

## Comparison of S<sub>N</sub>2 versus S<sub>N</sub>1 Reactions

### Effect of Nucleophile

-S<sub>N</sub>2 is a one step reaction where both the substrate and nucleophile are involved

-S<sub>N</sub>1 is a two step reaction involving the initial formation of a planar carbocation

Therefore:

S<sub>N</sub>2      strong nucleophiles are required

S<sub>N</sub>1      nucleophile strength does not affect rate

## Effect of Substrate

Two important considerations:

- as the number of substituents on the carbon increase the stability of a formed carbocation increases (therefore of lower energy)

For a  $S_N1$  reaction  $3^\circ$  halides are the best

- as the number of substituents increase, the bulkiness at the electrophilic carbon increases

For a  $S_N2$  reaction methyl halides are the best

$S_N1$  substrate:       $3^\circ > 2^\circ$  ( $1^\circ$  and methyl halide do not react)

$S_N2$  substrate:      methyl halide  $> 1^\circ > 2^\circ$  ( $3^\circ$  does not react)

## Effect of Leaving Group

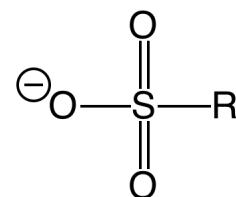
-in both reactions the bond between the electrophilic carbon and the leaving group breaks in the rate determining step

Therefore both S<sub>N</sub>1 and S<sub>N</sub>2 reactions required a good leaving group

Weak bases that are common leaving groups:



halides



sulfonate

## Effect of Solvent

In a typical S<sub>N</sub>1 reaction a neutral starting material is ionized to charged intermediates in the rate determining step

In a typical S<sub>N</sub>2 reaction the charge is kept constant during the rate determining step (charge changes places, but the total amount of charge is the same)

S <sub>N</sub> 1	good ionizing solvent favored
S <sub>N</sub> 2	solvent has less of an effect

\*Need to compare structures for starting material and transition state for rate determining step, if the amount of charge changes the effect of solvent on reaction rate will change

## Comparison of E1 and E2 Reactions

### Effect of Substrate

In a E1 reaction a carbocation is formed  
Thus a more substituted carbocation is more stable

In a E2 reaction an alkene is formed in the rate determining step  
Follows Zaitsev rule where a more substituted alkene is favored

Therefore both E1 and E2 reactions the rate follows the trend:

$3^\circ > 2^\circ > 1^\circ$  ( $1^\circ$  usually will not go by E1)

## Effect of Base

Single most important factor for eliminations

If the substrate is suitable for an elimination  
then a strong base will favor an E2 mechanism

A weak base will favor ionization (E1) first

Therefore:

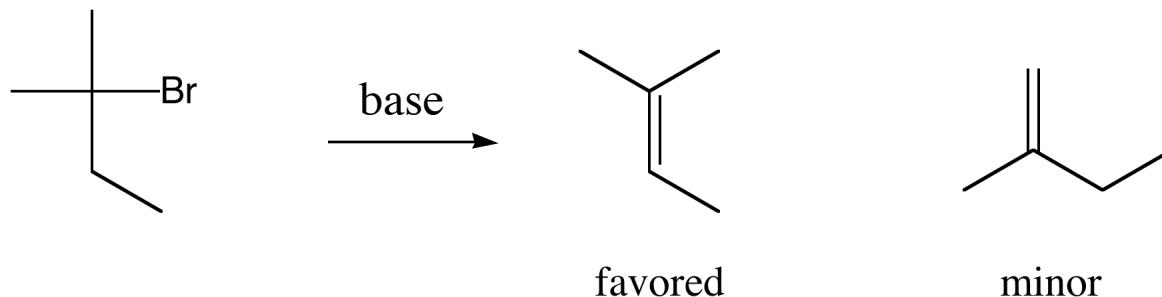
E2	strong base required
E1	base strength unimportant

strong bases:       $\ominus\text{OH}$ ,     $\ominus\text{OR}$ ,     $\ominus\text{NH}_2$ ,     $\ominus\text{CH}_3$

## Orientation of Eliminations

The product with the more substituted double bond will be favored

Zaitsev rule is followed by both E1 and E2



## Competition Between Substitution and Elimination

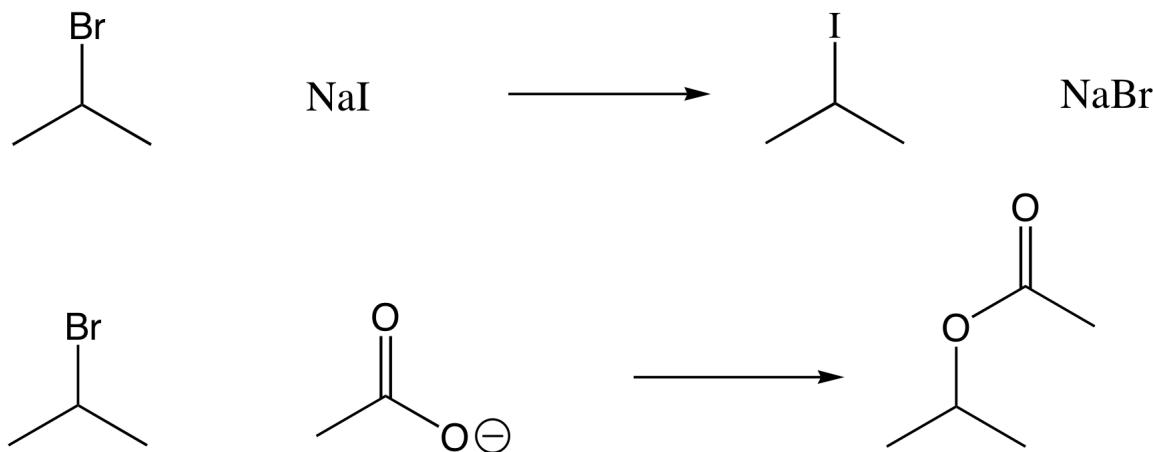
A reaction with a given alkyl halide can follow one of four mechanism ( $S_N2$ ,  $S_N1$ ,  $E2$ ,  $E1$ ) yielded different products

Trends to predict which mechanism will predominate

- 1) Weakly basic species that are good nucleophiles give predominantly substitution

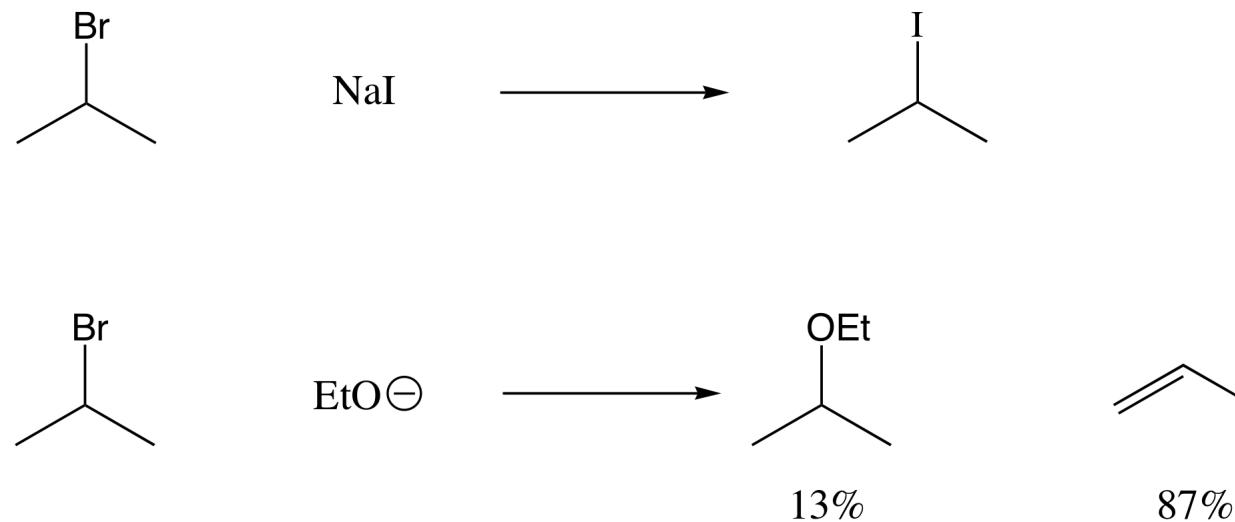
Examples: halides,  $RS^-$ ,  $N_3^-$ ,  $RCO_2^-$

Therefore  $1^\circ$  or  $2^\circ$  halides yield clean  $S_N2$   
 $3^\circ$  halides give predominantly  $S_N1$  ( $E1$  usually minor pathway)



2) Strongly basic nucleophiles give more eliminations

E2 mechanism starts to compete with S<sub>N</sub>2 as base strength increases

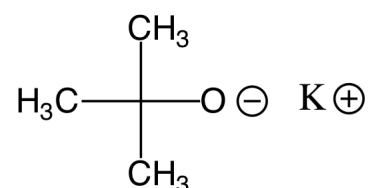


- with methyl halides or 1° halides S<sub>N</sub>2 predominates with strong base (nucleophile)
- with 3° halides S<sub>N</sub>2 mechanism is impossible and E2 predominates with strong base

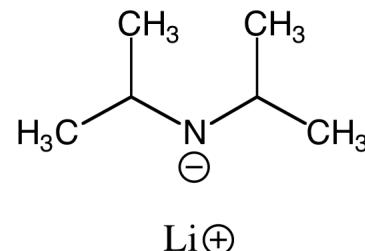
### 3) Sterically hindered basic nucleophiles favor eliminations

-Just as elimination becomes favored with sterically hindered substrates  
E2 becomes favored with sterically hindered bases

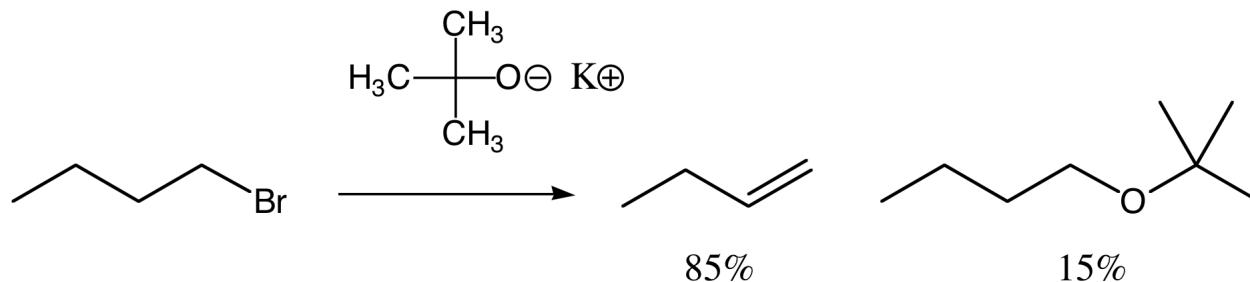
Some common sterically hindered bases



potassium tert-butoxide



lithium diisopropylamide (LDA)



## Factors for Substitution versus Elimination

### 1) Base strength of the nucleophile

Weak	Strong
Halides, RS-, N <sub>3</sub> -, NC-, RCO <sub>2</sub> -	HO-, RO-, H <sub>2</sub> N-
Substitution more likely	Elimination increases

### 2) Steric hindrance at reacting carbon

Sterically unhindered Methyl, 1° Substitution predominates	Sterically hindered Branched 1°, 2°, 3° Elimination increases
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### 3) Steric hindrance of strongly basic nucleophile

Sterically unhindered HO-, CH <sub>3</sub> O-, H <sub>2</sub> N- Substitution may occur	Sterically hindered (CH <sub>3</sub> ) <sub>3</sub> CO-, LDA Elimination favored
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## Summary of Reactivity of Alkyl Halides

### Methyl halide

Reacts only through  $S_N2$  pathway

- No other possibilities

- No adjacent carbons to form  $\pi$  bond

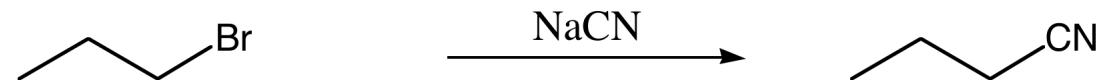
- Methyl cation is too high in energy to go through  $S_N1$  pathway

## Primary Alkyl Halides

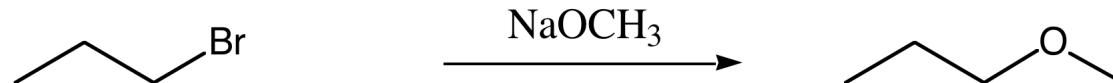
### Reactivity of R-X with nucleophiles

Unhindered primary R-X

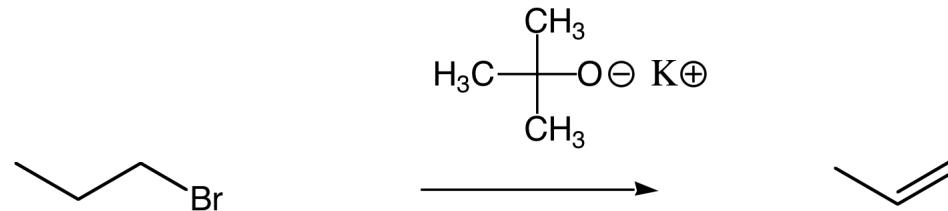
S<sub>N</sub>2 with good nucleophiles that are not strongly basic



S<sub>N</sub>2 with good nucleophile that are also strongly basic



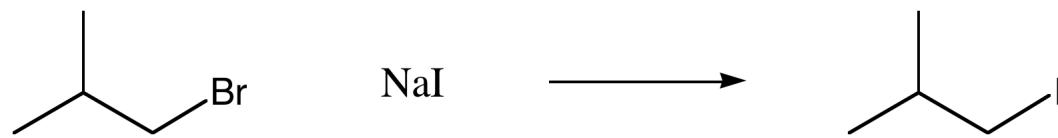
E2 with nucleophiles that are strongly basic and hindered



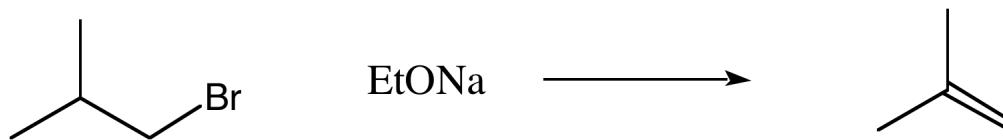
No, or exceedingly slow, reaction with poor nucleophiles

## Branched Primary Alkyl Halides

S<sub>N</sub>2 with good nucleophiles that are not strongly basic



E2 with nucleophiles that are strongly basic

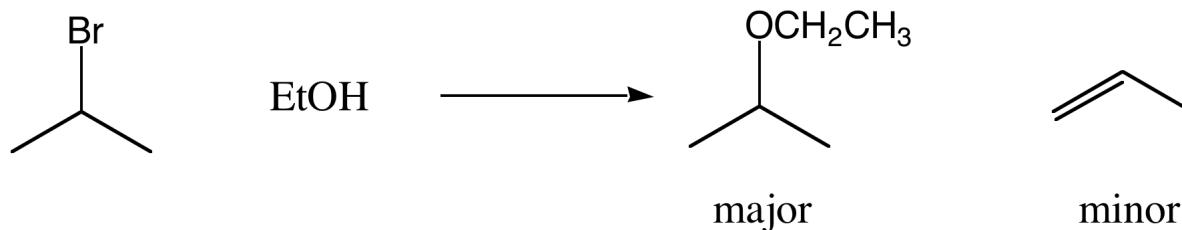


No reaction with poor nucleophiles

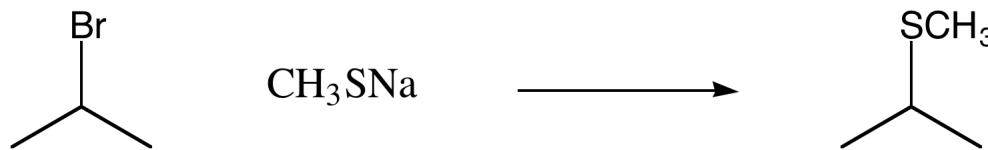
## Secondary Alkyl Halides

(hardest to predict – all four mechanisms are possible)

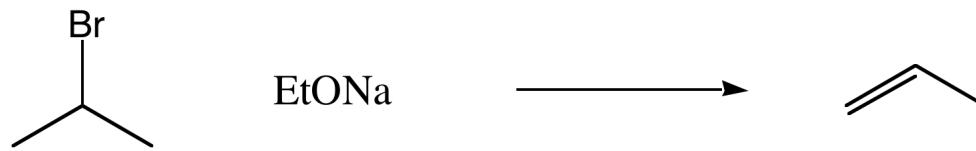
$S_N1$  or  $E1$  with good leaving group in polar solvent with weak nucleophile



$S_N2$  with good, weakly basic nucleophiles

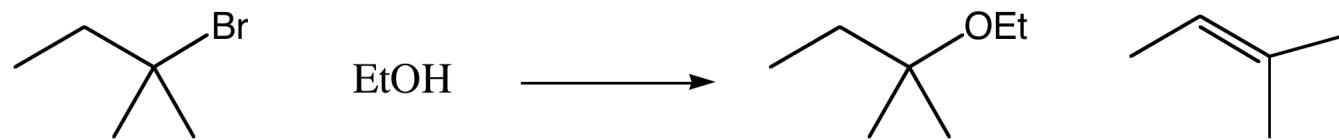


$E2$  with strongly basic nucleophiles

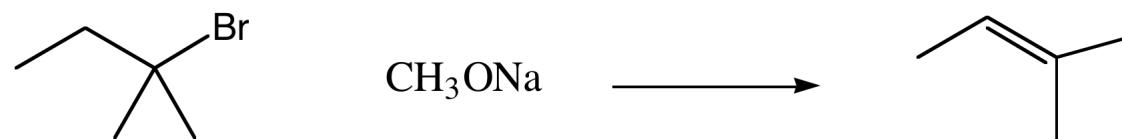


## Tertiary Alkyl Halides

$S_N1$  and  $E1$  with weak bases



$E2$  with strong base



As base strength increases, rate of  $E2$  increases

## Predicted Mechanisms by which Alkyl Halides React with Nucleophiles (or Bases)

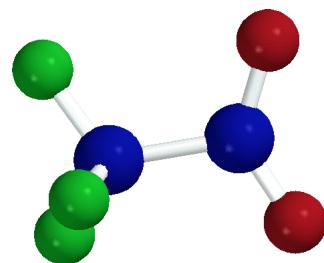
Type of Alkyl Halide	Poor NUC (e.g. EtOH)	Good NUC. Weak base (e.g. CH <sub>3</sub> SnNa)	Good NUC, strong, Unhindered base (e.g. CH <sub>3</sub> ONa)	Good NUC, strong, hindered base (e.g. (CH <sub>3</sub> ) <sub>3</sub> CONa)
methyl	No reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
1°				
unhindered	No reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	E2
branched	No reaction	S <sub>N</sub> 2	E2	E2
2°	Slow S <sub>N</sub> 1, E1	S <sub>N</sub> 2	S <sub>N</sub> 2 or E2	E2
3°	S <sub>N</sub> 1, E1	S <sub>N</sub> 1, E1	E2	E2

## Properties of Each Mechanism

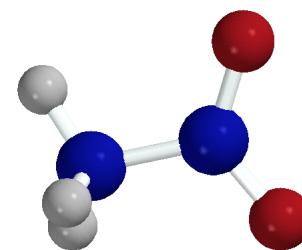
mechanism	stereochemistry	rate	rearrangements
S <sub>N</sub> 2	Inversion	k[substrate][NUC]	never
S <sub>N</sub> 1	Racemic, sometimes inversion preference	k[substrate]	Often, if possible
E2	Anti-coplanar Zaitsev rule	k[substrate][base]	never
E1	Zaitsev rule	k[substrate]	Often, if possible

## Description of Electron Control in Organic Chemistry

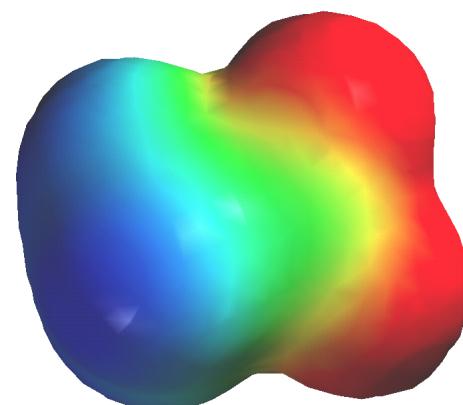
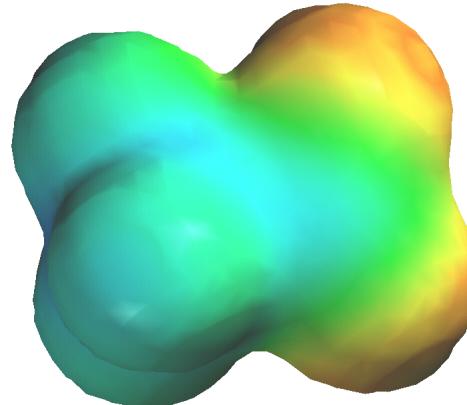
Stability of an organic compound (or intermediate) is dependent upon the molecules' ability to best fulfill the electronic demands throughout the molecule



trifluoroacetate



acetate



Trifluoroacetate is more stable electronically and thus the conjugate is more acidic

## Ways to Stabilize Sites

We have learned a couple of ways to stabilize sites electronically

### 1) Resonance

-stabilizes either electron rich or electron deficient sites

### 2) Substituent Effects

-we have learned about inductive and hyperconjugation effects

For alkyl substituents, more substituents raises the electron density  
carbon-carbon bonds are electron donating

For electron deficient sites this is good

(therefore radicals and carbocations favor more substituents:  $3^\circ > 2^\circ > 1^\circ >$  methyl)

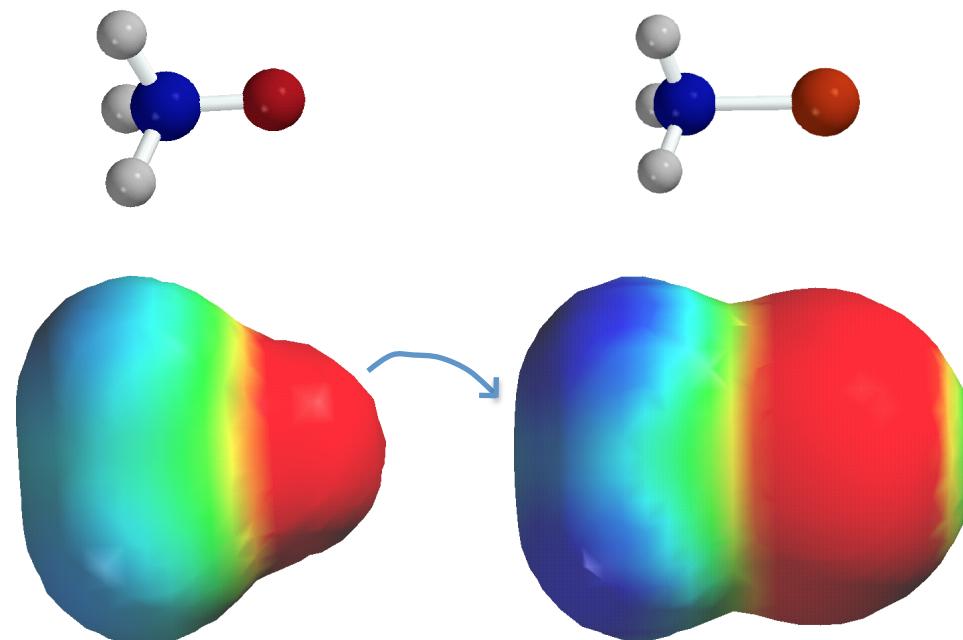
For electron rich sites this is bad

(therefore carbanions favor less substituents: methyl  $> 1^\circ > 2^\circ > 3^\circ$ )

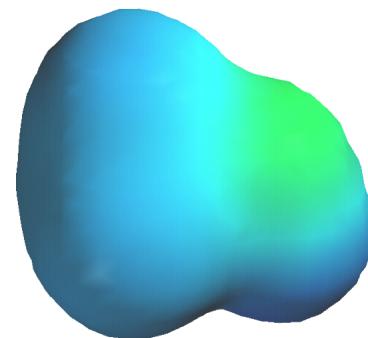
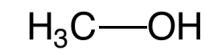
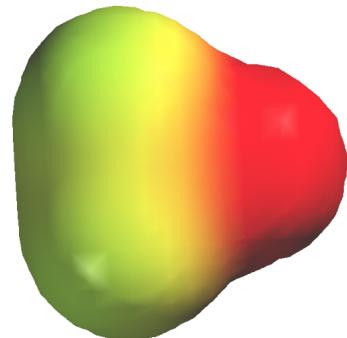
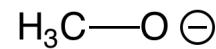
## Same Considerations for Organic Reactions

Organic reactions quite simply are species with high electron density (nucleophiles) reacting with species with low electron density (electrophiles)

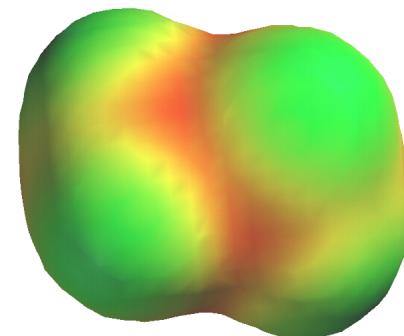
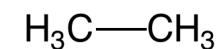
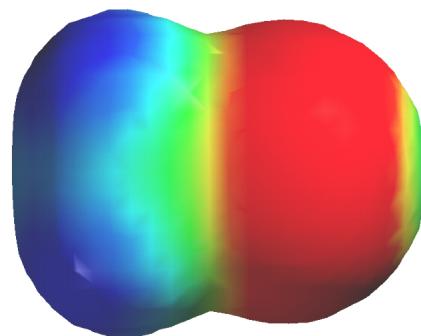
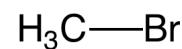
The FLOW of electrons occur to stabilize the electronic charge



Nucleophilicity thus merely refers to electron density  
-stronger nucleophiles have a higher electron density

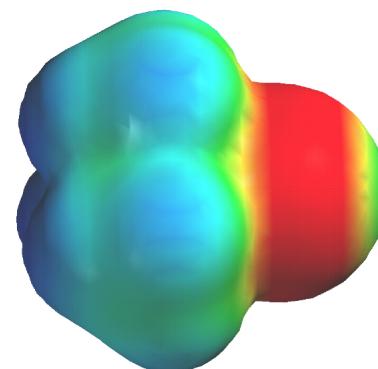
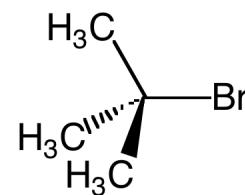
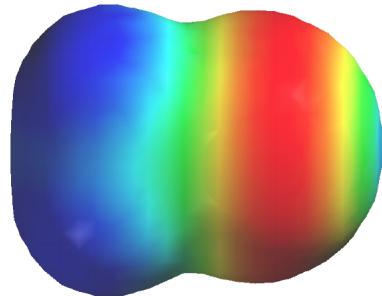
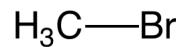


Electrophiles thus merely refer to a species with an electron deficient center  
-stronger electrophiles have a more electron deficient center



The only other consideration that we have dealt with is STERICS

Even if the nucleophile would react with the electrophile  
they need to be able to reach each other spatially in order to react



Now look at view of nucleophile approach

