CHEM 221 section 52

LECTURE #10 Thurs., March 13, 2008

ASSIGNED READINGS:

TODAY'S CLASS:

5.20-5.21	Alkene reactions:	stereochemistry
11.1-11.9	Alkane reactions:	functionalizing a hydrocarbon
8.1-8.2	Substitution rxns:	replacing a LEAVING GROUP with a nucleophile (new group…)

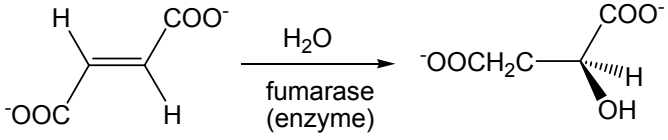
NEXT CLASS: continue Ch.8
problem set #2 due…

5.20: Stereochemistry of enzyme reactions

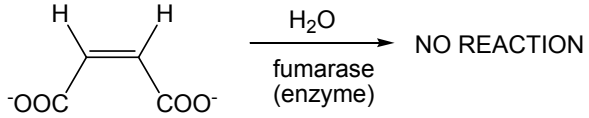
Biochemistry = study of reactions in biological systems
- nucleic acids, carbohydrates, proteins (*e.g.*, enzymes): CHIRAL…

Biological reactions involve: not additions of X_2, BH_3… but H_2O, yes!
- aqueous environment
- acidic (RCOOH) & basic (RNH_2) groups present in proteins
  ⇨ acid-catalyzed reactions of many kinds occur!
- catalysis by enzymes: rxns have **preferred reactant stereochemistry** AND **product stereochemistry**

fumarate --> (intermediate involved in energy metabolism)



maleate --> (isomer)



5.19 Stereochemistry of electrophilic additions

In ACHIRAL SETTING: Stereochemical outcome depends on fact that…

- Alkene π-bonds are planar
  - ⇨ Equal probability of rxn at either "face" of π-bond
  - ⇨ Possibility of forming > 1 stereoisomer (must analyze products to see if molecules are actually same)
- Carbocation & radical intermediates have an open-shell sp^2 atom
  - ⇨ Attack is equally likely from both faces…

⇨ Possibility of forming 1 or 2 new chiral centres, depending on rxn…

To predict stereochemistry, consider nature of rxn's mechanism:

1. **Concerted attack of E^+ & Nu^-:** hydroboration; hydrogenation?
   - no intermediate formed
   - stereochemistry results only from: syn addition to alkene

   OR
2. **Step-wise attack of E^+ & Nu^-:** rest of electrophilic additions?
   - intermediate forms, then reacts with nucleophile
   - E^+ atom in intermediate can be attacked from either face

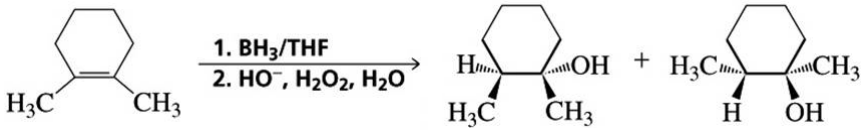
(3)

GENERAL STRATEGY: always analyze alkene reactant 1st

- if an sp^2 C has 3 different groups: if is 1 step away from being a chiral center (*i.e.*, is "prochiral")
- if not: addition will not result in formation of chiral centres

⇨ **Do not memorize outcomes: just picture mechanism happening!**

1A. Stereochemistry of Hydroboration–Oxidation



- Concerted attack of π e⁻s on B-H bond: **Always syn addition**
- In 1st step: H-B can add to either side of C=C initially, so get <u>both</u> possible syn products
- Subsequent steps to replace B by OH: stereochemistry defined is 1st step is unaffected (configurations of carbon atoms remain unchanged)
  - ⇨ described as proceeding with "retention of configuration"

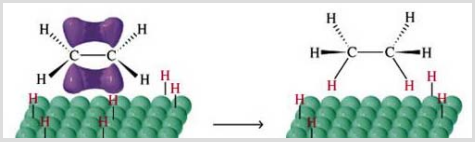
(4)

1B. Stereochemistry of hydrogenation

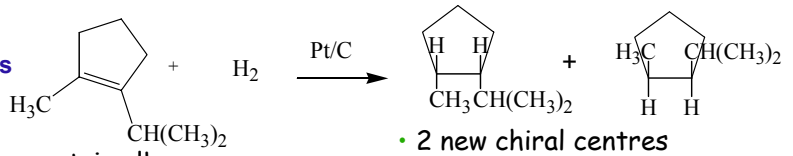
- Alkene "docks" onto metal surface: **Always syn addition**

  since H atoms replace bonds between Cs & metal surface

- note: 2 new stereocentres may be formed…



Cyclic alkenes

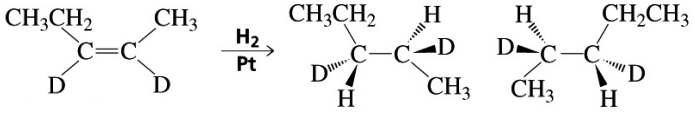


- Asymmetric alkene
- 2 C's one step away from being chiral centres ("prochiral")

- 2 new chiral centres
- syn add'n fixes relative config's

⇨ enantiomers

***cis*-2,3-dideuterio-2-pentene**



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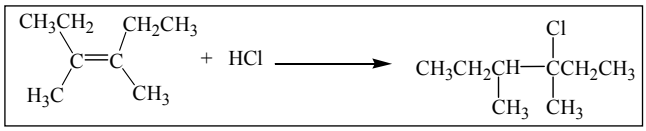
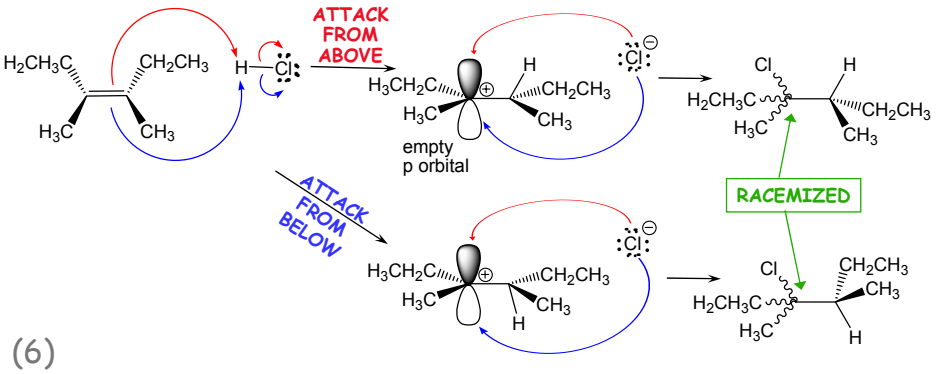
2A. Stereochemistry of hydrohalogenation



without showing stereochem (∴ incomplete!)

- H^+ can bond to either side of alkene ⇨ **1st C is racemized**
- Nucleophile can attack planar carbocationic centre from either side ⇨ **2nd C also racemized**!

THUS: can yield 4 stereoisomers!



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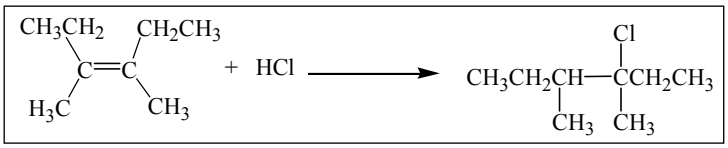

without showing stereochem (∴ incomplete!)

Complete description of products
INCLUDES STEREOCHEMISTRY OF ALL.

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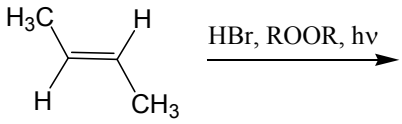
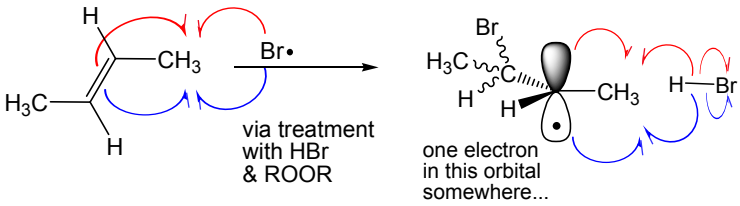
2B. Stereochemistry of radical hydrobromination



- bromine radical can add to either side of C=C ⇨ 2 possible config's
- then: alkyl radical intermediate can react with H from either side
  (*i.e.,*: R• abstracts H• via attack from either top or bottom face of C…)



THUS: can form 2 new asymmetric centers, both racemized

- **1st C is racemized** (attack from either face of C=C)
- **2nd C is racemized** (attack by either face of R•)

⇨ can form maximum of 4 stereoisomers

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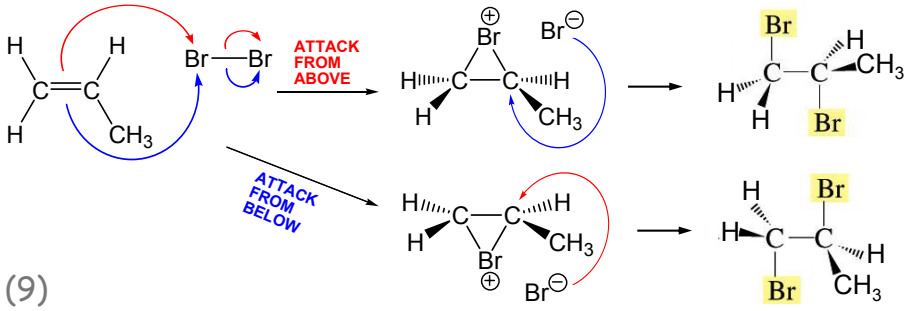
2C. Stereochemistry of halogenation of alkenes

- 1st halide atom can add to either side of C=C ⇨ 2 possible config's
- then: one face of C-C is blocked by large halogen atom
  so halide nucleophile must add from other side **(ANTI ADDITION)**

THUS: can form 2 new asymmetric centers

- **always 2 possible products: *1st X can go on either side…***
- **AND always have ANTI addition of halogens**
- if 2 C*'s just created are the only ones present in molecule
  ⇨ products will be enantiomers *(unless meso…)*
- if other chiral centers were already present in the molecule
  ⇨ products will be diastereomers



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Predict the major products of these rxns (include stereo…)

Chapter 11: Reactions of Alkanes

Chapter Goals

Appreciate the general unreactive nature of alkanes, plus the conditions that can lead to alkanes reacting.

- Understand mechanism of radical halogenation – *including stereochem.*

Chapter Outline: **(responsible for level of detail presented in the notes)**

11.1 The low reactivity of alkanes
11.2 Chlorination and bromination of alkanes: radical substitution
11.3-5 Factors that determine product distribution: radical stability
11.6 Addition of radicals to an alkene (already seen!)
11.7 Stereochemistry of radical reactions
11.8 Radical substitution of benzylic & allylic hydrogens
11.9 Planning a synthesis – more practice

[11.10 Radical reactions in biological systems]
[11.11 Radicals and stratospheric ozone]
} Interesting but not covered.

11.1 The low reactivity of alkanes

Could we predict the typical reactivity of alkanes? YES…

- nonpolar, with only C-C and C-H σ-bonds
  ⇨ **high pK_as, not electrophilic, not nucleophilic…**
- unreactive towards most other substances
- they only react with highly reactive species (or at very high T.)

1. **Combustion reactions:** oxidation via complex radical mechanism
   large activation energy (needs a spark…)

$$C_xH_y + {}^y/_2\, O_2 \rightarrow x\, CO_2 + {}^y/_2\, H_2O$$

2. **Catalytic cracking:** breakdown into shorter branched chains
   - important in petroleum refining
   - sort of like alkene hydrogenation in reverse, then back again
   - requires high temperatures & catalysts (*i.e.*, hard to do!)

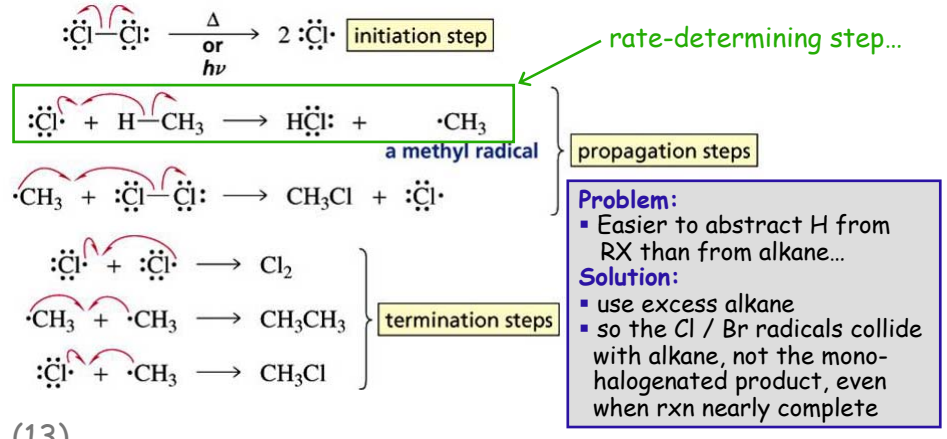
3. **Radical halogenation reactions:** not-so-complex radical mechanism

$$C_xH_y + \tfrac{1}{2}\, X_2 \rightarrow C_xH_{y-1}X + HX$$

11.2 Radical halogenation of alkanes (by Cl_2, Br_2)

- Cl_2 & Br_s are synthetically useful *(F_2 too dangerous; I_2 too slow)*
- High temperature or light needed: to homolytically cleave the X_2 bond
- Use excess alkane (X_2 as L.R.) to minimize dihalogenated product

Mechanism: radical chain reaction *(similar to alkene HBr/ROOR rxn)*



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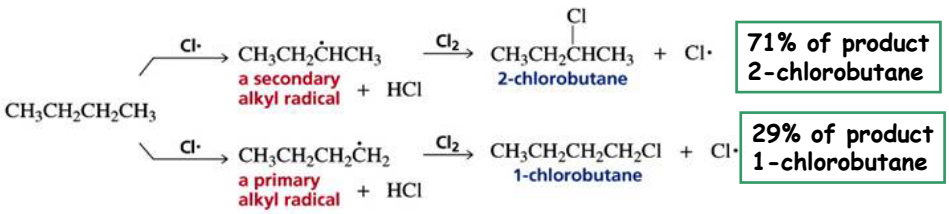
11.3-5 Factors that determine product distribution

1. **Radical intermediate involved:** *(produced in rxn's rate-limiting step)*
   - more stable radical intermediates will form faster *(lower E ‡)*
   - rearrangements do not occur for radicals

   ⇨ REGIOCHEMISTRY:
   X· prefers to abstract H· from the most highly substituted C
   (∴ X· later adds to…)

Relative rate of formation of R· by Cl· at RT:	tertiary	>	secondary	>	primary
	5.0		3.8		1.0



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2. Chlorine atoms (radicals) are more reactive than bromine atoms

- Smaller atom, higher effective nuclear charge
  - ⇨ Cl• has more driving force for abstracting H•
  - ⇨ Cl• is more reactive, thus "less selective", than Br•

REGIOSELECTIVITY BASED ON:
Reactivity towards that type of H
i.e., Relative rates of R• formation:

Cl• at RT: tertiary (5.0) > secondary (3.8) > primary (1.0)

Chlorine radicals are fast, but **unselective**!
→ lower yields since many products formed
→ lots of extra work separating products

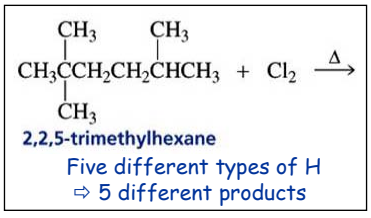
Br• at 125°C: tertiary (1600) > secondary (82) > primary (1)

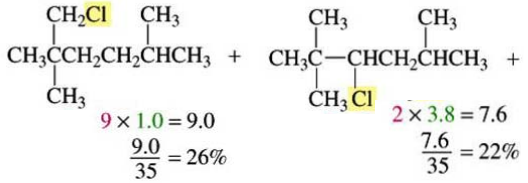
Bromine radicals require higher T, but **very useful**
→ Higher yield of one product

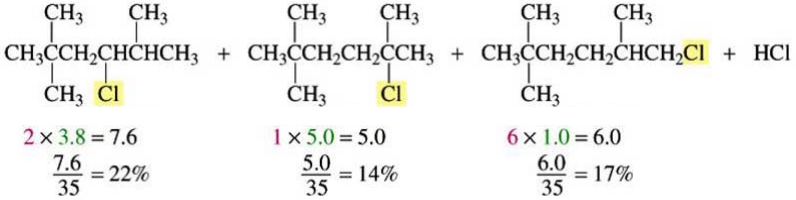
increasing rate of formation

Relative rates can be used to predict product yields:
- **Statistics:** How many H's of each type (1°,2°,3°…) is present?
- **Selectivity:** What is X•'s relative rate of abstraction of each H type?

Approach: Percentage of product halogenated at site of interest
= (number of Hs at that type of site) x (reactivity)



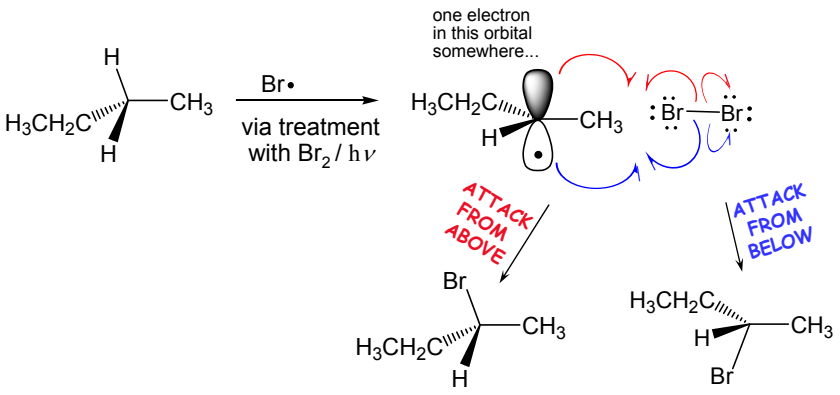




On your own: what would the product distribution be with $Br_2/h\nu$?)

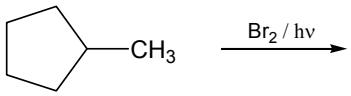
11.7 Stereochemistry of radical substitution

- halogen radical attacks C-H bond ⇨ planar radical intermediate
- then: alkyl radical intermediate can react with X• from either side
  (*i.e.,*: R• abstracts X• via attack from either top or bottom face of C…)

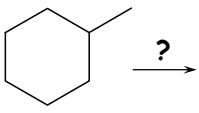


THUS: can form 1 new asymmetric center, but racemized
⇨ Form maximum of 2 stereoisomers (enantiomers here…)

When planning: consider regiochem, stereochem & control…



Would this mixture be optically active?
Why or why not?



Is it smarter to use Cl_2 / hν *or* Br_2 / hν ?
What product(s) will we get?

11.8 Radical Br'n at benzylic & allylic positions: selective reagent: NBS (*N*-bromosuccinimide)

Synthesis "break"…

So… where are we now?

BASIC TYPES OF ORGANIC REACTIONS *(…more in Organic II)*

Ch.11 ✓ **1. Radical halogenation:** adds a functional group to alkanes *(unreactive!)*

Ch.8 **2. Substitution:** change to a different functional group

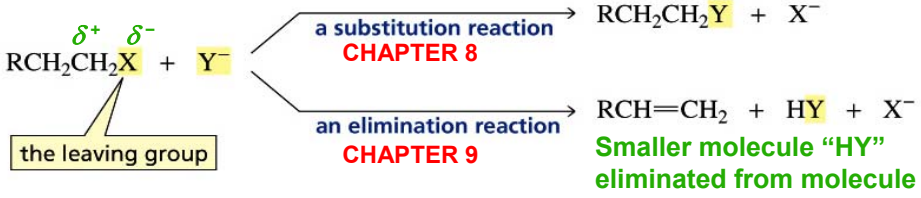
3. Elimination: create a π-bond

Ch.4 ✓ **4. Addition:** use π-bond to add a new functional group

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 is called a ***leaving group***

Ch.8: Substitution Reactions of Alkyl halides

Chapter Goals

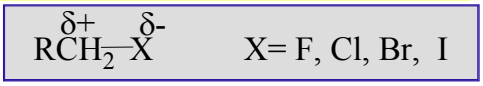
Understand the two basic types of substitution reactions.

- 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:

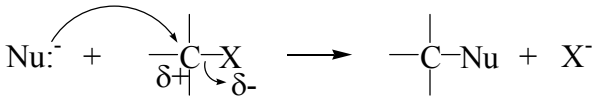
8.1 Alkyl halides react because of polarity

- **Halide can leave with the e⁻s, in TWO POSSIBLE WAYS:**



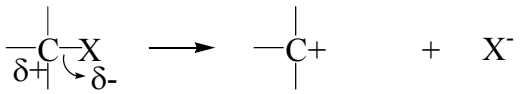
1.) Concerted (one-step) rxn: "S_N2"

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

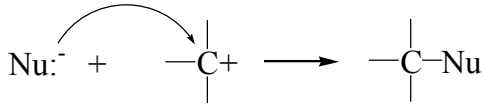


2.) Two-step rxn: "S_N1"

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



- Nucleophile reacts with electrophilic carbocation:



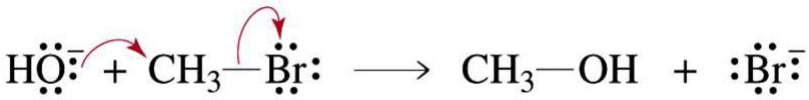
⇨ **2 mechanisms possible for substitution by nucleophile**

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

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

8.2 The Mechanism of an S_N2 Reaction



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

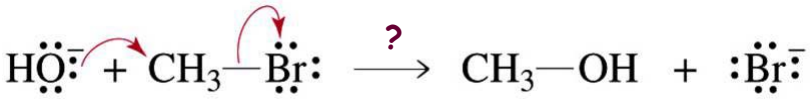
"SUBSTITUTION NUCLEOPHILIC BIMOLECULAR" = "S_N2"

Consider the kinetics of the reaction:

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

a second-order reaction

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



1. **2nd order kinetics:** rate of rxn depends on concentration of BOTH alkyl halide & nucleophile

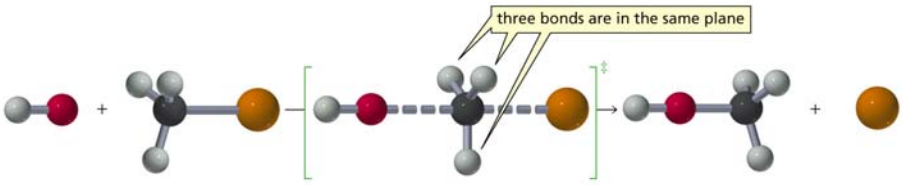
2. **Inhibited by bulk:** for rxn with a given Nu, rxn rate ↓ if steric bulk of alkyl halide ↑

Picture it: Nu must be able to reach the δ^+ C!

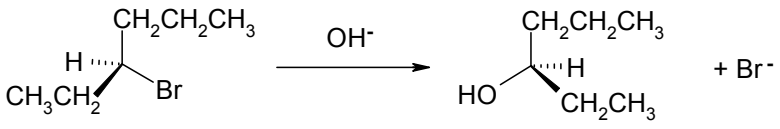
3. **Inversion:** configuration at attacked C inverted in product compared to reactant alkyl halide
   → only relevant for <u>asymmetric</u> δ^+ C's…

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:

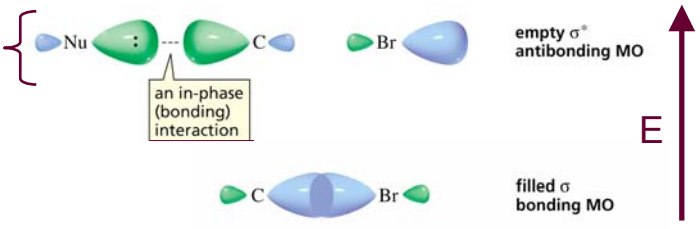


(*S*)-3-bromohexane **(*R*)-3-hexanol**

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

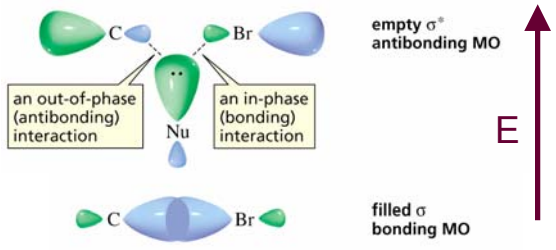
☑ BACK-SIDE ATTACK: opposite to C – LG bond

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



(29)Fig.8.1

What would be the major product(s) of these S_N2 rxns?

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

1. **2nd order kinetics:** rate of rxn depends on concentration of BOTH alkyl halide & nucleophile

2. **Inhibited by bulk:** for rxn with a given Nu, rxn rate ↓ if steric bulk of alkyl halide ↑

   Picture it: Nu must be able to reach the δ^+ C!

3. **Inversion:** configuration at attacked C inverted in product compared to reactant alkyl halide
   → only relevant for <u>asymmetric</u> δ^+ 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!

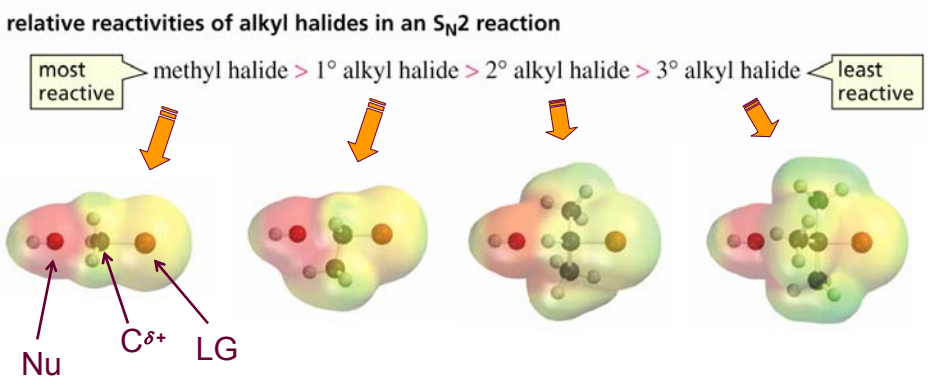


Fig.8.2

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 8.1 Relative Rates of S_N2 Reactions for Several Alkyl Halides

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

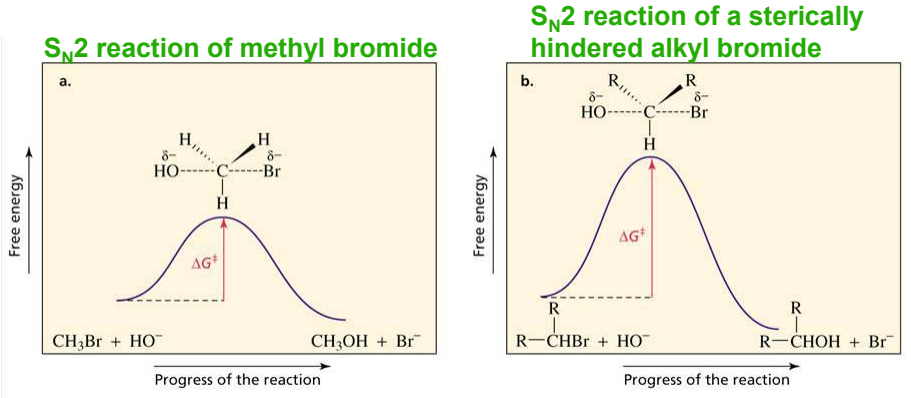
Alkyl halide	Class of alkyl halide	Relative rate
$CH_3{-}Br$	methyl	1200
$CH_3CH_2{-}Br$	primary	40
$CH_3CH_2CH_2{-}Br$	primary	16
$CH_3CH(CH_3){-}Br$	secondary	1
$CH_3C(CH_3)_2{-}Br$	tertiary	too slow to measure

(33)

Rxn 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 possible for both, but
ONLY OCCURS AT MEASURABLE RATES if low steric hindrance!



(34)

Fig.8.3

10.3 Factors affecting S_N2 reactions

- the concentration of the nucleophile
- the concentration of the alkyl halide

- the structure of the alkyl halide: its steric bulk
  AND its **leaving group**

- the reactivity of the nucleophile
- the solvent used for the reaction

S_N2 rxns: affected by nature of Leaving Group (LG)

Ability of group to "leave" correlates with basicity:

- strong bases = poor LGs ⇨ reactive, prefer to stay bonded to C
- weak bases = good LGs ⇨ less reactive, more stable,
  better at carrying lone pair

	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!

ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read: rest of Ch.5 (alkene rxn stereochem.)
Ch.11 (radical halogenation -superficially)
Ch.8 (substitution reactions)

Practice: writing reaction mechanisms
predicting products & stereochem.