**CHEM 221 section 01**

**LECTURE #24** Thurs., Nov.24, 2005

## ASSIGNED READINGS:

**TODAY'S CLASS:** Finish Ch.10, start Ch.11

**NEXT LECTURE:** Continue Ch.11

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

## 10.9 Competition between $S_N2$ & $S_N1$ reactions

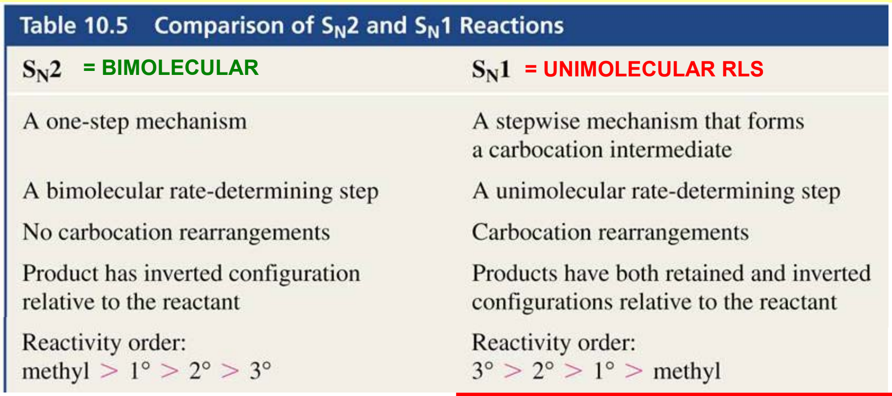


Table 10.5 Comparison of $S_N2$ and $S_N1$ Reactions

| $S_N2$ = BIMOLECULAR | $S_N1$ = UNIMOLECULAR RLS |
|---|---|
| A one-step mechanism | A stepwise mechanism that forms a carbocation intermediate |
| A bimolecular rate-determining step | A unimolecular rate-determining step |
| No carbocation rearrangements | Carbocation rearrangements |
| Product has inverted configuration relative to the reactant | Products have both retained and inverted configurations relative to the reactant |
| Reactivity order:<br>methyl > 1° > 2° > 3° | Reactivity order:<br>3° > 2° > 1° > methyl |

⇨ $S_N2$ rxns more synthetically useful because they have:
- predictable stereochemistry
- predictable regiochemistry

⇨ $S_N1$ rxns less synthetically useful because they involve:
- loss of stereochemistry
  (partial or full racemization)
- mixed regiochemistry
  (if >1 carbocation possible…
  …or >1 rearrangement possible!!)

## For many alkyl halides, BOTH types of rxn can occur…

THUS: the 2 types of substitution are "competing"
…but one will likely be significantly faster than the other

Total substitution rate = $k_{SN2}$[RX][Nu] + $k_{SN1}$[RX]

THIS COMPETITION BECOMES A SERIOUS ISSUE
IF THE TWO MECHANISMS YIELD DIFFERENT PRODUCTS!

SO: WHICH TYPES OF ALKYL HALIDES ARE "GOOD AT" BOTH TYPES OF SUBSTITUTION?

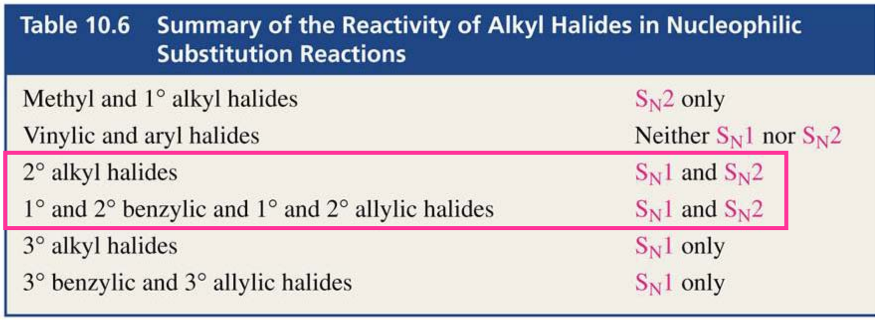


**Table 10.6** Summary of the Reactivity of Alkyl Halides in Nucleophilic Substitution Reactions

| | |
|---|---|
| Methyl and 1° alkyl halides | $S_N2$ only |
| Vinylic and aryl halides | Neither $S_N1$ nor $S_N2$ |
| 2° alkyl halides | $S_N1$ and $S_N2$ |
| 1° and 2° benzylic and 1° and 2° allylic halides | $S_N1$ and $S_N2$ |
| 3° alkyl halides | $S_N1$ only |
| 3° benzylic and 3° allylic halides | $S_N1$ only |

## Careful selection of rxn conditions helps us control which mechanism will dominate

1. Concentration of nucleophile
2. Reactivity of nucleophile
3. Choice of solvent

**$S_N2$:** rate = $k_{SN2}$ [RX] [Nu]

Favoured by:

- using high concentration of a good Nu
- using a solvent of lower polarity (see this soon)

**$S_N1$:** rate = $k_{SN1}$ [RX]

Favoured by:

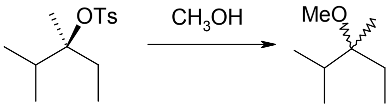
- using a low [Nu]
  *or*
- using a poor Nu

because these **disfavour** **$S_N2$**, so slow $S_N1$ can compete

- using a solvent of higher polarity

**And recall: protic solvents can "mask" strong bases (*i.e.*, interact strongly & prevent them from acting as good Nu's…)**

## Which type of substitution rxn will dominate?

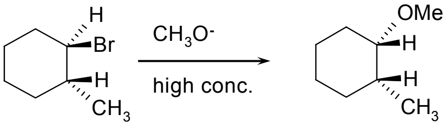


squiggle-bonds
mean "either way"
..... racemic !

Product after $H^+$ transfer
to solvent (MeOH *i.e.*, $CH_3OH$)

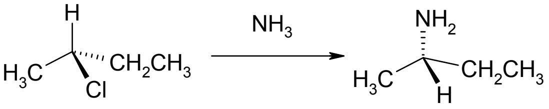
- 3° halide ⇨ $S_N1$
- good LG ($TsO^-$) ⇨ either
- weak Nu ⇨ $S_N1$

OVERALL: $S_N1$ favoured



- 2° halide ⇨ either
- good LG (Br-) ⇨ either
- strong Nu, high [] ⇨ $S_N2$

OVERALL: $S_N2$ favoured



Product after $H^+$ transfer
to solvent (not identified...)

- 2° halide ⇨ either
- moderate LG ($Cl^-$) ⇨ $S_N2$
- moderate Nu ⇨ either

OVERALL: $S_N2$ favoured

## 10.10 The role of solvent in $S_N2$ *vs.* $S_N1$ rxns

**Polar solvents are good at solvating charged species**

- due to electrostatic interactions between $\delta+/\delta-$ of solvent molecules & full charges of ions
- RESULT: <u>stabilize</u> charged species (including transition states!)

→ **carbocations (easier to form in polar solvents)**
→ **anionic nucleophiles (less reactive in polar solvents)**

**Nonpolar solvents are good at solvating nonpolar species**

- due to van der Waals interactions dominating...

- Difficult to estimate overall polarity using only chemical structure (balance between dipole moment & nonpolar vdw contacts)
- **Practical measure of polarity = dielectric constant ($\varepsilon$)**

→ a measure of how well a solvent can insulate charges from each other (how good at solvating ions...)
→ high $\varepsilon$ = high polarity

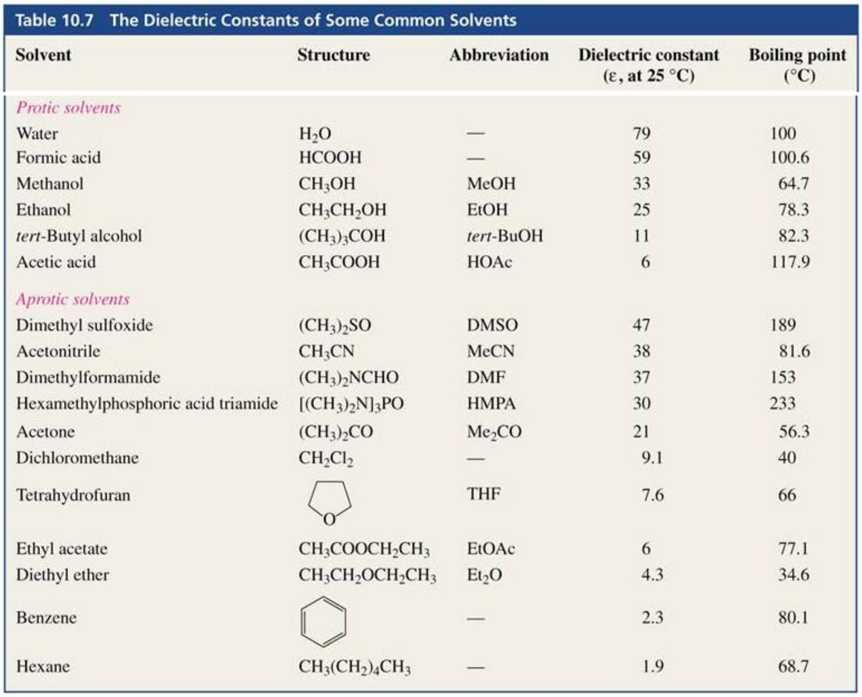


**Table 10.7 The Dielectric Constants of Some Common Solvents**

| Solvent | Structure | Abbreviation | Dielectric constant (ε, at 25 °C) | Boiling point (°C) |
|---|---|---|---|---|
| *Protic solvents* | | | | |
| Water | $H_2O$ | — | 79 | 100 |
| Formic acid | HCOOH | — | 59 | 100.6 |
| Methanol | $CH_3OH$ | MeOH | 33 | 64.7 |
| Ethanol | $CH_3CH_2OH$ | EtOH | 25 | 78.3 |
| *tert*-Butyl alcohol | $(CH_3)_3COH$ | *tert*-BuOH | 11 | 82.3 |
| Acetic acid | $CH_3COOH$ | HOAc | 6 | 117.9 |
| *Aprotic solvents* | | | | |
| Dimethyl sulfoxide | $(CH_3)_2SO$ | DMSO | 47 | 189 |
| Acetonitrile | $CH_3CN$ | MeCN | 38 | 81.6 |
| Dimethylformamide | $(CH_3)_2NCHO$ | DMF | 37 | 153 |
| Hexamethylphosphoric acid triamide | $[(CH_3)_2N]_3PO$ | HMPA | 30 | 233 |
| Acetone | $(CH_3)_2CO$ | $Me_2CO$ | 21 | 56.3 |
| Dichloromethane | $CH_2Cl_2$ | — | 9.1 | 40 |
| Tetrahydrofuran | O | THF | 7.6 | 66 |
| Ethyl acetate | $CH_3COOCH_2CH_3$ | EtOAc | 6 | 77.1 |
| Diethyl ether | $CH_3CH_2OCH_2CH_3$ | $Et_2O$ | 4.3 | 34.6 |
| Benzene | | — | 2.3 | 80.1 |
| Hexane | $CH_3(CH_2)_4CH_3$ | — | 1.9 | 68.7 |

# Protic solvents vs. Aprotic solvents

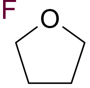
**Protic solvents:**
- have O-H or N-H bonds
- hydrogen bond donors

alcohols, amines

**Aprotic solvents:**
- DO NOT have O-H or N-H bonds
- cannot act as H-bond donors
- some can act as H-bond acceptors

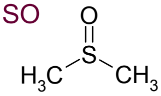
Some H-bond acceptors:
ethers, acetonitrile, acetone,

THF



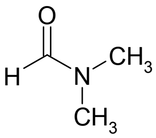
(tetrahydrofuran)

DMSO



(dimethylsulfoxide)

DMF (dimethylformamide)



Some "nonpolar" solvents:
dichloromethane, hexane, benzene

You don't have to memorize all of these, but it's helpful to be able recognize them…

FOR EXAMS:
sufficient to identify whether you need a protic *vs.* an aprotic solvent (see next slides…)

## Encouraging the rxn you want: Choose a solvent that stabilizes the transition state (‡) of the desired reaction

**General approach: Is the ‡ more or less charged than the reactants?**

Polar solvents make $S_N1$ rxns FASTER (stabilize charged ‡):

RLS: $R–X \rightarrow [\ \delta^+ R\cdots X\ \delta^-\ ]^{\ddagger}$

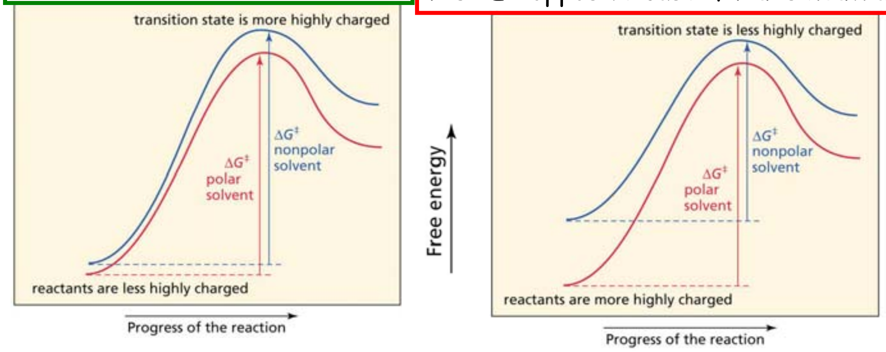
more charged

Polar solvents CAN make $S_N2$ rxns SLOWER for RXs (stabilize reactants):

$Nu{:}^- + R–X \rightarrow [\delta^- Nu\cdots R\cdots X\ \delta^-\ ]^{\ddagger}$

less charged

NOTE: opposite case if Nu is neutral!



## SUMMARY: Controlling $S_N2$ / $S_N1$ competition

For alkyl halides whose structures allow them to do BOTH $S_N2$ & $S_N1$ reactions:

If you WANT $S_N2$: use high concentration of a strong, negatively charged Nu
in the least polar solvent possible
(as long as your reactants will dissolve… likely need to use a polar aprotic solvent)

If you WANT $S_N1$: use low concentration of weak Nu
in the most polar solvent possible
(as long as your reactants will dissolve…)

IMPORTANT: consider each case on its own to be more versatile!
*i.e.,* charge on transition state of RLS compared to reactants!
& suddenly you can think about substitutions of all sorts of LG!

## More examples…

$CH_3CH_2{-}Br \ + \ {}^{-}OEt \xrightarrow{DMSO}$

$CH_3CH_2{-}Br \ + \ {}^{-}OEt \xrightarrow{EtOH}$

*Q: WHICH WILL BE FASTER?*

- $1^{ST}$: rxn type will be…
  strong **-ve** Nu, good LG, 1° R…

⇨ $S_N2$, & faster in less polar solvent

- DMSO: polar, aprotic solvent
- EtOH: polar, protic! Will “mask” Nu.

⇨ **DMSO will yield FASTER rxn.**

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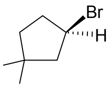
*Q: UNDER WHICH CONDITIONS WOULD (R)-1-BROMO-3,3-DIMETHYLCYCLOPENTANE YIELD THE MOST (R)-3,3-DIMETHYLCYCLOPENTANOL?*



*Options: $OH^-$ in 100% EtOH* ***or*** *$OH^-$ in 50% $H_2O$ 50% EtOH ?*

- **$1^{ST}$:** desired rxn type is: **$S_N1$** desired product same config. as reactant
- **$S_N1$ favoured by**: polar solvents (here, both are…)
  weak Nu (not here! ∴ mask it in very polar solvent)
- **$S_N2$ favoured by**: -ve Nu + R-X → [ Nu---R---X ] less polar ‡
  fastest with less polar solvent
  ⇨ we don’t want this, ∴ let’s use the more polar solvent!

**OVERALL: choose water-ethanol mix**
**(favours desired $S_N1$, disfavours undesired $S_N2$)**

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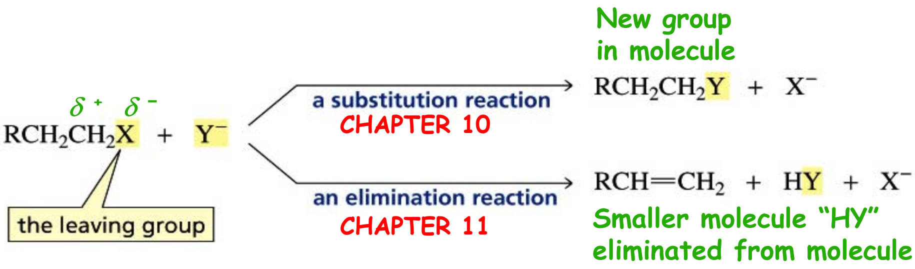
## So: where are we?

## Reaction pathways: substitutions & elimination



New group in molecule

$\overset{\delta+}{}\ \overset{\delta-}{}$

$RCH_2CH_2X + Y^-$ → a substitution reaction CHAPTER 10 → $RCH_2CH_2Y + X^-$

$RCH_2CH_2X + Y^-$ → an elimination reaction CHAPTER 11 → $RCH{=}CH_2 + HY + X^-$

the leaving group

Smaller molecule “HY” eliminated from molecule

**Now:**
**CHAPTER 11 – Elimination reaction of alkyl halides**
**& Competition between substitution & elimination**

# Ch.11: Elimination Reactions of Alkyl halides

Chapter Goals

*Understand the two basic types of elimination reactions,*
*and the competition between substitution and elimination.*

- Learn the mechanisms of E1 & E2 rxns – *including stereochemistry.*
- Understand the competition between different reaction pathways.
- Learn the basics of designing synthetic routes to desired molecules.

Chapter Outline:
11.1 The E2 reaction
11.2 The regioselectivity of the E2 reaction
11.3 The E1 reaction
11.4 Competition between E1 and E2 reactions
11.5 Stereochemistry of E1 and E2 reactions
11.6 Elimination from cyclic compounds
*[11.7 A kinetic isotope effect]*
11.8 Competition between substitution and elimination
11.9 Substitution and elimination reactions in synthesis
11.10 Consecutive E2 elimination reactions
11.11 Intermolecular vs. intramolecular reactions
11.12 Designing a synthesis: Approaching the problem

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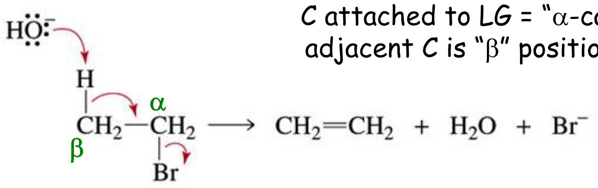
# 11.1 The E2 reaction: one-step, bimolecular process

$$\underset{\textbf{ethyl bromide}}{CH_3CH_2Br} + HO^- \longrightarrow \underset{\textbf{ethene}}{CH_2{=}CH_2} + H_2O + Br^-$$

$$\text{rate} = k[\text{alkyl halide}][\text{base}]$$

**Mechanism of the E2 reaction: "1,2-elimination" or "β-elimination"**



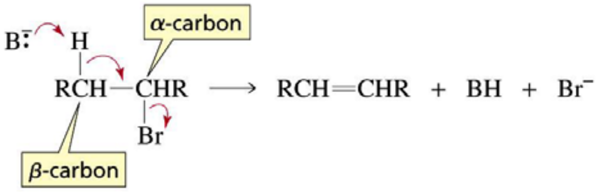
C attached to LG = "α-carbon";
adjacent C is "β" position

**The H on a C adjacent to an electronegative atom (*e.g.*, a halogen) is more acidic than typical H's bonded to C…because a rxn can ensue!**

- H at β-position susceptible to attack by a base (B:)
- $e^-$s from C-H bond forced to be held by the C ⇨ lone pair on C?!
- better to share this $e^-$ pair with the neighbouring C
- forces leaving group to leave with the C-X bonding pair

⇨ All of the above happens in one concerted process!

## A typical elimination: "dehydrohalogenation" (loss of HX)



"HX" is lost overall…
but the H ends up
bonded to the base,
& the X is a free ion

**Like $S_N2$:**

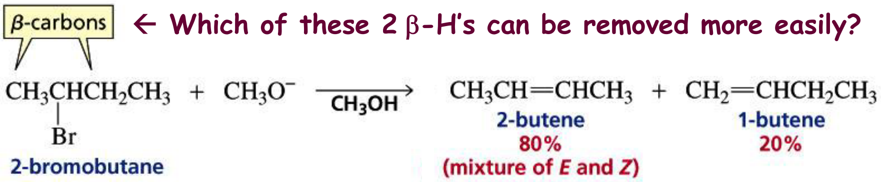
**Concerted, bimolecular rxn → faster with better LG…**
**→ also faster with stronger B:**

**Recall: The weaker the base, the better it is as a leaving group.**
**THUS:**

most reactive via E2 — RI > RBr > RCl > RF — least reactive via E2

## 11.2 The Regioselectivity of the E2 Reaction

**← Which of these 2 β-H's can be removed more easily?**



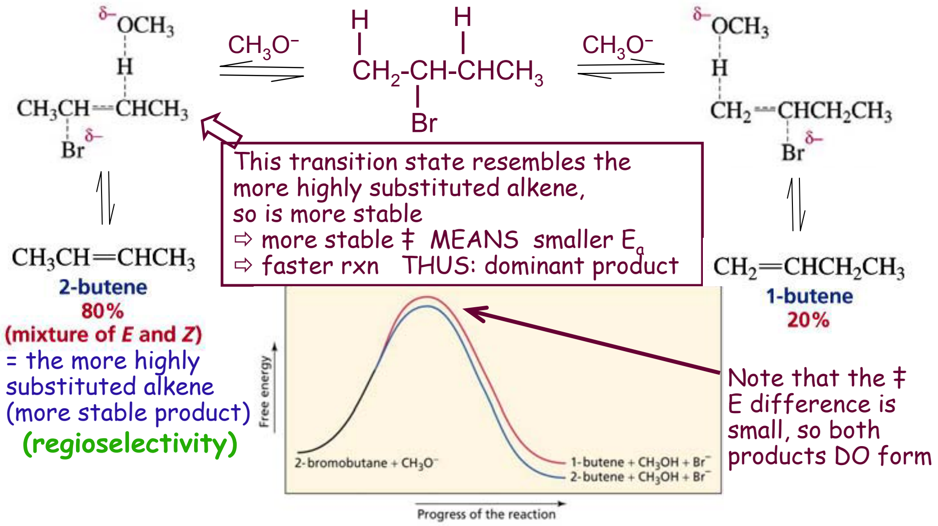
**The major product of an E2 reaction is the more stable alkene (Zaitsev's rule…also known as Saytzeff).**

**WHY?**

- the transition state that results in the formation of the more stable alkene is lower in E (easier to form)
- recall: the more highly substituted the alkene,
  the more stable it is…

## E2 rxn of 2-bromobutane & methoxide: 2 pathways → 2 products…

**Important: E2 rxn transition states resemble alkenes (not anions), ∴any factor that stabilizes an alkene will stabilize an E2's ‡**



This transition state resembles the more highly substituted alkene, so is more stable
⇨ more stable ‡ MEANS smaller $E_a$
⇨ faster rxn THUS: dominant product

**2-butene**
**80%**
**(mixture of *E* and *Z*)**
= the more highly substituted alkene (more stable product)
**(regioselectivity)**

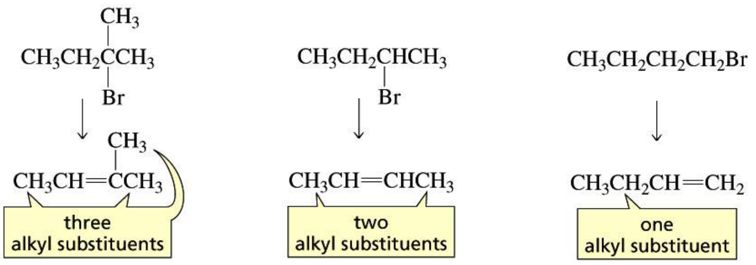
**1-butene**
**20%**

Note that the ‡ E difference is small, so both products DO form

## More highly substituted alkyl halides react faster by E2

**relative reactivities of alkyl halides in an E2 reaction**

**tertiary alkyl halide > secondary alkyl halide > primary alkyl halide**



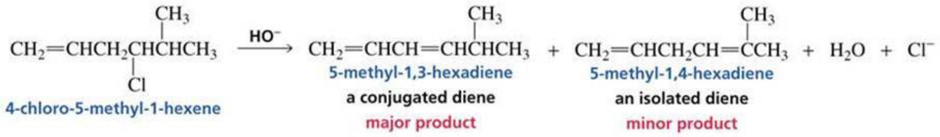
**The products shown here are the "Zaitsev products" *i.e.,* the major products (the more stable alkenes)**

**The less stable alkene product (minor product) will ALSO always form too…just not quite as much.**

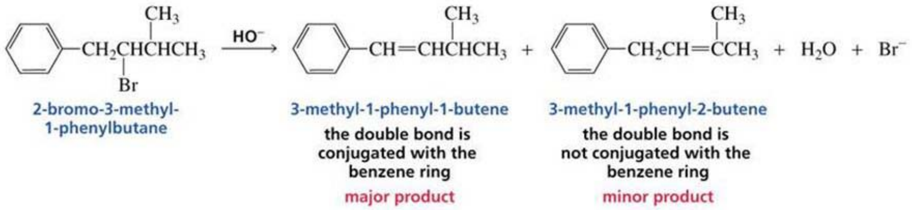
**If it is possible to form conjugated alkene products (*i.e.*, extended $\pi$-systems)…**

…they will form preferentially because they are very stable!

THUS: major product will not be the Zaitsev product.



4-chloro-5-methyl-1-hexene → 5-methyl-1,3-hexadiene (a conjugated diene, major product) + 5-methyl-1,4-hexadiene (an isolated diene, minor product) + $H_2O$ + $Cl^-$



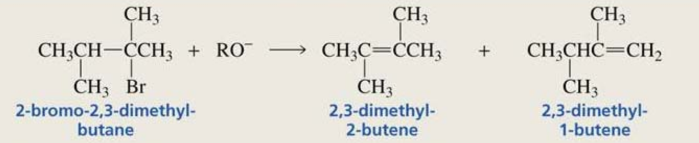
2-bromo-3-methyl-1-phenylbutane → 3-methyl-1-phenyl-1-butene (the double bond is conjugated with the benzene ring, major product) + 3-methyl-1-phenyl-2-butene (the double bond is not conjugated with the benzene ring, minor product) + $H_2O$ + $Br^-$

Be on the lookout for conjugation.
Do not <u>blindly</u> use Zaitsev's rule to predict the major product.

## Steric hindrance affects product distribution

- BULKY bases will attack the most accessible H more often
- If <u>hindered</u> alkyl halide too, get <u>less-sub'd</u> alkene as <u>major product</u>

**Table 11.1**



2-bromo-2,3-dimethylbutane + $RO^-$ → 2,3-dimethyl-2-butene + 2,3-dimethyl-1-butene

| Base | More substituted product | Less substituted product |
|---|---|---|
| $CH_3CH_2O^-$ | 79% | 21% |
| $CH_3\overset{CH_3}{\underset{CH_3}{C}}O^-$ | 27% | 73% |
| $CH_3\overset{CH_3}{\underset{CH_2CH_3}{C}}O^-$ | 19% | 81% |
| $CH_3CH_2\overset{CH_2CH_3}{\underset{CH_2CH_3}{C}}O^-$ | 8% | 92% |

Zaitsev's rule does not predict major product

## Another exception to Zaitsev's rule: when $F^-$ is the LG

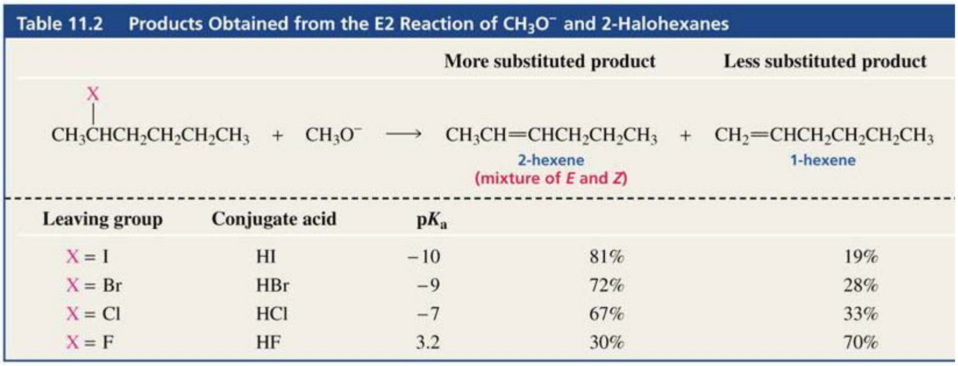


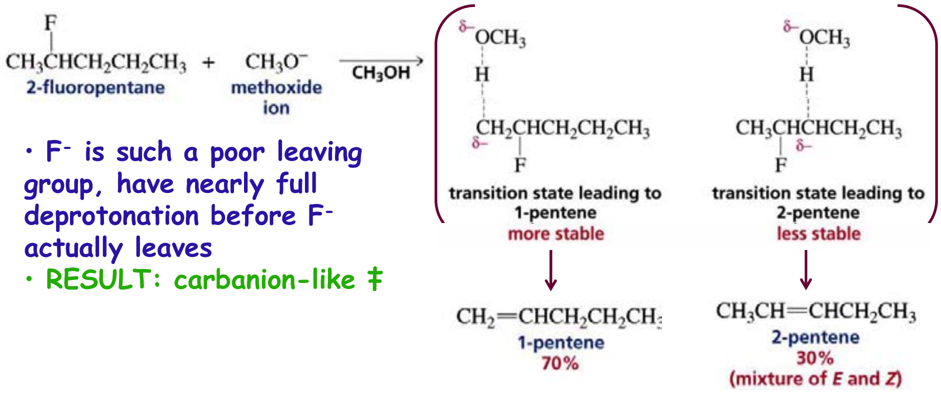
**Table 11.2** Products Obtained from the E2 Reaction of $CH_3O^-$ and 2-Halohexanes

$$CH_3\overset{X}{\overset{|}{C}}HCH_2CH_2CH_2CH_3 + CH_3O^- \longrightarrow \underset{\substack{\text{2-hexene}\\ \text{(mixture of } E \text{ and } Z)}}{CH_3CH{=}CHCH_2CH_2CH_3} + \underset{\text{1-hexene}}{CH_2{=}CHCH_2CH_2CH_2CH_3}$$

| Leaving group | Conjugate acid | $pK_a$ | More substituted product | Less substituted product |
|---|---|---|---|---|
| X = I | HI | −10 | 81% | 19% |
| X = Br | HBr | −9 | 72% | 28% |
| X = Cl | HCl | −7 | 67% | 33% |
| X = F | HF | 3.2 | 30% | 70% |

Don't worry too much about this:
$F^-$ isn't a great LG, so we don't use it this way much!

## Special case: For FLUORIDE as leaving group (uncommon)

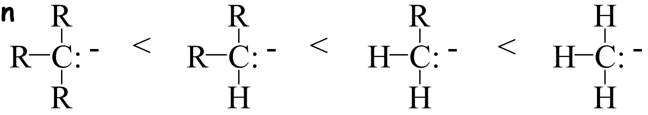


$$CH_3\overset{F}{\overset{|}{C}}HCH_2CH_2CH_3 + CH_3O^- \xrightarrow{CH_3OH}$$

- $F^-$ is such a poor leaving group, have nearly full deprotonation before $F^-$ actually leaves
- RESULT: carbanion-like ‡

## CARBANION STABILITY: 3°<2°<1°<Me (opposite to C+ & C•)

Inductive e⁻-donation from alkyl groups makes lone pair MORE reactive



$$\begin{array}{c}R\\ |\\ R{-}C:^-\\ |\\ R\end{array} < \begin{array}{c}R\\ |\\ R{-}C:^-\\ |\\ H\end{array} < \begin{array}{c}R\\ |\\ H{-}C:^-\\ |\\ H\end{array} < \begin{array}{c}H\\ |\\ H{-}C:^-\\ |\\ H\end{array}$$

## E2 reactions: summary

**The MAJOR product of E2 elimination will be the MORE STABLE ALKENE:**

- **most highly substituted** (normally) ***or***
- **most conjugated alkene** (if possible…)

***UNLESS***

1. **The reactants are highly STERICALLY HINDERED**
2. **The leaving group is POOR**

**BEST PLAN:**

1. Remember that more stable product dominates at eqm…
   …*but*…can't reach eqm if have huge steric effects
2. **Always think through relative stability of ‡**
   **to predict fastest forming product !**

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## ASSIGNED READINGS

### BEFORE NEXT LECTURE:

**Read:** Ch.11 up to 11.2

**Practice:** predicting products & stereochemistry