CHEM 221 section 01

LECTURE #21 Tues., Nov.15, 2005

ASSIGNED READINGS:

TODAY'S CLASS: finish Ch.9, start Ch.10

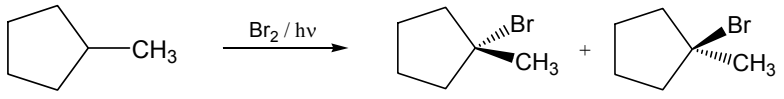
NEXT LECTURE: continue Ch.10

http://artsandscience.concordia.ca/facstaff/P-R/rogers

9.7 Radical substitution of cyclic compounds

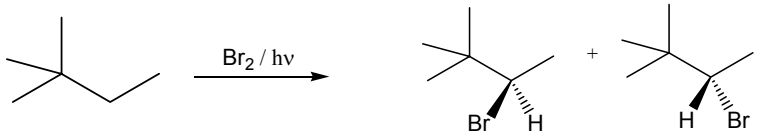
- No different than acyclic alkanes!

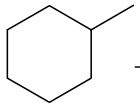
So let's see some examples, cyclic & acyclic:



Bromination is selective for most highly substituted site!

Are these molecules enantiomers?





? Is it smarter to use $Cl_2 / h\nu$ *or* $Br_2 / h\nu$?

⇨ Cl• yields mix of 5 regio-isomers (then add stereo…),
⇨ Br• cleanly yields ONE !

Ch.10: Substitution Reactions of Alkyl halides

Chapter Goals

Understand the two basic types of substitution reactions.

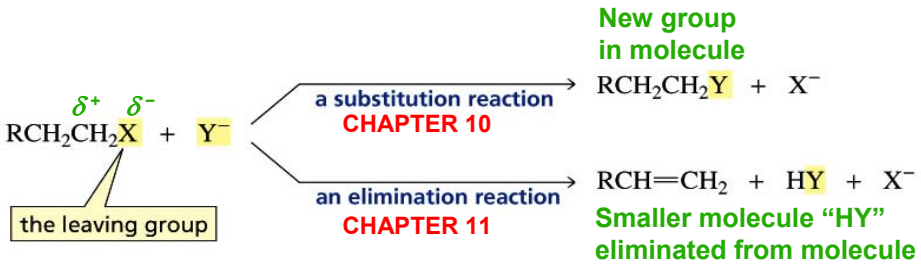
- Learn the mechanisms of S_N1 & S_N2 rxns – *including stereochemistry.*
- Understand the concept of nucleophilicity and its role in reactions.
- Understand competition between different reaction pathways.
- Understand the effect of solvent on relative reaction rates.

Chapter Outline:

Reaction pathways: substitutions & eliminations

Typical reactions observed with:

- compounds with an electronegative atom X (or group) bonded to an sp^3-hybridized C atom *e.g.,* alkyl halides
  - ⇨ POLAR nature of molecule defines their reactivity !



The atom or group that is substituted or eliminated in these rxns is called a ***leaving group***

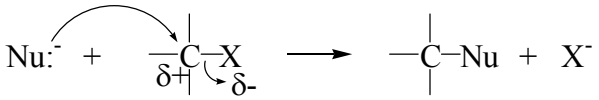
10.1 Alkyl halides react because of polarity

- Polar C-X bond: X δ^-, C δ^+ (X pulls harder on bonding e⁻s)
- Halide can "leave" with the e⁻s, in TWO WAYS:

1.) Concerted (one-step) reaction: "S_N2"

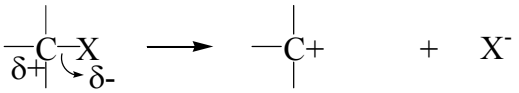
$\overset{\delta+}{R}CH_2\overset{\delta-}{-X}$ X= F, Cl, Br, I

- Halide leaving group "LG" pushed off by nucleophile "Nu":

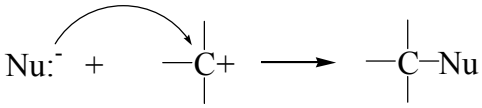


2.) Two-step rxn: "S_N1"

- Heterolytic cleavage of C-X bond (X takes e⁻s):



- Nucleophile reacts with electrophilic carbocation:



(5)

Because a nucleophile substitutes for the halogen, these reactions are known as nucleophilic substitution reactions

The reaction mechanism that predominates (one-step S_N2 *vs.* two-step S_N1) depends on:

- the structure of the alkyl halide
- the reactivity of the nucleophile
- the concentration of the nucleophile
- the solvent used for the reaction

(6)

10.2 The Mechanism of an S_N2 Reaction

A single-collision rxn (elementary step) between 2 molecules = "bimolecular"

"SUBSTITUTION NUCLEOPHILIC BIMOLECULAR" = "S_N2"

Consider the kinetics of the reaction:

Rate = *k* [alkyl halide][nucleophile]

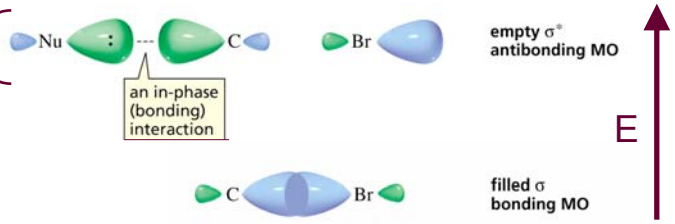
a second-order reaction

(7)

"Back-side attack" by Nu: explained using M.O.'s

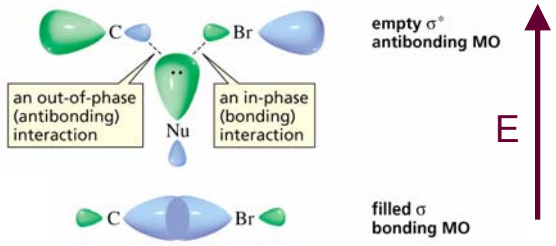
☑ BACK-SIDE ATTACK: opposite to C – LG bond

C-Br bond's σ & σ* orbitals now both filled
⇨ C-Br bond BREAKS!
⇨ & have new Nu-C bond



☒ FRONT-SIDE ATTACK: directly attacking C – LG bond

Net interaction is zero... no rxn if Nu collides in this orientation



(8) Fig.10.1

EXPERIMENTAL EVIDENCE: How can we tell if a substitution is occurring via the S_N2 mechanism?

1. The rate of the reaction is dependent on concentration of BOTH alkyl halide and nucleophile

2. The rate of the reaction with a given nucleophile decreases with increasing size of the alkyl halide

   → Steric effects: Nu must be able to reach the δ^+ C !

3. The configuration at the "attacked" centre is inverted in the product compared to the configuration of the reacting alkyl halide

   → only relevant for <u>asymmetric</u> d^+ C's…

STERIC HINDRANCE: A bulky substituent in the alkyl halide reduces the reactivity of the alkyl halide

Picture it: can the nucleophile get where it needs to go??

- Nucleophile must make contact with the δ^+ C atom
- Larger substituents on this C block Nu's access!

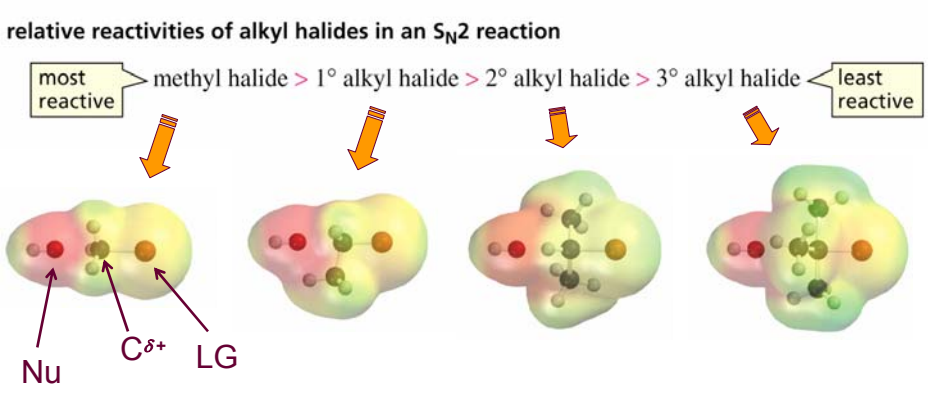


Fig.10.2

relative reactivities of alkyl halides in an S_N2 reaction

most reactive > methyl halide > 1° alkyl halide > 2° alkyl halide > 3° alkyl halide < least reactive

Table 10.1 Relative Rates of S_N2 Reactions for Several Alkyl Halides

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

Alkyl halide	Class of alkyl halide	Relative rate
$CH_3{-}Br$	methyl	1200
$CH_3CH_2{-}Br$	primary	40
$CH_3CH_2CH_2{-}Br$	primary	16
$CH_3CH(CH_3){-}Br$	secondary	1
$CH_3C(CH_3)_2{-}Br$	tertiary	too slow to measure

Reaction coordinate diagrams: picturing energetics

- Thermodynamics: products *vs.* reactants similar in E for both
- Kinetics: MUCH larger E_a for sterically hindered halide!
- THUS: S_N2 rxn is <u>possible</u> for both, but ONLY OCCURS AT MEASURABLE RATES when have low steric hindrance!

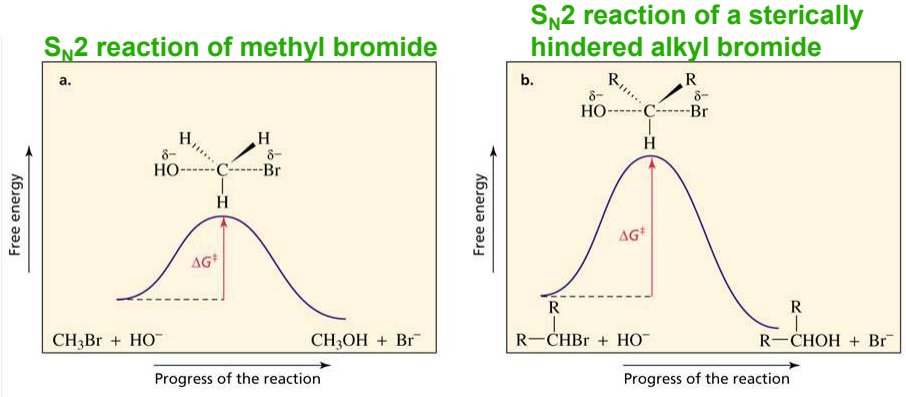


Fig.10.3

EXPERIMENTAL EVIDENCE: How can we tell if a substitution is occurring via the S_N2 mechanism?

1. The rate of the reaction is dependent on concentration of BOTH alkyl halide and nucleophile

2. The rate of the reaction with a given nucleophile decreases with increasing size of the alkyl halide

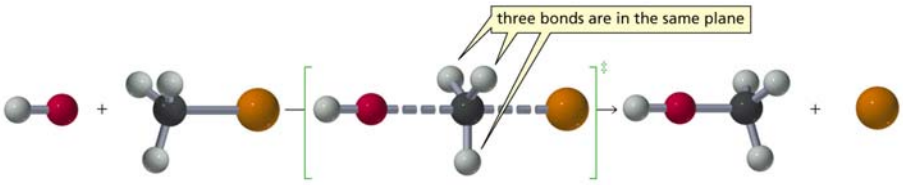
   → Steric effects: Nu must be able to reach the δ^+ C !

3. The configuration at the "attacked" centre is inverted in the product compared to the configuration of the reacting alkyl halide

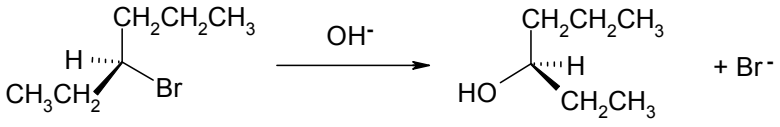
   → only relevant for <u>asymmetric</u> d^+ C's…

Stereochemistry of S_N2 reaction: "inversion"

- inversion of configuration at C attacked by Nu
- because of back side attack
- THUS: S_N2 is a "stereospecific" reaction
  (always forms one stereoisomer only)



e.g., if OH^- attacks (S)-3-bromohexane:



(*S*)-3-bromohexane **(*R*)-3-hexanol**

10.3 Factors affecting S_N2 reactions

- the structure of the alkyl halide (its leaving group)
- the concentration of the nucleophile
- the reactivity of the nucleophile
- the solvent used for the reaction

S_N2 reactions: affected by nature of Leaving Group

Ability of group to "leave" depends on its basicity:

- strong bases = poor leaving groups
  → highly reactive, prefer to stay bonded to C
- weak bases = good leaving groups
  → less reactive, more stable, better at carrying charge

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

$I^- < Br^- < Cl^- < F^-$

weakest base, most stable base

best leaving group

This is a general trend…not only for halides.

strongest base, least stable base

worst leaving group

THINK ABOUT THIS *(as we did at start of term…)*
Carbon and iodide have the same electronegativity

Why is RI the most reactive, since it's not very polar?

relative reactivities of alkyl halides in an S_N2 reaction

most reactive — RI > RBr > RCl > RF — least reactive

Explanation:

- Large atoms are more polarizable than small atoms
- The high polarizability of a large iodide atom causes it to react <u>as if it were polar</u>

…and I^- is a very weak base, good at carrying charge…therefore a very good leaving group!

The nucleophile affects an S_N2 reaction

"**Nucleophilicity**" = a measure of how readily a compound (a nucleophile) is able to attack an electron-deficient atom

- measured by a rate constant (k) ⇨ it is a kinetic parameter

NOT SAME AS

"**Basicity**" = a measure of how well a compound (a base) shares its lone pair with a <u>proton</u>

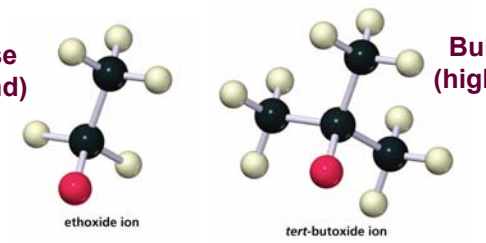
- measured via acid dissociation constant (K_a)
  …*i.e.,* for the conjugate acid of the base in question
  ⇨ it is a thermodynamic parameter!

Nucleophilicity & basicity are based on similar phenomena…
…the main practical difference is what you're thinking about the species bonding to: a δ^+ C *versus* a H^+

Nucleophilicity is affected by Nu's steric demand

- Nucleophilicity is a kinetic parameter
- How quickly can the Nu react with the δ^+ C?
  → depends on access…
  → big Nu's have trouble squeezing into the back-side attack position of Td C's!

Small strong base (low steric demand) ⇨ Good Nu



Bulky strong base (high steric demand) ⇨ Poor Nu

Steric effects influence nucleophilicity, but not basicity

- Acting as a base involves attacking Hs
- Hs are on the periphery of molecules, not buried like δ^+ Cs…
- **If want to deprotonate, but not substitute: use a bulky base!**

GETTING A FEELING FOR NUCLEOPHILICITY:
When comparing molecules with the same attacking atom (and also similar steric demand…)

STRONGER BASE ⇨ BETTER NUCLEOPHILE

Anions are better nucleophiles than neutral molecules:
***i.e.*, the conjugate base is always a better nucleophile than its conjugate acid.**

stronger base, better nucleophile		weaker base, poorer nucleophile
OH^-	>	H_2O
CH_3O^-	>	CH_3OH
$^-NH_2$	>	NH_3
$CH_3CH_2NH^-$	>	$CH_3CH_2NH_2$

When comparing molecules with attacking atoms of approximately the same size:

STRONGER BASE → BETTER NUCLEOPHILE

relative base strengths and relative nucleophilicities

strongest base

$^{-}NH_2 > HO^{-} > F^{-}$

best nucleophile

Correlates with:

relative acid strengths

weakest acid

$NH_3 < H_2O < HF$

(21)

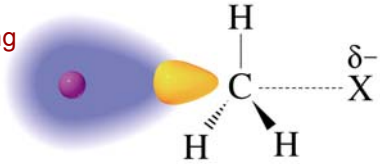
When comparing molecules with attacking groups that are very different in size, (*e.g.*, comparing group members)

BASICITY ENDS UP NOT BEING THE ONLY FACTOR…
Think about POLARIZABILITY of Nu's attacking atom:

Larger, more polarizable Nu has better overlap with C at farther distance away! more bonding

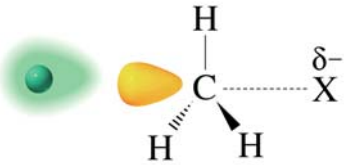
IODINE IS "SOFT"
Highly polarizable
Better nucleophile

The S_N2 transition state:



Smaller, less polarizable Nu has less overlap with C until very very close!

FLUORINE IS "HARD" little bonding
Not very polarizable
Poorer nucleophile



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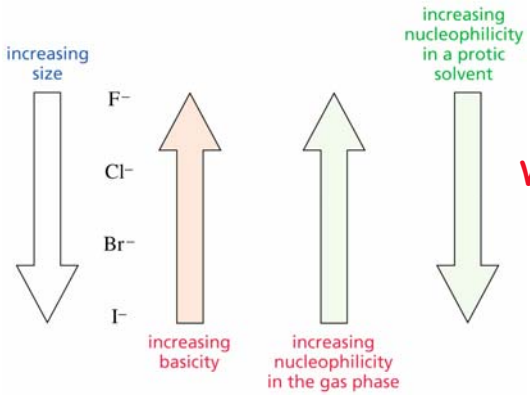
Is polarizability always more important than basicity for determining nucleophilicity?

Depends on reaction conditions:

- In the gas phase: stronger bases always better Nu's
  (not typical conditions!) ⇨ **polarizability ISN'T important…**
- **IN SOLUTION**: polarizability DOES beat out basicity



What is going on here?

ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read: Ch.10 up to 10.3

Practice: understanding nucleophilicity