Comparison of S_N2 versus S_N1 Reactions

Effect of Nucleophile

- S_N2 is a one step reaction where both the substrate and nucleophile are involved

- S_N1 is a two step reaction involving the initial formation of a planar carbocation

therefore:

S_N1	nucleophile strength is unimportant
S_N2	strong nucleophiles are required

Effect of Substrate

two important considerations:

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

for a S_N1 reaction 3° halides are best

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

for S_N2 reactions methyl halide is the best

S_N1 substrate	3°	>	2°	(1° and methyl halide do not react)			
S_N2 substrate	methyl halide	>	1°	>	2°	(3° does not react)	

Effect of Leaving Group

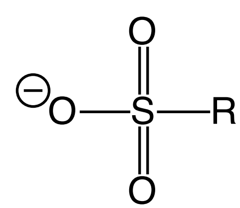
- in both reactions the bond between the electrophilic carbon and the leaving group is broken in the rate determining step

therefore both S_N1 and S_N2 reactions require a good leaving group

weak bases that are common leaving groups

$I^{\ominus}$ $Br^{\ominus}$ $Cl^{\ominus}$

halides



sulfonate

Effect of Solvent

in the S_N1 reaction a neutral starting material is ionized to charged intermediates in the rate determining step

in the S_N2 reaction often the charge is kept constant during the rate determining step

S_N1	good ionizing solvent favored
S_N2	dependent on reaction

Comparison of E1 and E2 Reactions

Effect of Substrate

in a E1 reaction a carbocation is formed

in a E2 reaction an alkene is formed in the rate determining step

- follows Zaitsev rule where a more substituted alkene is favored

therefore for both E1 and E2 reactions the stability follows the trend:

$3^\circ > 2^\circ > 1^\circ$ (1° 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 first

therefore:

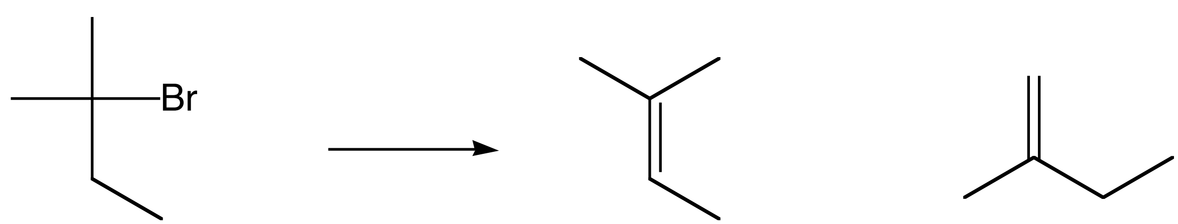
E2	strong base is required
E1	base strength is unimportant

strong bases: $^{\ominus}OH$, $^{\ominus}OR$, $^{\ominus}NH_2$, $^{\ominus}CH_3$

Orientation of Eliminations

the product with the more substituted double bond will be favored

Zaitsev rule is followed for both E1 and E2



favored

minor

Competition Between Substitution and Elimination

a given reaction with a haloalkane can follow four mechanisms
(S_N2, S_N1, E2, E1) yielding different products

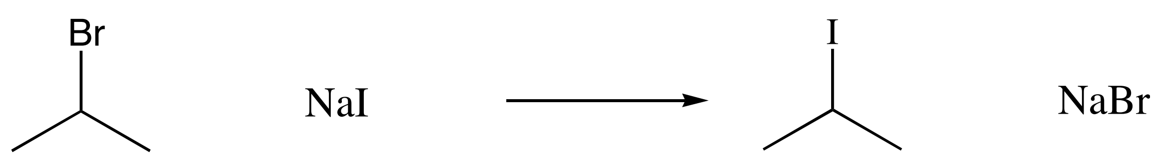
trends to predict which mechanism will predominate:

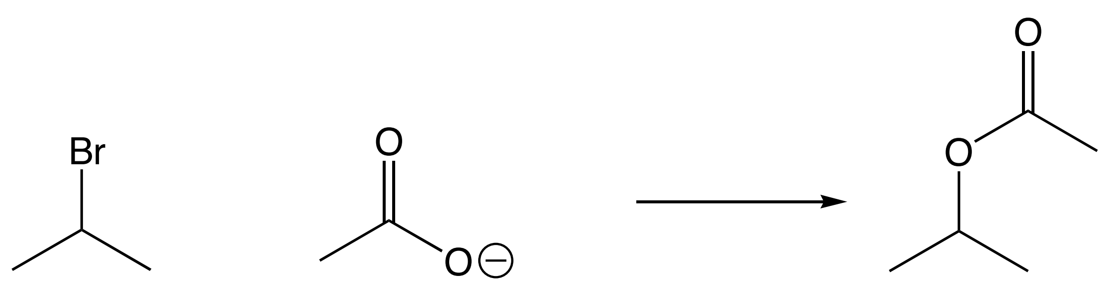
1) weakly basic species that are good nucleophiles give predominantly substitution

examples: I-, Br-, Cl-, RS-, N_3-, RCO_2-

therefore 1° or 2° halides give clean S_N2

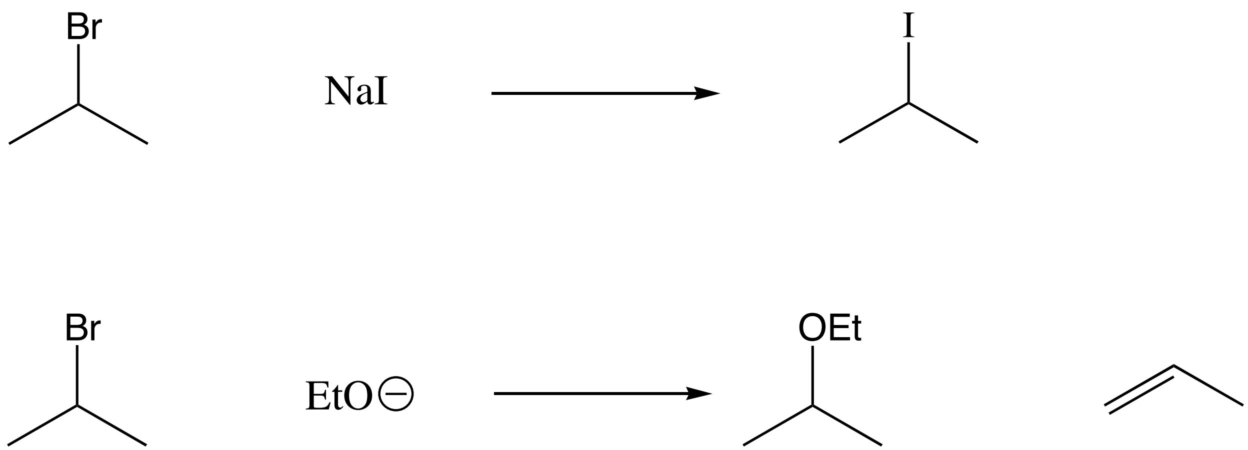
with 3° halides give predominantly S_N1 (E1 is usually minor pathway)





2) strongly basic nucleophiles give more eliminations

E2 mechanism starts to compete with S_N2 as base strength increases



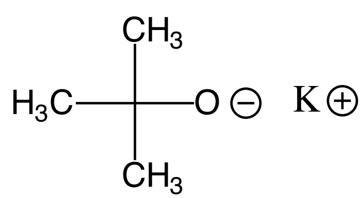
13% 87%

- with methyl halide or 1° halides S_N2 predominates with strong base
- with 3° halides S_N2 mechanism is impossible and E2 mechanism predominates with strong base

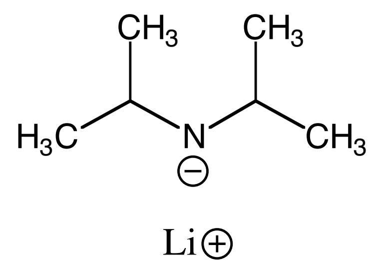
3) sterically hindered basic nucleophiles favor eliminations

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

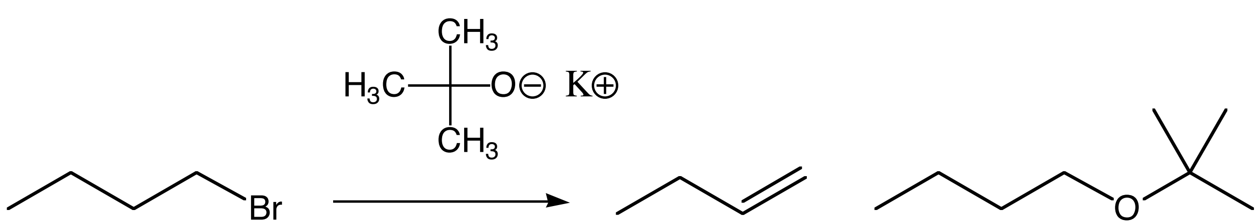
some common sterically hindered bases



potassium tert-butoxide



lithium diisopropylamide (LDA)



85%

15%

Factors for Substitution versus Elimination

1) base strength of the nucleophile

weak	strong
halides, RS-, N_3-, CN-, RCO_2-	HO-, RO-, H_2N-, R_2N-
substitution more likely	elimination increases

2) steric hindrance at reacting carbon

sterically unhindered	sterically hindered
methyl, 1°	branched 1°, 2°, 3°
substitution predominates	elimination increase

3) steric hindrance of strongly basic nucleophile

sterically unhindered	sterically hindered
HO-, CH_3O-, H_2N-	$(CH_3)_3CO$-, LDA
substitution may occur	elimination favored

Summary of Reactivity of Haloalkanes

methyl halide

reacts only through S_N2 pathway

- no other possibility

no adjacent H's

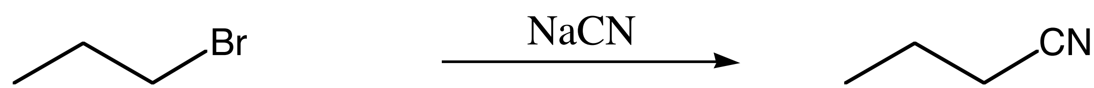
methyl cation is too high in energy to go through S_N1 pathway

Primary Haloalkane

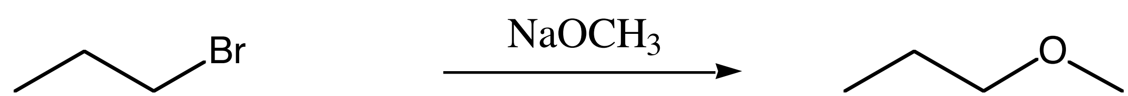
reactivity of R-X with nucleophiles

unhindered primary R-X

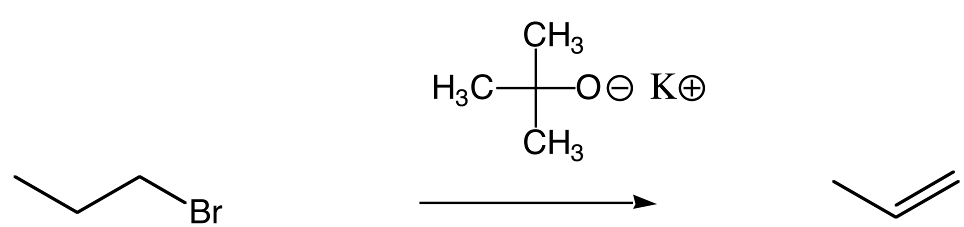
S_N2 with good nucleophiles that are not strongly basic



S_N2 with good nucleophiles that are also strongly basic but unhindered



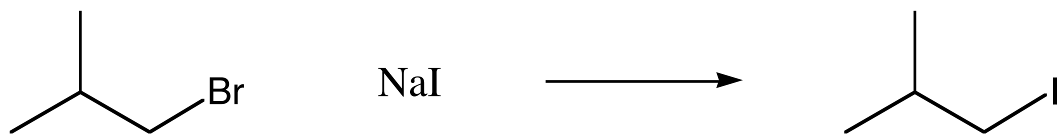
E2 with nucleophiles that are strongly basic and hindered



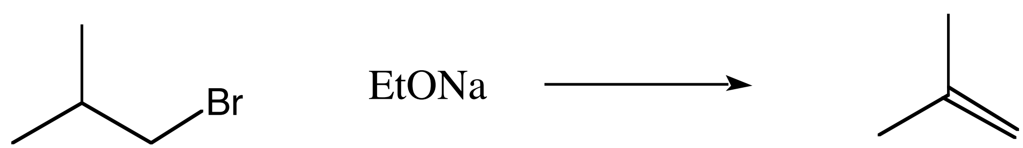
no, or exceedingly slow, reaction with poor nucleophiles

Branched Primary Haloalkane

S_N2 with good nucleophiles that are not strongly basic



E2 with nucleophiles that are strongly basic (hindered or unhindered)

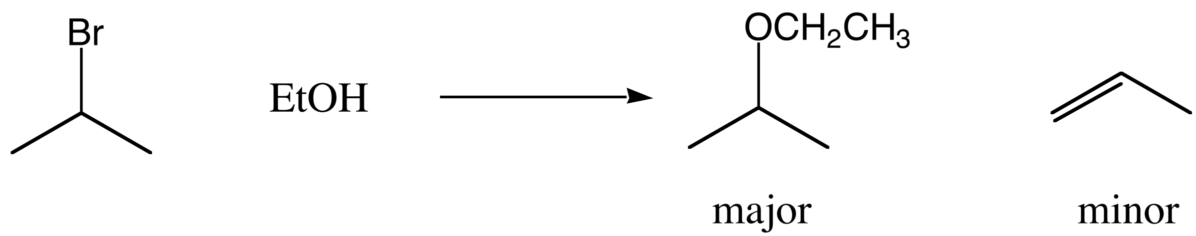


no reaction with poor nucleophiles

Secondary Haloalkanes

(hardest to predict)

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

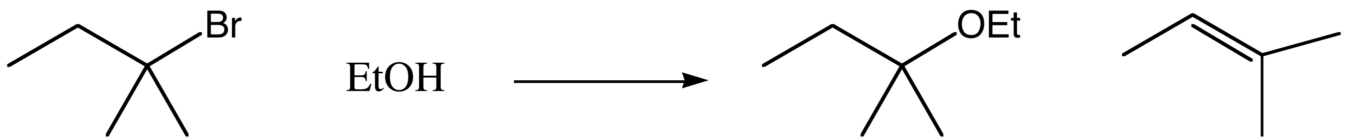


S_N2 with good, weakly basic nucleophiles

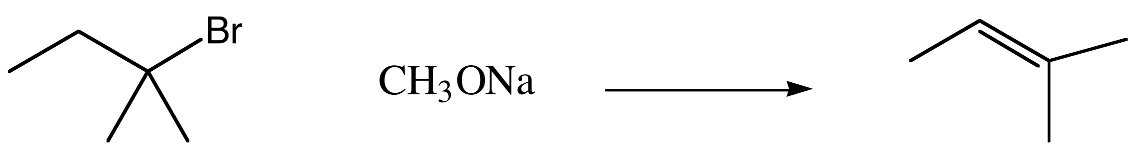
E2 with strongly basic nucleophiles in polar solvent

Tertiary Haloalkanes

S_N1 and E1 with weak bases



E2 with strong base



Predicted Mechanisms by Which Haloalkanes React with Nucleophiles (or Bases)

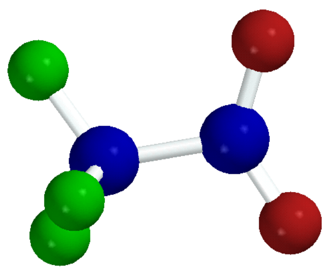
type of haloalkane	poor NUC (e.g. EtOH)	good NUC, weak base (e.g. I-)	good NUC, strong, unhindered base (e.g. CH_3O-)	good NUC, strong, hindered base (e.g. $(CH_3)_3CO$-)
		type of nucleophile (base)		
methyl	no reaction	S_N2	S_N2	S_N2
1°				
unhindered	no reaction	S_N2	S_N2	E2
branched	no reaction	S_N2	E2	E2
2°	slow S_N1, E1	S_N2	E2 or S_N2	E2
3°	S_N1, E1	S_N1, E1	E2	E2

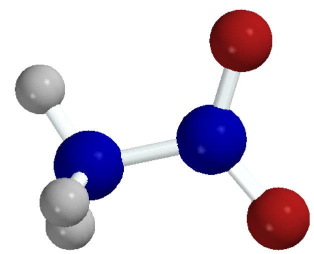
Properties of Each Process

	stereochemistry	rate	rearrangements
S_N2	inversion	k[substrate][NUC]	never
S_N1	racemic, sometimes inversion pref.	k[substrate]	often, if possible
E2	anti-coplanar Zaitsev rule	k[substrate][base]	never
E1	Zaitsev rule	k[substrate]	often, if possible

Description of Electrons Control Organic Chemistry

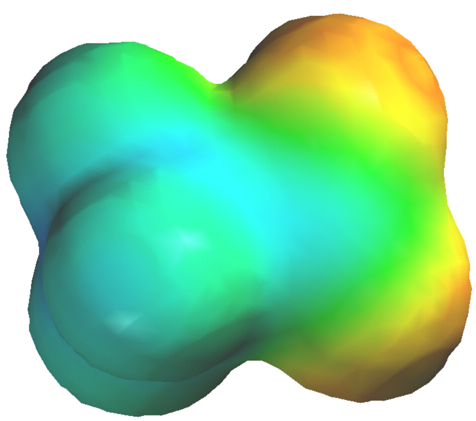
Stability of an organic compound (or intermediate) is dependent upon the molecules ability to best fulfill the electronic demand throughout the molecule

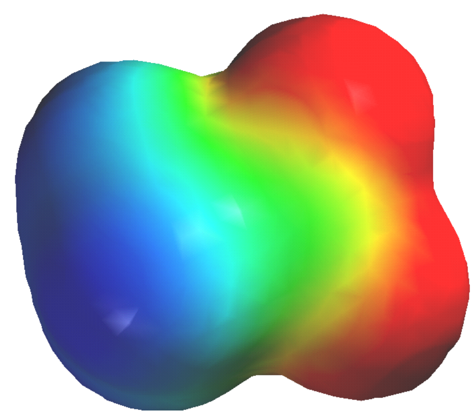




trifluoroacetate

acetate





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
- biggest factor of anything

2) Substituent Effects

- we have learned about inductive and hyperconjugation effects

for alkyl substituents: as substituents increase the electron density increases

- for electron deficient sites this is good

(therefore radicals and carbocations favor more substituents; 3° > 2° > 1° > methyl)

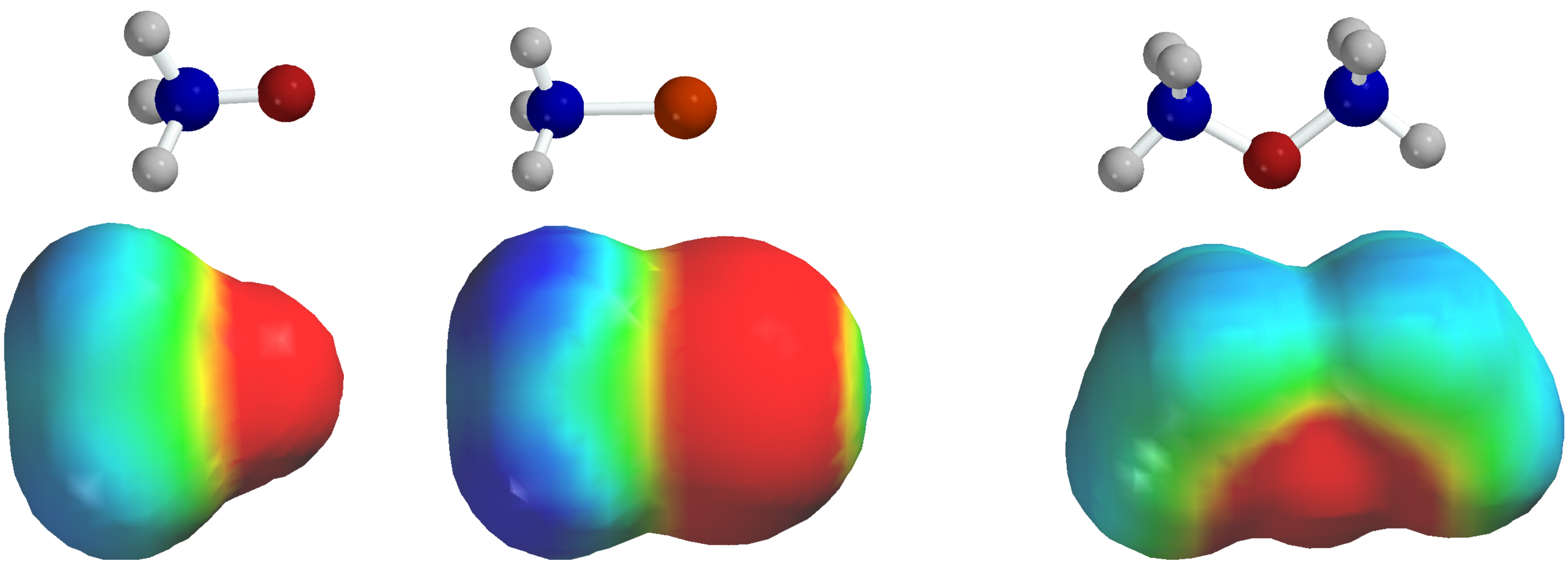
- for electron rich sites this is bad

(therefore carbanions favor less substituents; methyl > 1° > 2° > 3°)

Same Considerations for Organic Reactions

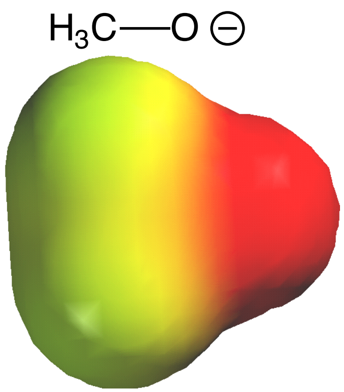
organic reactions quite simply are merely species with high electron density (nucleophiles) reacting with species with low electron density (electrophiles)

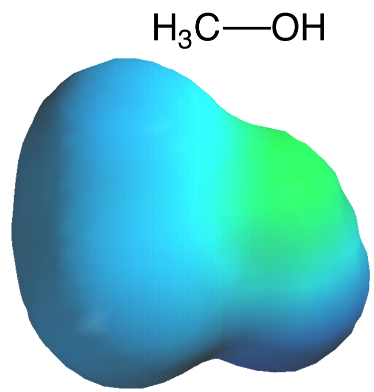
the FLOW of electrons occur to stabilize the electronic charge



Nucleophilicity thus merely refers to electron density

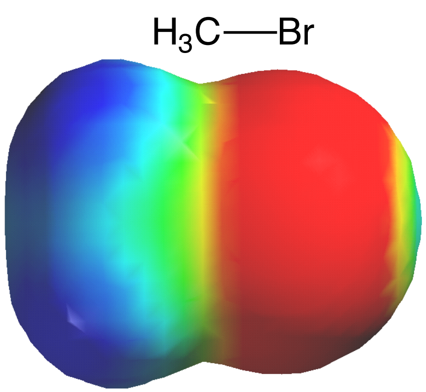
- stronger nucleophiles have a higher electron density

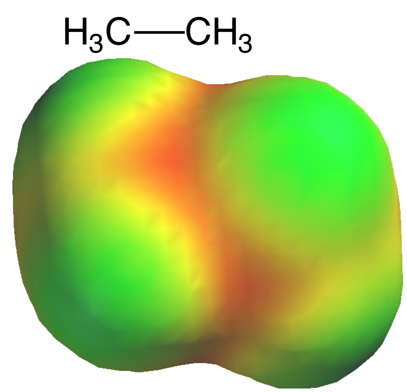




Electrophiles thus merely refer to a species with a electron deficient center

- stronger electrophiles have a more electron deficient center

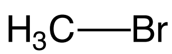


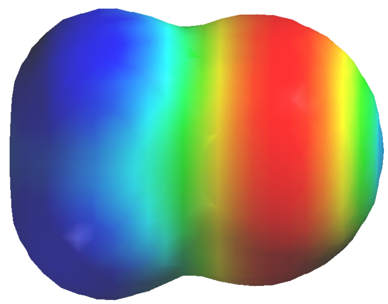


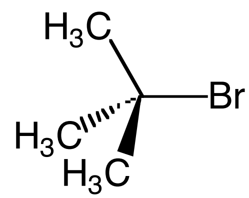
The only other consideration that we have dealt with is STERICS

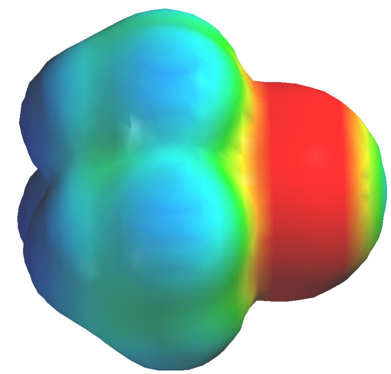
even if the nucleophile would react with the electrophile

they need to be able to reach other spatially in order to react









now look at view of nucleophile approach