{\ominus}$ <	$:\ddot{Br}^{\ominus}$ <	$:\ddot{Cl}^{\ominus}$ <	$:\ddot{F}^{\ominus}$
		basicity →		
Polar protic	$:\ddot{F}^{\ominus}$ <	$:\ddot{Cl}^{\ominus}$ <	$:\ddot{Br}^{\ominus}$ <	$:\ddot{I}^{\ominus}$



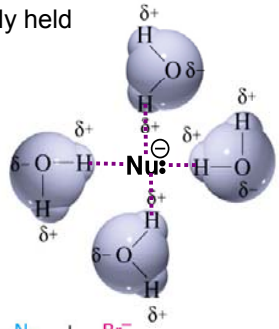
Nucleophilicity also depends on the solvent
The interaction between solvent and nucleophile: solvation

In polar aprotic solvents (DMSO, acetone, acetonitrile, DMF) relative nucleophilicities parallel relative basicities.

Reason: Cations are effectively solvated but anions are poorly solvated and thus the nucleophile is not shielded by solvent.

Nucleophilicity and Solvent

In polar protic solvents, the solvent shell is tightly held around the nucleophile due to hydrogen bonding



The smaller the ion, the tighter the solvent shell. Thus, for nucleophiles of different size (moving up or down in the periodic table) the better the size, the larger the nucleophile (opposite to base strength).

a S_N2 reaction

$CH_3CH_2CH_2CH_2{-}Br + N_3^- \longrightarrow CH_3CH_2CH_2CH_2{-}N_3 + Br^-$

Solvent	CH_3OH	H_2O	DMSO	DMF	CH_3CN	HMPA
Relative reactivity	1	7	1300	2800	5000	200,000

Solvent reactivity →

Generally, polar protic solvents slow down the S_N2 reactions by solvation of the nucleophile, thereby lowering its energy and reactivity , and polar aprotic solvents increase the rates of S_N2 reactions by raising the ground-state energy of the nucleophile.

Common Nucleophiles

increasing nucleophilicity ↑

stronger bases negative charges

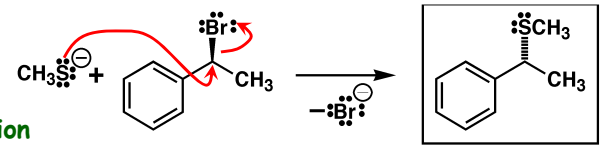
good: $:\ddot{Br}^{\ominus}$ $:\ddot{I}^{\ominus}$ $CH_3\ddot{S}^{\ominus}$ $H\ddot{O}^{\ominus}$ $CH_3\ddot{O}^{\ominus}$ $:N{\equiv}C^{\ominus}$ $^{\ominus}\ddot{N}{=}\overset{\oplus}{N}{=}\ddot{N}^{\ominus}$

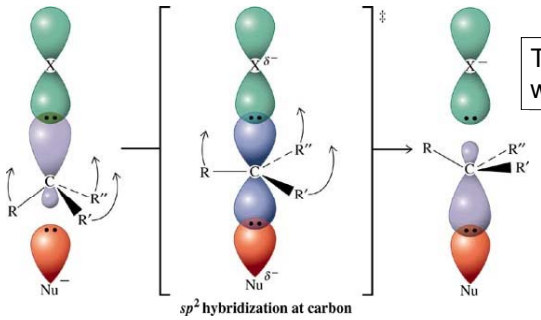
moderate: $CH_3C(=O)\ddot{O}^{\ominus}$ $CH_3\ddot{S}H$ $CH_3\ddot{S}CH_3$ $:NH_3$ $CH_3\ddot{N}H_2$ $(CH_3)_2\ddot{N}H$ $(CH_3)_3\ddot{N}$

weak bases neutral charges

poor: $H_2\ddot{O}:$ $CH_3\ddot{O}H$ $CH_3C(=O)\ddot{O}H$

Stereochemistry of the S_N2 Reaction





The S_N2 reactions proceeds with inversion of configuration.

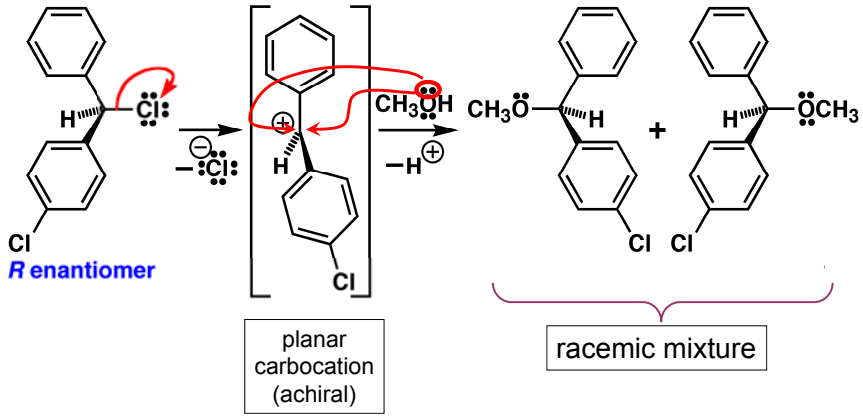
Stereospecific or Stereoselective?

Stereospecific: Required by the reaction mechanism, a stereoisomer of the starting material is transformed into a single, specific stereoisomer of the product.

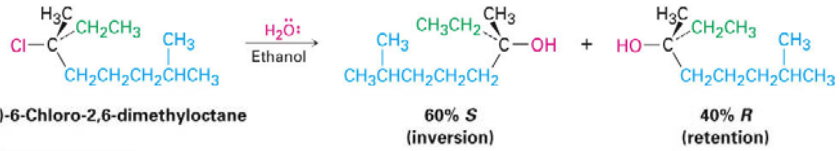
Stereoelective: A reaction that leads to the predominant (or exclusive) formation of one of several possible stereoisomeric products.

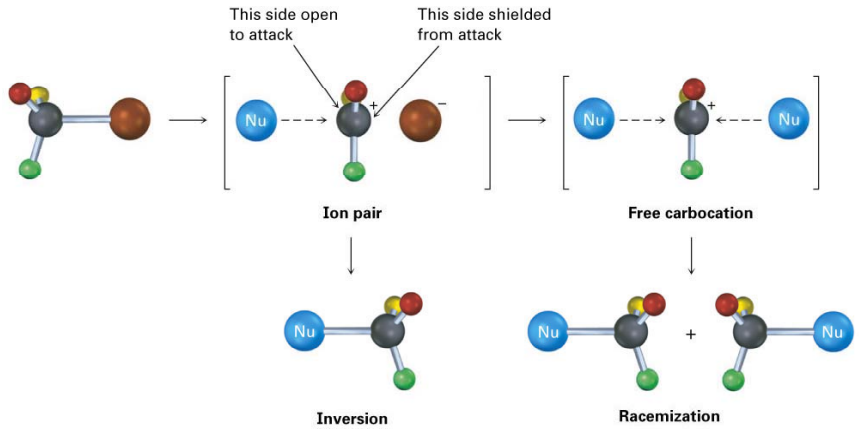
Stereochemistry of the S_N1 Reaction

Enatiomers formed with equal probability, with 50% each.



Winstein Ion Pair in a S_N1 Reaction





A Summary of S_N2 Reaction

- S_N2 reactions exhibit an **inversion** of configuration at the reacting center;
- Follows **second order** reaction kinetics (a bimolecular reaction at RDS);
- Reaction rate is sensitive to the steric hindrance in the substrate: S_N2 reactions are **best for methyl and primary substrate**, slow for secondary substrates, and tertiary substrates do not react by S_N2 mechanism;
- **Basic, negatively charged nucleophiles** are favorable for S_N2 reactions;
- **Good leaving groups** accelerate the S_N2 reaction rate;
- Protic solvents slow down S_N2 reactions due to solvation of the nucleophile; **polar aprotic solvents** are more favorable for S_N2 reactions.

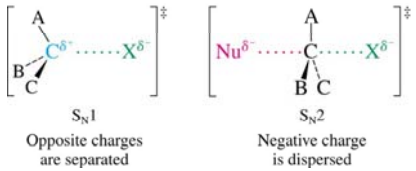
A Summary of S_N1 Reaction

- S_N1 reactions result in (partial) **racemerization** of optical pure reactants;
- Follows **first order** reaction kinetics as a unimolecular reaction at RDS;
- Reaction rate is controlled by stability of the carbocation intermediate; tertiary alkyl, allylic and benzylic halide are best for this mechanism (Hammond postulate: "Any factor that stabilizes a high-energy intermediate stabilizes transition state leading to that intermediate");
- Good leaving groups increase the reaction rate;
- Reaction rate is **not** normally affected by nature or concentration of the nucleophile, but nucleophile should be nonbasic to prevent competitive **elimination reaction**;
- Polar solvents are usually more favorable for S_N1 reactions.

Solvent Effect on S_N1 Reaction

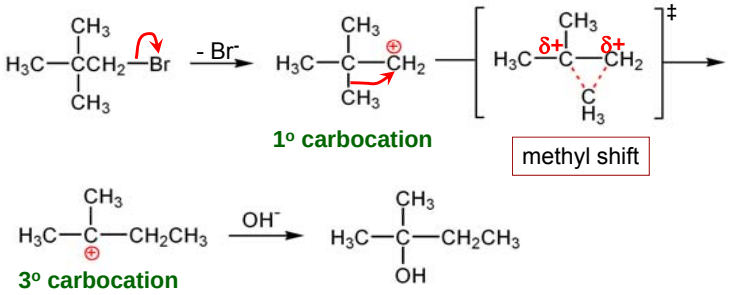
Polar solvents are usually more favorable for S_N1 reactions.

TS‡ is more polar than the reactant



TS‡ is less polar than the reactant

Rearrangements May Occur with S_N1 Mechanisms



Rearrangement in S_N1 Reaction