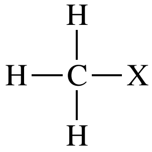
Lecture Notes
Chem 51A
S. King

Chapter 7 Alkyl Halides and Nucleophilic Substitution

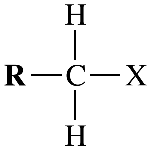
I. Introduction to Alkyl Halides

Alkyl halides are organic molecules containing a halogen atom X bonded to an sp^2 or sp^3 hybridized carbon atom.

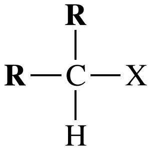
X bonded to sp^3–C examples:



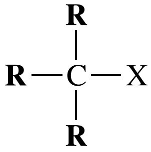
$$\begin{array}{c} H \\ | \\ H-C-X \\ | \\ H \end{array}$$



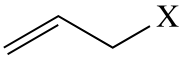
$$\begin{array}{c} H \\ | \\ \mathbf{R}-C-X \\ | \\ H \end{array}$$

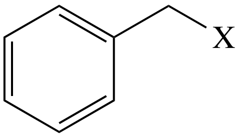


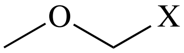
$$\begin{array}{c} \mathbf{R} \\ | \\ \mathbf{R}-C-X \\ | \\ H \end{array}$$



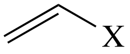
$$\begin{array}{c} \mathbf{R} \\ | \\ \mathbf{R}-C-X \\ | \\ \mathbf{R} \end{array}$$

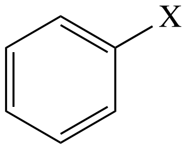






X bonded to sp^2–C examples:

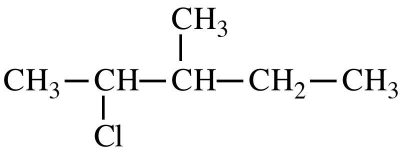




A. Nomenclature of Alkyl Halides

Common name: Alkyl Halide
IUPAC: Haloalkane (fluoro-, chloro-, bromo-, iodo-,)

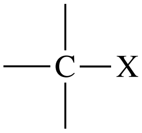
The rules are the same as with alkanes, except there are halogens present. Halides are given prefixes of chloro-, fluoro-, bromo-, and iodo-.



$$\begin{array}{l} \qquad\qquad\quad CH_3 \\ \qquad\qquad\quad | \\ CH_3-CH-CH-CH_2-CH_3 \\ \qquad\;\; | \\ \qquad\;\; Cl \end{array}$$

II. Reactions of Alkyl Halides

Alkyl halides contain a polar carbon-halogen bond, and an electrophilic carbon:



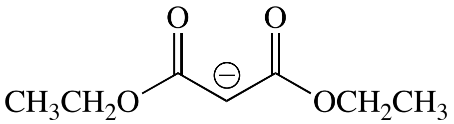
- *The characteristic reactions of alkyl halides are nucleophilic substitution and elimination.*

A. Nucleophilic Substitution Reactions

When a methyl halide or a primary alkyl halide reacts with a nucleophile such as sodium ethoxide, a reaction occurs in which the nucleophile replaces the halogen, which is expelled as a halide ion.

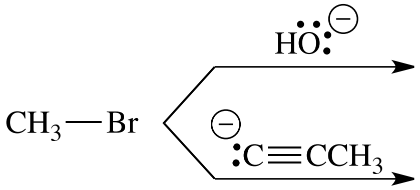
$$CH_3CH_2{-}Br \;+\; Na^{\oplus}\; CH_3CH_2O^{\ominus} \longrightarrow CH_3CH_2O{-}CH_2CH_3 \;+\; Na^{\oplus}\; Br^{\ominus}$$

Common nucleophilic reagents for creating new bonds to carbon:

C-O Bonds	C-S Bonds	C-N Bonds	C-C Bonds
$HO^{\ominus}$	$HS^{\ominus}$	NH_3	${}^{\ominus}C\equiv N$
$RO^{\ominus}$	$RS^{\ominus}$	RNH_2	$RC\equiv C^{\ominus}$
$PhO^{\ominus}$	$PhS^{\ominus}$	$N_3^{\ominus}$	

** Nucleophilic substitution reactions can be used to transform alkyl halides into a variety of other functional groups!

Examples:



❖ *Substitution is more complicated than it looks!*

As we’ve seen, when a 1° or methyl halide reacts with ethoxide ion, substitution takes place. When the nucleophile is changed to ethanol, no reaction occurs. But when ethanol reacts with a tertiary alkyl halide, substitution *does* occur.

$$CH_3CH_2—Br \quad + \quad CH_3CH_2OH \longrightarrow$$

$$(CH_3)_3C—Br \quad + \quad CH_3CH_2OH \longrightarrow$$

Reacting a tertiary alkyl halide with ethoxide ion, on the other hand, results in a completely different reaction, elimination:

$$(CH_3)_3C—Br \quad + \quad CH_3CH_2O^{\ominus} \longrightarrow$$

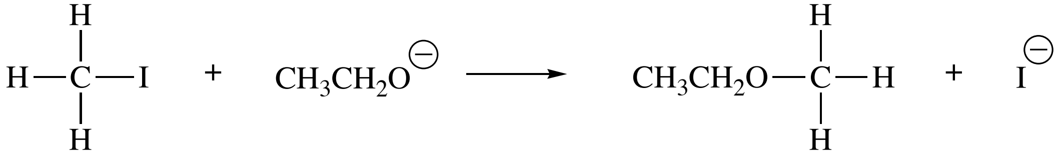
To complicate things further, a methoxymethyl alkyl halide, an allyl halide, and a benzyl halide react with both ethanol and ethoxide ion to form substitution product!

$$CH_3OCH_2—Br \quad + \quad \begin{matrix} CH_3CH_2O^{\ominus} \\ \textit{or} \\ CH_3CH_2OH \end{matrix} \longrightarrow$$

What’s going on???

There are actually two mechanisms for nucleophilic substitution, and these two mechanisms are in competition with each other!

III. Substitution, Nucleophilic, Bimolecular: The S_N2 Reaction



$$\mathrm{H{-}\underset{H}{\overset{H}{C}}{-}I} + CH_3CH_2O^{\ominus} \longrightarrow \mathrm{CH_3CH_2O{-}\underset{H}{\overset{H}{C}}{-}H} + I^{\ominus}$$

The rate law for a reaction often gives clues to the mechanism for a reaction.

Kinetics: If we measure the rate of the reaction as a function of varying initial concentrations of reactants we find that:

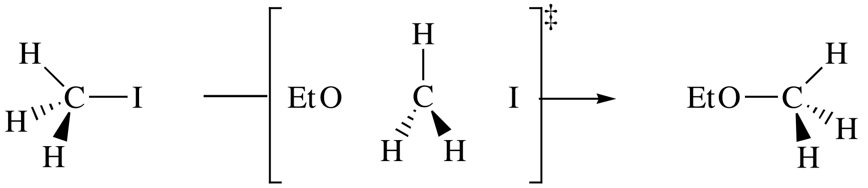
rate $\propto$ $[CH_3I][CH_3CH_2O^-]$

We can conclude that:

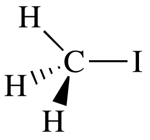
- the reaction is second order
- the reaction is bimolecular

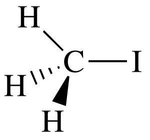
- We call this an S_N2 reaction: (Substitution, Nucleophilic, Bimolecular)

The following mechanism is consistent with the rate law:



Although the rate law indicates what atoms are present in the transition state, it provides no information about how they are arranged!

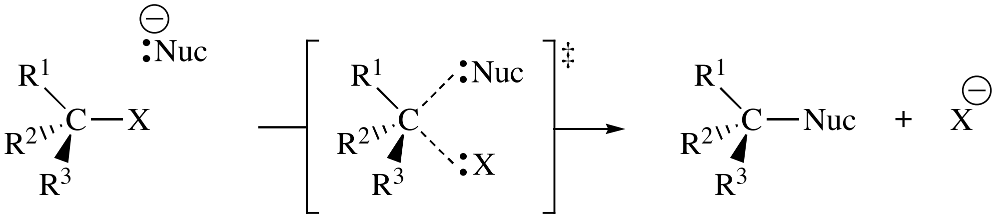




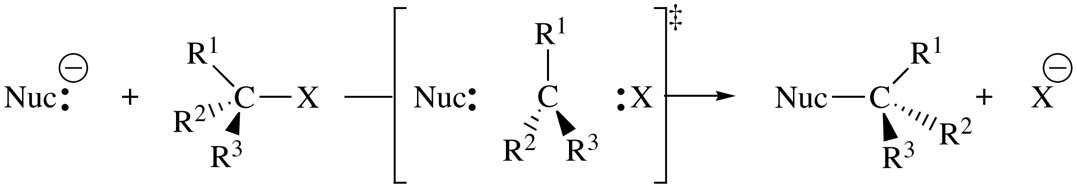
In order to decide how the atoms are arranged in the transition state we have to look at the stereochemistry of the reaction.

There are three possibilities:

#1: If frontside attack:



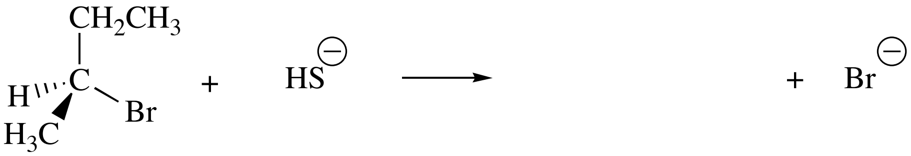
#2: If backside attack:



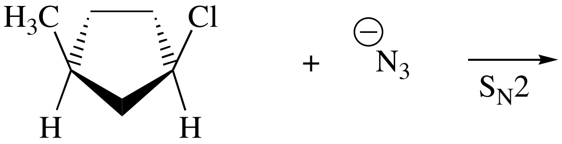
#3: If both attacks occur at equal rates you will get both inversion & retention of configuration!

What are the experimental results?

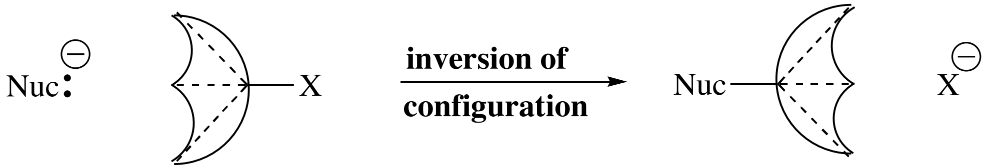
Example 1 (using a chiral alkyl bromide):



Example 2:



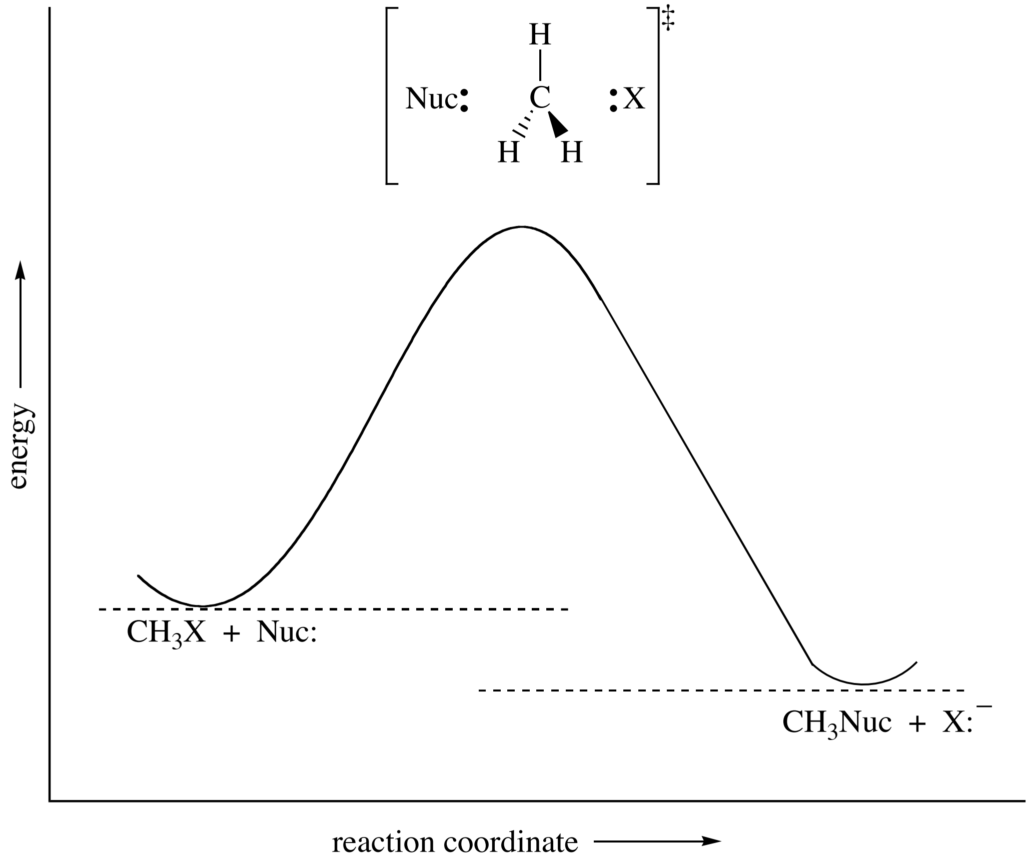
Conclusion:



Backside attack results in an inversion of the carbon atom's tetrahedron, like the inversion of an umbrella caught by the wind

Why is backside attack favored?

Look @ the energy diagram:

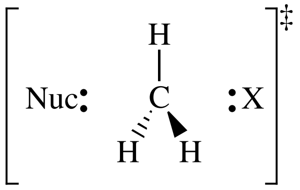


IV. Factors that Affect the Rate of the S_N2 Reaction

We know:

$$\text{rate} \propto [\text{alkyl halide}][\text{Nuc}]$$

Transition State:



- The bond to the nucleophile forms while the bond to the leaving group breaks.
- The transition state involves five groups around carbon.

Predict:

The factors that affect the rates of S_N2 reactions:

A. The structure of the substrate

B. The concentration and reactivity of the nucleophile

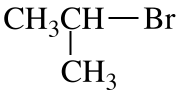
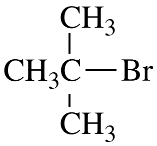
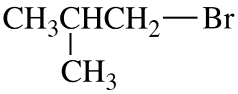
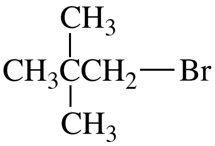
C. The effect of the solvent

D. The nature of the leaving group

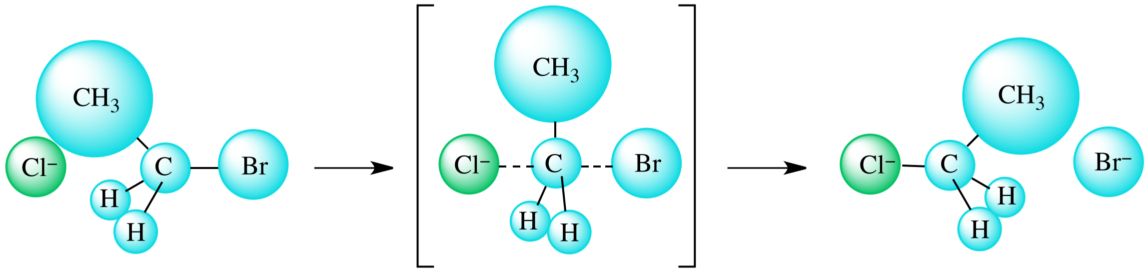
A. The Structure of the Substrate

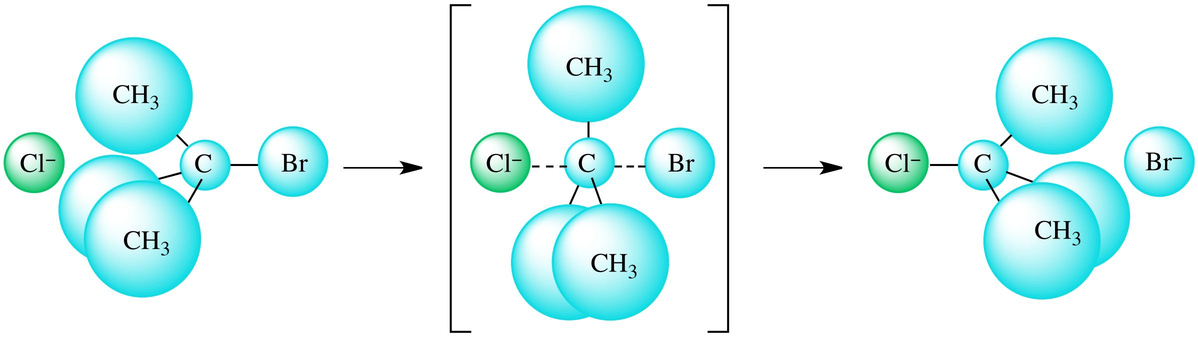
Look @ the relative rates of S_N2 reactions for various alkyl bromides:

$$R{-}Br \;+\; Cl^{\ominus} \xrightarrow{S_N2} R{-}Cl \;+\; Br^{\ominus}$$

Alkyl Bromide	**Type**	**Relative Rate**
$CH_3{-}Br$	methyl	1200
$CH_3CH_2{-}Br$	primary	40
$CH_3CH_2CH_2{-}Br$	primary	16
 $CH_3\underset{CH_3}{\underset{\mid}{CH}}{-}Br$	secondary	1
 $CH_3\overset{CH_3}{\overset{\mid}{\underset{CH_3}{\underset{\mid}{C}}}}{-}Br$	tertiary	negligible
 $CH_3\underset{CH_3}{\underset{\mid}{CH}}CH_2{-}Br$	primary hindered	0.6
 $CH_3\overset{CH_3}{\overset{\mid}{\underset{CH_3}{\underset{\mid}{C}}}}CH_2{-}Br$	primary hindered	0.0003

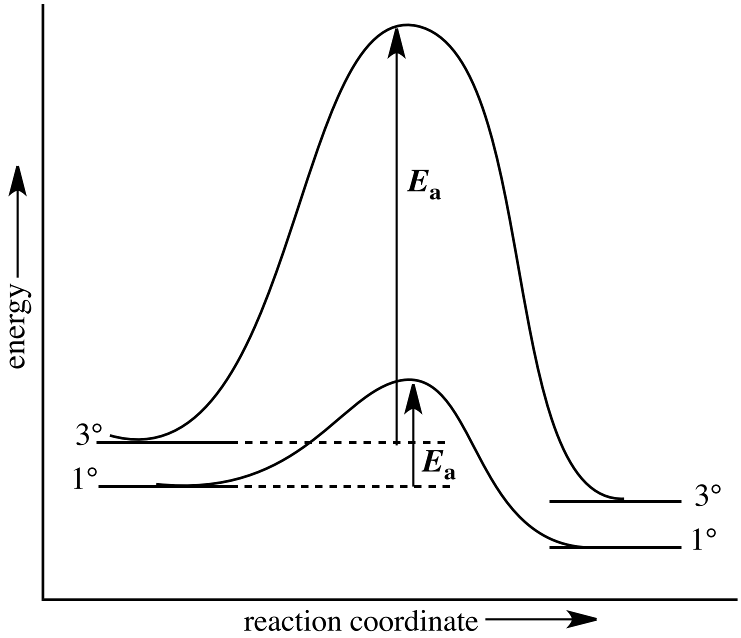
In the S_N2 reaction, the rate of the reaction is slowed by bulky groups near the reaction center due to ***steric hindrance***.





- crowding in the T.S. raises the activation energy and slows the reaction.

Look at the energy diagram for a 1° and 3° alkyl bromide:



B. The Effect of the Concentration and Strength of the Nucleophile

The strength & the concentration of the nucleophile greatly effects the rate of an S_N2 reaction.

Q. **How do we determine nucleophilic strength?**
A. **By measuring the rates of substitution reactions**

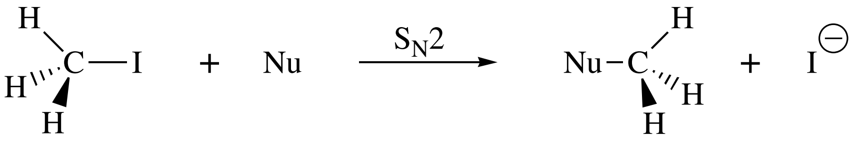
Look @ the relative rates of reaction of various nucleophiles with iodomethane (*next page*):

Nucleophilicity depends on a variety of factors: concentration of charge, solvent, polarizability and the nature of the substituents.

Best Nucleophiles:

- have high concentration of negative charge
- are highly polarizable
- are less solvated
- are not too hindered

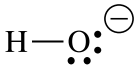
Relative Rates of S_N2 Reaction of Various Nucleophiles with Iodomethane in Methanol:



Nucleophile	**Relative Rate**
H_2O	1
CH_3OH	1
$F^{\ominus}$	500
$CH_3\overset{\overset{O}{\|}}{C}O^{\ominus}$	20,000
$Cl^{\ominus}$	23,500
NH_3	316,000
$PhO^{\ominus}$	630,000
$N_3^{\ominus}$	630,000
$Br^{\ominus}$	630,000
$CH_3O^{\ominus}$	1,995,000
$HO^{\ominus}$	3,163,000
$(CH_3CH_2)_3N$	5,010,000
$CN^{\ominus}$	5,010,000
$I^{\ominus}$	25,100,000
$(CH_3CH_2)_3P$	501,000,000
$HS^{\ominus}$	1,000,000,000
$PhS^{\ominus}$	7,943,000,000
$PhSe^{\ominus}$	50,000,000,000

Trends:

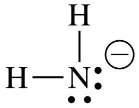
1. Increasing negative charge increases nucleophilicity.



$HO^{\ominus}$

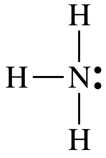
vs.

H_2O



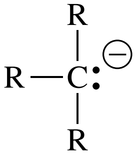
$H_2N^{\ominus}$

vs.

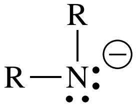


NH_3

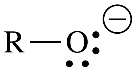
2. Nucleophilicity decreases to the right in the periodic table (this correlates with basicity).



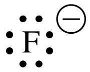
$R_3C^{\ominus}$



$R_2N^{\ominus}$



$RO^{\ominus}$



$F^{\ominus}$

3. Nucleophilicity increases as you go down a row in the periodic table (this does not correlate with basicity!!)

$(CH_3CH_2)_3N$	H_2O	$PhO^{\ominus}$	$F^{\ominus}$
$(CH_3CH_2)_3P$	H_2S	$PhS^{\ominus}$	$Cl^{\ominus}$
	H_2Se	$PhSe^{\ominus}$	$Br^{\ominus}$
			$I^{\ominus}$

Q. Why doesn't nucleophilicity always correlate with basicity?
A. Basicity is a thermodynamic property, measured by an equilibrium constant.

$$\text{H-A} \quad + \quad \text{H}_2\text{O} \quad \overset{K}{\rightleftarrows} \quad \text{A}^{\ominus} \quad + \quad \text{H}_3\text{O}^{\oplus} \qquad K = \text{equilibrium constant}$$

In contrast, nucleophilicity is a kinetic phenomenon, measured by comparing rates of reaction.

$$\text{R—X} \quad + \quad \text{Nu}^{\ominus} \quad \xrightarrow{k} \quad \text{R—Nu} \quad + \quad \text{X}^{\ominus} \qquad k = \text{rate constant}$$

As we go ***down*** a row in the periodic table, two things happen:

1. **The atoms get larger and the charge becomes less concentrated**. Smaller anions are more tightly solvated than larger atoms because their charge is more concentrated, so F^- is more heavily solvated than I^-.

   - *Solvation weakens a nucleophile because it impedes its ability to attack an electrophile!*

2. **Polarizability increases.** Larger elements have larger, more diffuse, and more polarizable electron clouds. These electron clouds allow for more effective orbital overlap in the S_N2 transition state.

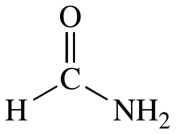
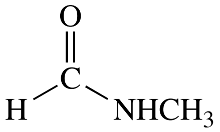
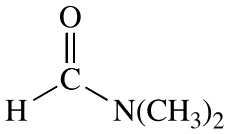
Result:

C. The Effect of Solvent on the Rate of Reaction

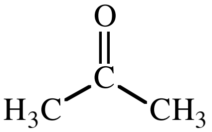
The rates of many S_N2 reactions are strongly affected by the solvent used. ***Why?***

Look @ the effect of solvent on the S_N2 rxn. of methyl iodide with chloride ion:

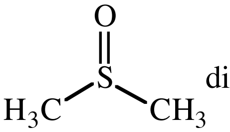
$$CH_3{-}I \quad + \quad Cl^{\ominus} \xrightarrow[k_{rel}]{\text{solvent}} CH_3{-}Cl \quad + \quad I^{\ominus}$$

Solvent			
Formula	**Name**	**Classification**	**Relative Rate**
CH_3OH	methanol	protic	1
	formamide	protic	12.5
	*N*-methylformamide	protic	45.3
	*N,N*-dimethylformamide	aprotic	1,200,000

Other common polar aprotic solvents:

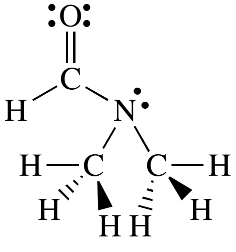


acetone

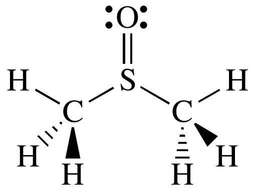


dimethylsulfoxide

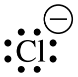
Compare solvation of Cl^- in a polar aprotic solvent, *vs*. a polar protic solvent(DMSO):



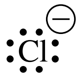
DMF



DMSO



vs.



- Polar aprotic solvents solvate anions relatively weakly because they cannot hydrogen bond, and the positive part of the solvent is in the center of the molecule! On the other hand, polar aprotic solvents solvate cations very well.

Na^+

Result:

- Anions are freer to react because they are unencumbered by solvent molecules.
- Rates of S_N2 reactions are greatly enhanced in polar aprotic solvents!

☛ ***The reactivity order as we descend a row in the periodic table is reversed when we switch to a polar aprotic solvent!!***

In protic solvents (e.g. H_2O, alcohol): $I^- > Br^- > Cl^- > F^-$

In polar aprotic solvent: $F^- > Cl^- > Br^- > I^-$

> In polar aprotic solvents, nucleophilicity more closely approximates basicity.

Summarizing Periodic Trends for nucleophile strength in polar and aprotic solvents:

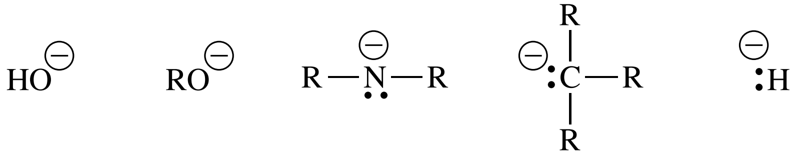
D. The Nature of the Leaving Group

Good leaving groups are weak bases. The same factors that make a species a weak base also make it a good leaving group.

(Look for conjugate bases of strong acids in the top half of the pK_a table with pK_a values less than *about* 8.)

$—I > —Br > —Cl > —F$

Never Leaving Groups in Nucleophilic Substitution!



$HO^{\ominus}$ $RO^{\ominus}$ $R—\underset{\cdot\cdot}{\overset{\ominus}{N}}—R$ $^{\ominus}\!:\!CR_3$ $^{\ominus}\!:\!H$

V. The Reversibility of an S_N2 Reaction

Many different kinds of nucleophiles can react with alkyl halides, and a wide variety of organic compounds can be synthesized by means of S_N2 reactions:

Examples:

$$CH_3CH_2Cl + HO^{\ominus} \longrightarrow CH_3CH_2OH + Cl^{\ominus}$$

$$CH_3CH_2Br + HS^{\ominus} \longrightarrow CH_3CH_2SH + Br^{\ominus}$$

$$CH_3CH_2Cl + H_2N^{\ominus} \longrightarrow CH_3CH_2NH_2 + Cl^{\ominus}$$

$$CH_3CH_2I + {}^{\ominus}C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + I^{\ominus}$$

Q: Can the reverse reaction occur by nucleophilic substitution?
A:

Look at the TS for the S_N2 reaction:

- The reverse reaction cannot occur because hydroxide ion is a terrible leaving group! The reaction is only reversible if the two possible leaving groups have similar leaving group abilities (*ie. they have similar basicities)*

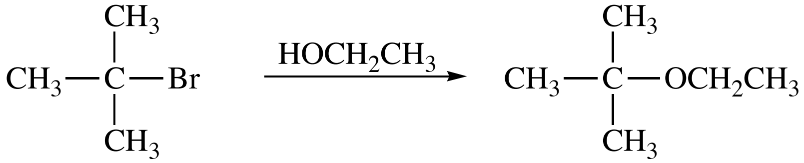
Example of reversible S_N2 reaction:

$$CH_3CH_2Br + I^{\ominus} \rightleftharpoons CH_3CH_2I + Br^{\ominus}$$

- The equilibrium can be driven to favor the desired products by using **Le Châtelier's principle** *(if an equilibrium is disturbed, the system will adjust to offset the disturbance.)*

VI. Substitution, Nucleophilic, Unimolecular: The S_N1 Reaction

When a primary alkyl halide is dissolved in an alcohol solvent with *no added base*, *no* reaction takes place. When a tertiary alkyl halide is subjected to the same conditions, *substitution* occurs.



$$\mathrm{CH_3}-\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{Br} \xrightarrow{\mathrm{HOCH_2CH_3}} \mathrm{CH_3}-\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{OCH_2CH_3}$$

This is a ***solvolysis***, a nucleophilic substitution where the nucleophile is the solvent.

A. Rate Law and Mechanism of S_N1 Reaction

Kinetics: If we measure the rate of the reaction as a function of varying initial concentrations of reactants we find that:

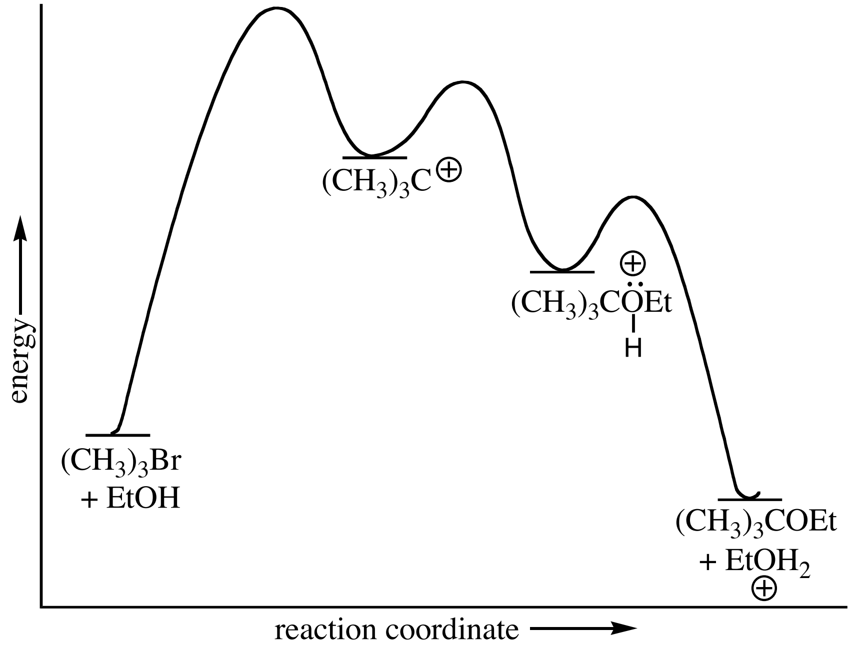
rate $\propto$ [*tert*-BuBr]

We can conclude:

- The reaction is 1st order.
- Any involvement of solvent in the reaction *cannot* be detected in the rate law because the concentration of the solvent is essentially constant. *However the nature of the solvent does play a critical role in this reaction.*
- Reaction is S_N1: (Substitution, Nucleophilic, Unimolecular)

Mechanism:

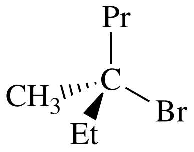
Free Energy Diagram:



B. The Stereochemistry of the S_N1 reaction:

Racemization

Look at the ***solvolysis*** of (S)-3-Bromo-3-methylhexane:

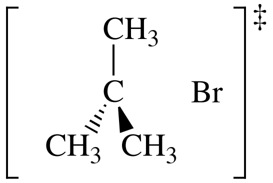


VII. Factors that Affect the Rate of the S_N1 Reaction

We know:

rate $\propto$ [*tert*-BuBr]

Transition state for the rate determining step:



- The bond to the leaving group breaks, as a carbocation forms.
- A carbocation is a high energy intermediate

Predict:

The factors that affect the rates of S_N1 reactions:

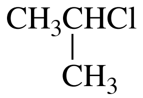
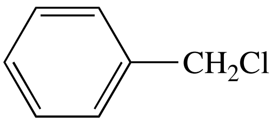
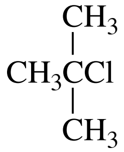
A. The structure of the substrate

B. The effect of the solvent

C. The nature of the leaving group

A. The Structure of the Substrate

Look @ the relative rates of S_N1 reactions for various alkyl chlorides:

	Krel
CH_3Cl	1.0
CH_3CH_2Cl	1.0
 $CH_3CH(CH_3)Cl$	12
$H_2C{=}CHCH_2Cl$	40
	120
$CH_3O\text{-}CH_2\text{-}Cl$	$>10^3$
 $(CH_3)_3CCl$	$>10^6$

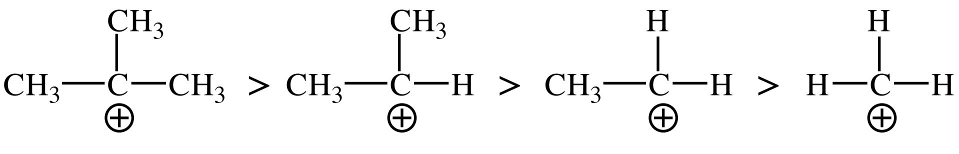
These compounds ionize easily even though they are primary carbons because the carbocation formed by ionization is stabilized by **resonance delocalization**

Notice:

- As the number of R groups on the carbon with the leaving group increases, the rate of the S_N1 reaction increases.
- Alkyl halides that form resonance stabilized carbocations have a faster rate of reaction.

☛ ***The rates of S_N1 reactions correspond to the stability of the corresponding carbocations!***

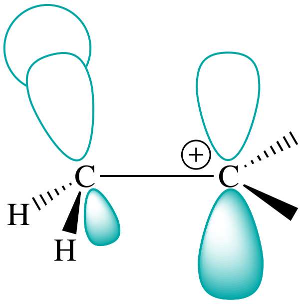
Stability of carbocations:



$$(CH_3)_3C^+ > (CH_3)_2CH^+ > CH_3CH_2^+ > CH_3^+$$

- the more alkyl groups bonded to the positively charged carbon, the more stable the carbocation. Why?

Hyperconjugation: Partial overlapping of the sigma bonding orbital of an adjacent C-H or C-C bond with the vacant 2p orbital of the cationic carbon.



- Delocalization of the charge through hyperconjugation stabilizes the (+)-charge on the carbocation.
- Can also think of this as an inductive effect:

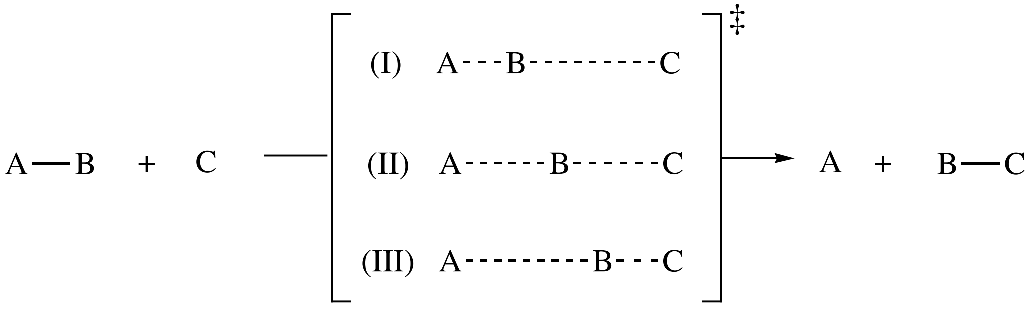
What does the stability of the carbocation intermediate have to do with the rate of the S_N1 reaction? We know the rate of a reaction depends on the magnitude of $\boldsymbol{E}_\mathbf{a}$, not on the stability of the reactants, products or intermediates. The magnitude of $\boldsymbol{E}_\mathbf{a}$ depends on the energy of the transition state.

Q. How can we estimate the energy of a transition state?

A:

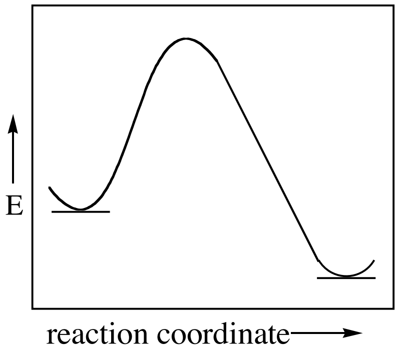
1. The Structure of the Transition State: Hammond's Postulate

We know that the structure of a transition state lies between the structure of the reactants and the structure of the products. It does not necessarily mean that the structure is *halfway* in between. The transition state can resemble products more closely than reactants, or reactants more closely than products:

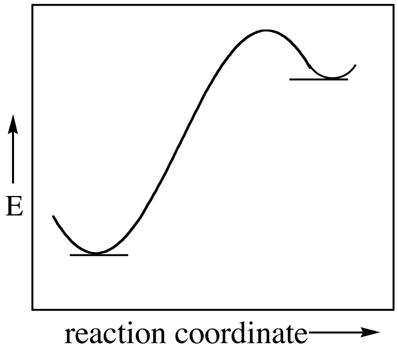


According to **Hammond’s postulate**, *the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy*.

Exothermic reaction:

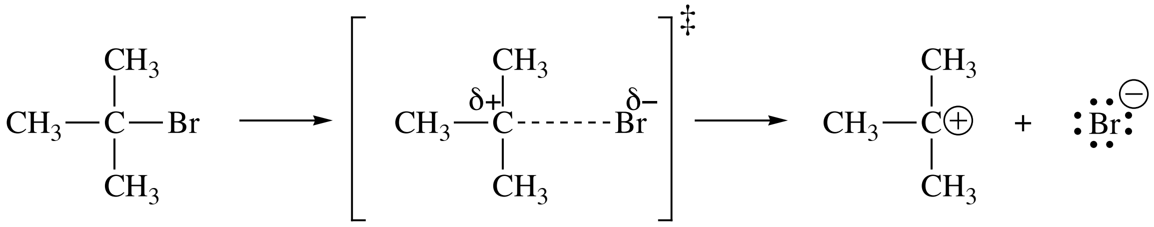


Endothermic reaction:



Since the rate-determining step in an S_N1 reaction is formation of a carbocation intermediate, an endothermic process, the transition state will *resemble the product of this step, a carbocation, more than the reactants*.

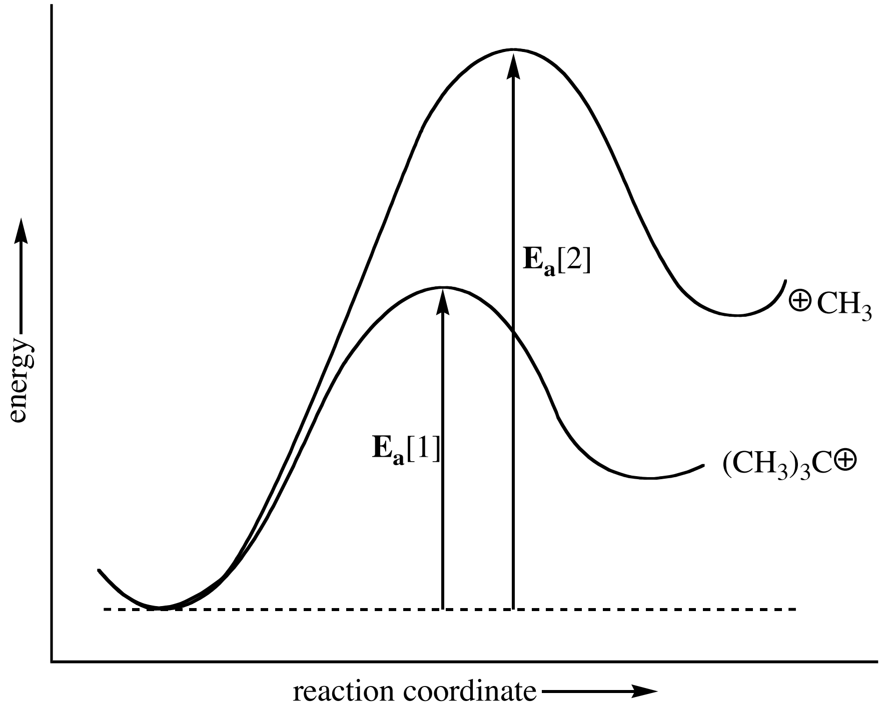
Look at the structure of the transition state for the rate-determining step in an S_N1 reaction of tert-butyl bromide:



transition state

- This transition state more closely resembles the carbocation intermediate, since the carbocation intermediate is *closest* in energy. The major factor contributing to the instability of this transition state are the same ones that make the carbocation unstable: *development of an electron deficient site*.

Compare energy diagrams for formation of methyl and 3° carbocations in the S_N1 reaction:

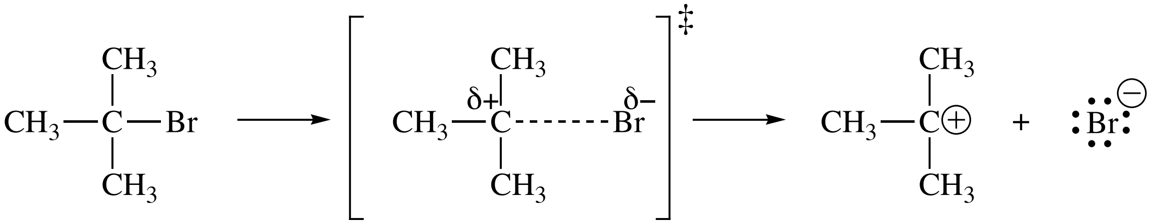


- The relative rates of formation of the two carbocations is determined by the relative free energies of the transition states for carbocation formation.
- Since CH_3^+ is less stable than $(CH_3)_3C^+$, and the transition states resemble these two carbocations, then $E_a[2] > E_a[1]$, and reaction 2 is slower.

B. The Effect of Solvent on the Rate of Reaction

Polar protic solvents greatly enhance the rate of ionization of an alkyl halide in an S_N1 reaction.

WHY? Solvation stabilizes the transition state leading to the carbocation. This lowers $\boldsymbol{E}_a$.



- The higher the ***dielectric constant***, the better a solvent's ability to solvate ions.

Look **at the ionization of *tert*-butyl chloride in various solvents:**

Solvent	**dielectric constant**	**K_{rel}**
water	80	8000
methanol	33	1000
ethanol	24	200
acetone	21	1
diethyl ether	4.3	0.001
hexane	2.0	< 0.0001

Best:

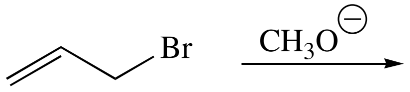
Alcohol:

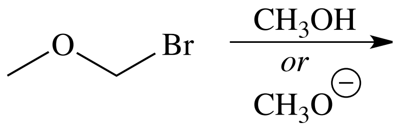
C. The Nature of the Leaving Group

Good leaving groups are also important in the S_N1 reaction!

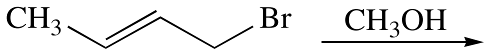
VIII. Benzylic Halides, Allylic Halides, Methoxymethyl Halides, Vinylic Halides, and Aryl Halides

Benzylic, allylic, and methoxymethyl halides readily undergo S_N2 reactions unless they are tertiary, *and* they also undergo S_N1 reactions even if they are primary, because they form stable carbocations.



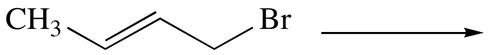


If the resonance contributors of the allylic carbocation intermediate have different groups bonded to their sp^2 carbons, two substitution products will be obtained under S_N1 conditions:



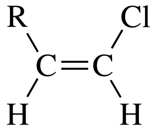
Q: *To avoid this happening what do you do?*

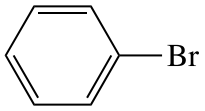
A:



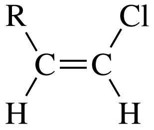
☛ **Vinylic and Aryl Halides do not undergo S_N1 or S_N2 reactions!** Why?

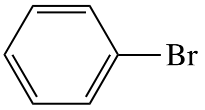
There is **no S_N2** because as the nucleophile approaches on the backside of the sp^2 carbon, it is repelled by the π-electron cloud of the double bond or the aromatic ring.





There is **no S_N1** because vinylic and aryl carbocations are extremely unstable, and the bond between an sp^2-carbon and a halogen is much stronger, and therefore harder to break:





IX. Competing Mechanisms for Nucleophilic Substitution

The S_N1 reaction is in competition with the S_N2 reaction!

Q. Why does methyl chloride react by an S_N2 mechanism and *tert*-butyl chloride react by an S_N1 reaction?

A. The relative rates of the possible reactions dictate the outcome of the reaction.

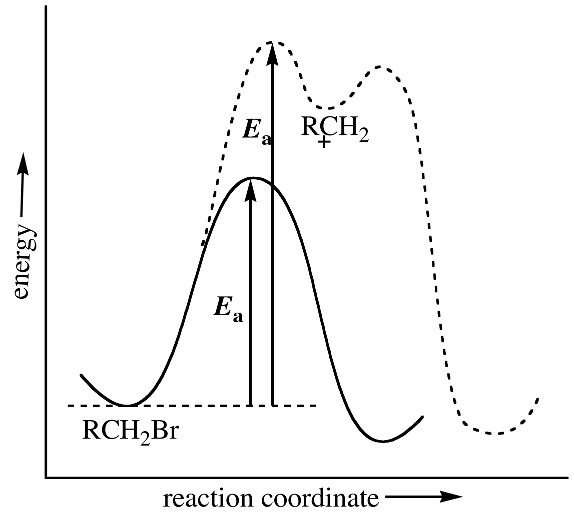
i.e. The rate of an S_N2 reaction for methyl chloride is exceedingly faster than the rate of an S_N1 reaction for methyl chloride.

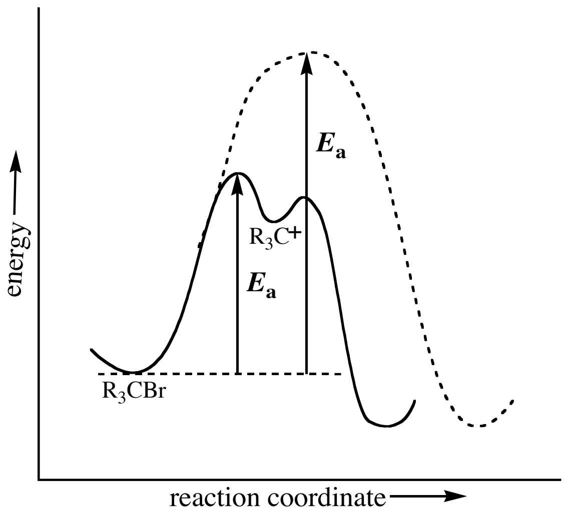
Remember the order of reactivity:

S_N2 reaction: methyl > 1° > 2° > 3°

S_N1 reaction: 3° > 2° > 1° > methyl

Compare energy diagrams for S_N1 & S_N2 reaction of a 1° & 3° alkyl halide:





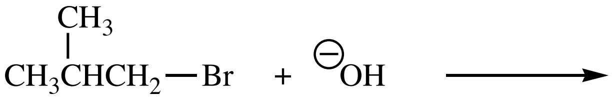
For 2° alkyl halides the rates of S_N1 vs. S_N2 are much more competitive!

- 2° alkyl halides react with good nucleophiles by S_N2 reactions.
- If a 2° alkyl halide is in a good ionizing solvent and no good nucleophile is present, S_N1 reactions will predominate.

X. Organic Synthesis

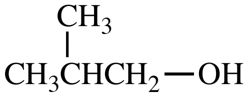
In organic chemistry, you have to predict products that are formed when reagents react, and you also have to be able look at a compound and see how you can synthesize it using reactions that you have learned.

Predict the product:



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2{-}Br \quad + \quad {}^{\ominus}OH \quad \longrightarrow$$

Show how to synthesize the following compound (*what starting material an reagent are needed to make it?*):



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2{-}OH$$

Example of a synthesis problem:

Starting with an alkyl halide, show how the following compound can be synthesized: