CHEM 221   section 52

LECTURE #06   Thurs., Feb.07, 2008

ASSIGNED READINGS:

TODAY'S CLASS:

3.6–3.8	Introduction to organic rxn mechanisms
4.1–4.5	Alkene reactions
	electrophilic addition mechanism
	carbocation stability & rearrangements

NEXT CLASS: finish Ch.4
start Ch.5

(1)

Organic synthesis: Playing with molecular building blocks

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

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

2. Substitution:
change to a different
functional group

3. Elimination:
create a π-bond

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

(2)

Chapter 4: Reactions of Alkenes
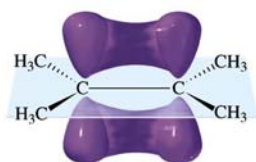
Chapter Goals

To learn the typical reaction of π-systems: electrophilic addition

- Learn how various electrophiles react with alkenes
- Understand the factors that determine product distribution
- Understand the relative stabilities of carbocations & alkenes
- Begin to think about synthesizing molecules of interest

(3)

3.6 How alkenes react: electrophilic addition

Electrons in π-bonds are very "exposed"
- not held tightly between nuclei like σ-bond e⁻s
- very polarizable
- quite reactive!
    → alkenes behave as if "electron-rich"

Alkenes react with electrophiles (*i.e.,* e⁻ pair acceptors / LEWIS ACIDS)
- common electrophiles: H⁺ (*i.e.,* δ^+ H's), metal cations, boron compounds…

(4)

Electrophiles & Nucleophiles

LEWIS ACIDS = e⁻ pair acceptors	LEWIS BASES = e⁻ pair donors

LEWIS ACIDS = e^- pair acceptors

Electrophile E+ *(attracted to e⁻s)*

LEWIS BASES = e^- pair donors

Nucleophile Nu⁻ *(attracted to nuclei)*

H^+ *(or δ^+ H)* } Empty s orbital *(or nearly empty)*

⊕CR_3 } Empty p orbital

BR_3
AlR_3 } "trivalent elements" Empty p orbital

Zn(II)
Fe(III) } Metal cations: Empty orbitals...

React with electron-rich species

Any species with a lone pair

Can react in two ways:
Same mechanism, different outcome

1. As a Brønsted base
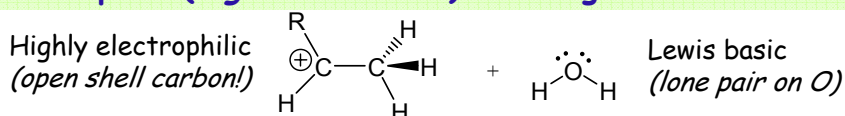- React with δ^+ H atoms

2. As a nucleophile
- React with δ^+ carbon or other non-H atoms

React with e⁻-deficient species

Review Bruice sect. 1.26

(5)

Electrophile (*e.g.* carbocation) reacting with Lewis base

Highly electrophilic *(open shell carbon!)*

Lewis basic *(lone pair on O)*

Depending on how the molecules collide & other structural factors
(later: *basicity, size, accessibility…*), **the rxn will occur in one of 2 ways:**

Acting as a Nu⁻

Leads to net ADDITION or SUBSTITUTION
Details: Ch.3, 4, 8

Acting as a base

Leads to net ELIMINATION
Details: Ch.9
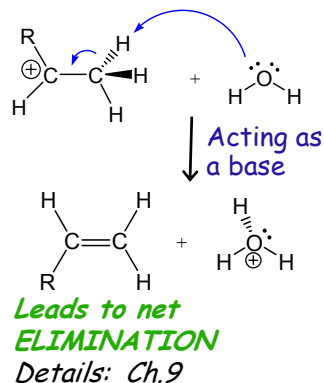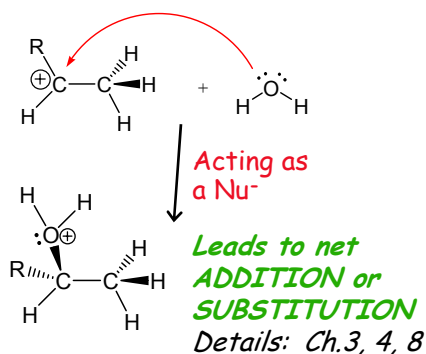
(6)

3.6 How alkenes react: electrophilic addition

π–e⁻s = polarizable & reactive

React with electrophiles…

In ELECTROPHILIC ADDITION reactions:

- an electrophile (a δ^+ centre) reacts with alkene's π-electrons
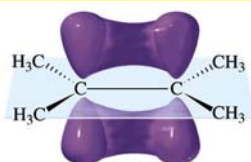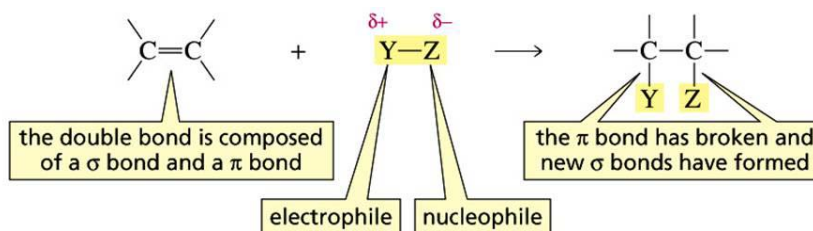- end up with a small molecule " Y-Z " *adding across* the double bond
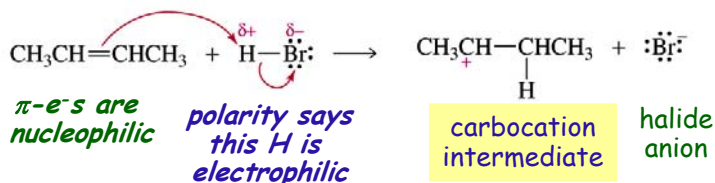- many types of molecules do this, all via similar mechanism *(next slide)*

$$\begin{array}{ccccc} \diagdown\!\!C\!=\!C\diagup & + & \overset{\delta+\quad\delta-}{Y\!-\!Z} & \longrightarrow & \diagup\!\!\overset{|}{C}\!-\!\overset{|}{C}\!\diagdown \\ & & & & \diagup\!\!\overset{Y}{}\quad\overset{Z}{} \end{array}$$

the double bond is composed of a σ bond and a π bond

the π bond has broken and new σ bonds have formed

electrophile   nucleophile

(7)

General mechanism of electrophilic addition rxns
e.g., hydrohalogenation = addition of H-X   (3.6, 4.1)

STEP 1:
alkene
π-electrons
attack
electrophile

$$CH_3CH\!=\!CHCH_3 + \overset{\delta+\quad\delta-}{H\!-\!\ddot{B}r:} \longrightarrow CH_3CH\!\underset{+}{-}CHCH_3 + :\ddot{B}\!\ddot{r}:^- $$

π-e⁻s are nucleophilic   *polarity says this H is electrophilic*

carbocation intermediate

halide anion

STEP 2:
nucleophile
attacks
carbocation
intermediate

$$CH_3\underset{+}{CH}\!-\!\underset{H}{CHCH_3} + :\ddot{B}\!\ddot{r}:^- \longrightarrow CH_3CH\!-\!CHCH_3 $$

E⁺   H   Nu: :Br: H

Product
= alkyl halide
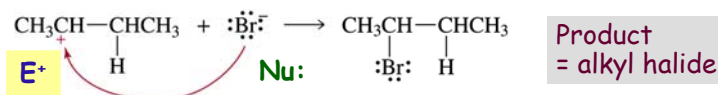
- All hydrogen halides react this way with alkenes
  - rxn faster as HX acidity ↑ ⇐ because H is more δ^+

- Use polar, *noncoordinating* solvents (*i.e.,* not Nu-ic)
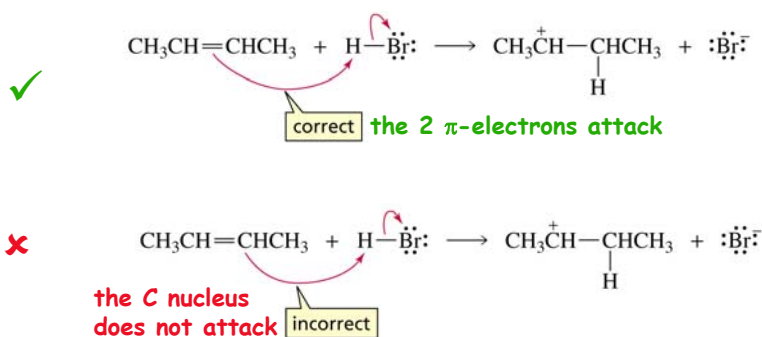 - ⇒ X⁻ = the only nucleophile encountered by C+ int.

(8)

"**Arrow pushing**" illustrates rxn's mechanism: shows where e⁻s are going
  - arrows start at e⁻ rich centre (bond or lone pair):   **Nu:**
  - arrows point to e⁻ deficient centre (empty orbital or δ^+ atom):   **E⁺**

IMPORTANT: see text for examples of correct *vs.* incorrect arrow usage

✓

$CH_3CH=CHCH_3 + H-\ddot{B}r: \longrightarrow CH_3\overset{+}{C}H-CHCH_3 + :\ddot{B}r:^-$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | $
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad H$

correct **the 2 π-electrons attack**

✗

$CH_3CH=CHCH_3 + H-\ddot{B}r: \longrightarrow CH_3\overset{+}{C}H-CHCH_3 + :\ddot{B}r:^-$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | $
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad H$

**the C nucleus
does <u>not</u> attack** incorrect

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**Which step here
is slower?**

- larger $\Delta G^{\ddagger}$
  ⇨ smaller rate
    constant, k
  ⇨ slower rxn

- To speed up rxn:
  choose solvent
  that stabilizes $\ddagger_1$

**resembles
carbocation!**
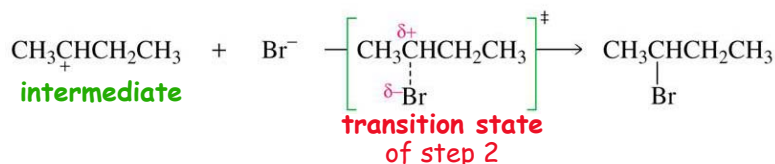
Fig. 3.7: Rxn of 2-butene with HBr

The Hammond postulate:
A rxn's transition state will resemble the species (reactant, product)
to which it is energetically closer (*i.e.,* structurally similar)

**Note: few slides at end = brief kinetics/thermodynamics review
BUT: read through Bruice section 3.7 yourselves**

(10)

A closer look at the electrophilic addition mechanism: Transition States (‡) *versus* Intermediate

$$CH_3CH{=}CHCH_3 \ + \ HBr \quad - \left[\begin{array}{c} \overset{\delta+}{CH_3CH}{=}\overline{=}CHCH_3 \\ | \\ H \\ \vdots \\ \overset{\delta-}{Br} \end{array} \right]^{\ddagger} \longrightarrow \quad CH_3\overset{+}{C}HCH_2CH_3 \ + \ Br^-$$

intermediate

transition state
of step 1

$$CH_3\overset{+}{C}HCH_2CH_3 \ + \ Br^- \quad - \left[\begin{array}{c} \overset{\delta+}{CH_3CHCH_2CH_3} \\ \vdots \\ \overset{\delta-}{Br} \end{array} \right]^{\ddagger} \longrightarrow \quad \begin{array}{c} CH_3CHCH_2CH_3 \\ | \\ Br \end{array}$$

intermediate

transition state
of step 2

Transition state = the most unstable moment during the reaction step
▪ some bonds partially broken, other bonds partially formed
▪ exists so transiently, no other species could collide with it…

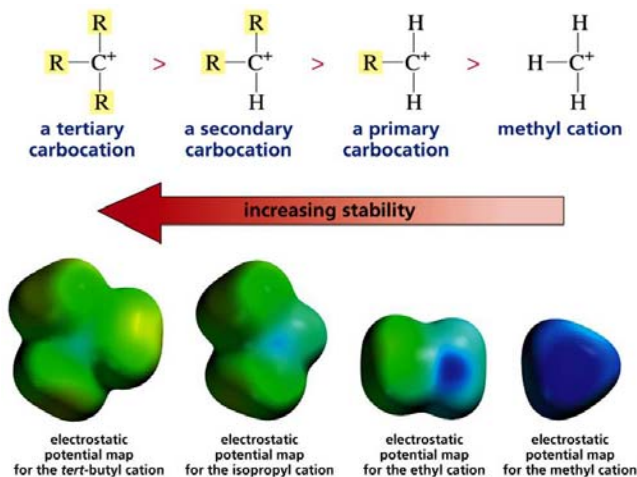Intermediate = "stable" species that can collide with other species
▪ have only full bonds (no partially formed bonds)
▪ but if have an open-shell atom (*e.g.,* carbocation) ⇨ very reactive!

(11)

4.2 Carbocation stabilities: more stable ⇨ easier to form

Alkyl groups (EDGs)
stabilize carbocations:

▪ by decreasing density
of + charge at the
carbocationic centre

a tertiary carbocation > a secondary carbocation > a primary carbocation > methyl cation

increasing stability

electrostatic potential map for the *tert*-butyl cation

electrostatic potential map for the isopropyl cation

electrostatic potential map for the ethyl cation

electrostatic potential map for the methyl cation

**How does this *inductive electron donation* happen?**

(12)

Hyperconjugation: Partial delocalization of electrons

Can rationalize via inductive stabilization by electron-rich R groups,
but orbitals give a more concrete explanation   (also applies to radicals)

Consider methyl cation $\overset{\oplus}{C}H_3$ ← planar (sp²-hyb. C, empty p-orbital)
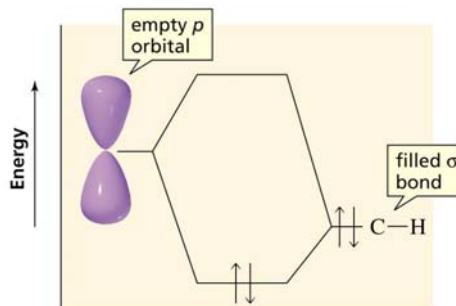C already bonded to all available e⁻s

vs. ethyl cation $\overset{\oplus}{C}H_3CH_2$

Can adopt conformation
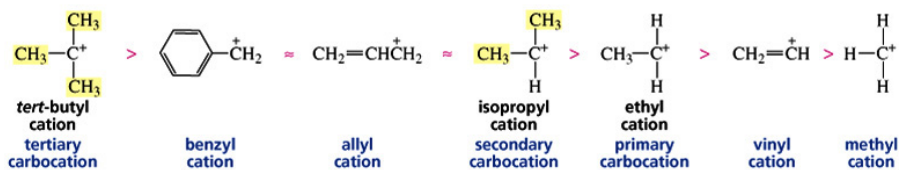where adjacent σ-bonds
line up with empty p-orbital:
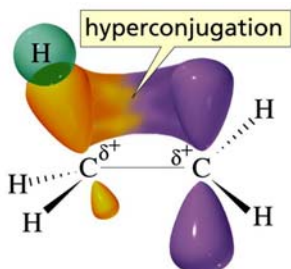
Fig. 4.2 M.O. diagram showing
orbitals on neighbouring C's in
an alkyl-substituted carbocation

(13) Bruice Fig.4.1

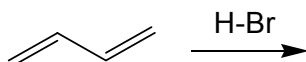
Relative stabilities of C⊕s: inductive & resonance effects

WHY IS C⊕ STABILITY IMPORTANT?

more stable carbocation intermediates form more easily

i.e., lower $\Delta G^{\ddagger}$ to reach C⊕ –like ‡ ⇨ faster rxn via that path

⇨ **can predict dominant product if ≥2 possible**

Ex.: hydrobromination of 1,3-butadiene

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"Regio" refers to the site in the molecule where the rxn takes place
e.g., if more than C could end up bonded to the electrophile,
then you must worry about which "regiochemistry" is preferred

$$CH_3\overset{\underset{|}{CH_3}}{\underset{+}{C}}CH_3 \quad \text{tert-butyl cation} \quad \xrightarrow{Cl^-} \quad CH_3\overset{\underset{|}{CH_3}}{\underset{\underset{|}{Cl}}{C}}CH_3 \quad \textbf{\textit{tert-butyl chloride}} \text{ only product formed}$$

$$CH_3\overset{\underset{|}{CH_3}}{C}=CH_2 + HCl$$

$$CH_3\overset{\underset{|}{CH_3}}{CH}\overset{+}{CH_2} \quad \text{isobutyl cation} \quad \xrightarrow{Cl^-} \quad CH_3\overset{\underset{|}{CH_3}}{CH}CH_2Cl \quad \textbf{\textit{isobutyl chloride}} \text{ not formed}$$

the difference in the stabilities of the transition states

$CH_3\overset{\underset{|}{CH_3}}{CH}\overset{+}{CH_2}$ isobutyl cation

$CH_3\overset{\underset{|}{CH_3}}{\underset{+}{C}}CH_3$ tert-butyl cation

the difference in the stabilities of the carbocations

Free energy

$\Delta G^\ddagger$ $\Delta G^\ddagger$

Progress of the reaction

2 constitutional isomers possible as products…
but only 1 forms
⇨ reaction is "regioselective"

(15)

$$\xrightarrow{\text{HBr}} \quad \textbf{?}$$
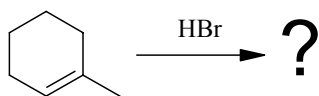
MARKOVNIKOV ADDITIONS: when electrophile = δ^+ H atom
- 1st step: H attaches to less highly substituted sp² C
- Result: C+ centre on more highly substituted sp² C (more stable)

- Examples: addition of HX, acid-catalyzed addition of H_2O, HOR…
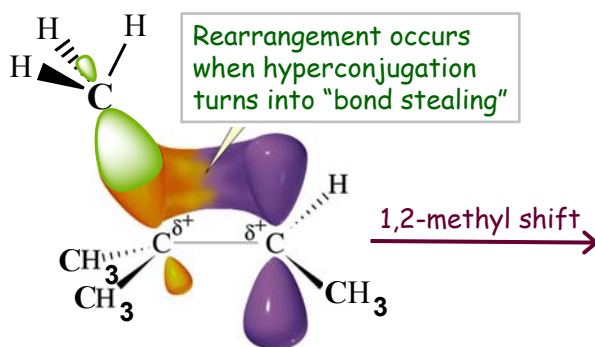(16)   (see 4.5)

4.6 Carbocations rearrange: to form most stable C+ possible

Carbocations = HIGHLY REACTIVE open-shell species
with 2 options to "*solve their problem*"...

1.) "*search within themselves*" (always happens first) ⇨ **REARRANGE**	OR	2.) "*find solace in others*" (slower - requires collision) ⇨ **REACT WITH A Nu**

Rearrangement occurs when hyperconjugation turns into "bond stealing"
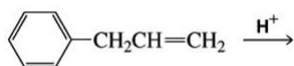
1,2-methyl shift

(17)

Rearrangements = Hydride shift OR alkyl shift

Mechanism: bonding pair from **adjacent C** is "stolen" by C+ centre
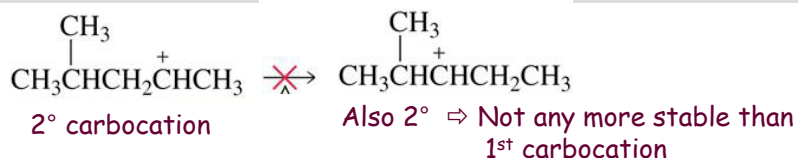⇨ substituent moves onto C+ centre, **leaving behind a more stable C+**

$CH_3C-CHCH_3$ with CH_3 above and H below

1,2-hydride shift

2° C+   **3° C+**

Ex.: hydrobromination of 3-phenylpropene

$-CH_2CH{=}CH_2 \xrightarrow{H^+}$

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Carbocations do not always rearrange ...

$$CH_3\overset{CH_3}{\underset{|}{CH}}CH_2\overset{+}{CH}CH_3 \quad \cancel{\longrightarrow} \quad CH_3\overset{CH_3}{\underset{|}{CH}}\overset{+}{CH}CH_2CH_3$$

2° carbocation   Also 2° ⇨ Not any more stable than 1st carbocation

Carbocation rearrangment can lead to "Ring Expansion" (driven by relief of ring strain)

Keep on the watch for:
carbocationic centres
1 bond away from a ring

& then see if the
ring-expanded product
has significantly lower
ring strain or not

(19)

4.5 Addition of water & addition of alcohols
Markovnikov addition: occurs in acid; electrophile = H+

NET RESULT: Add H-OH or H-OR across the C=C bond

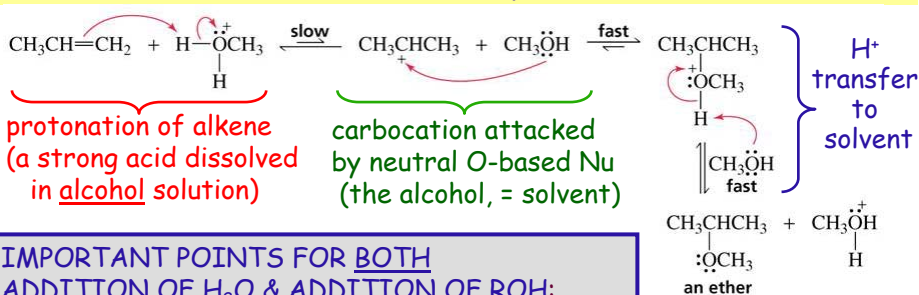**MECHANISM:** *electrophile = H+   (rxn won't happen without acid...)*
1.) strong acid protonates C=C bond ⇨ carbocation intermediate
2.) nucleophile (water or alcohol) attacks carbocationic centre
3.) H+ transfer to solvent ⇨ neutral alcohol or ether product

Hydration of an alkene:

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product = an ALCOHOL

Same mechanism for acid–catalyzed addition of alcohols

$$CH_3CH=CH_2 + H-\overset{+}{\underset{H}{O}}CH_3 \xrightarrow{\text{slow}} CH_3\overset{+}{CH}CH_3 + CH_3\ddot{O}H \xrightarrow{\text{fast}} CH_3CHCH_3$$

protonation of alkene
(a strong acid dissolved
in <u>alcohol</u> solution)

carbocation attacked
by neutral O-based Nu
(the alcohol, = solvent)

$$CH_3CHCH_3$$
$$\overset{+}{:}OCH_3$$
$$H$$
$$\Big\| CH_3\ddot{O}H \quad \text{fast}$$
$$CH_3CHCH_3 + CH_3\overset{+}{O}H$$
$$:\underset{}{O}CH_3 \qquad H$$
an ether

H⁺
transfer
to
solvent

> IMPORTANT POINTS FOR <u>BOTH</u>
> ADDITION OF H_2O & ADDITION OF ROH:
> ▪ strong acid required (often written just "H⁺")
> ▪ carbocation intermediate (rearrangements, *etc.*)
> ▪ <u>solvent</u> acts as nucleophile (H_2O or ROH)

DIFFERENCE:
product = an ETHER

WHICH ACID?
▪ acid's conj. base must be less nucleophilic than water or ROH
⇨ so <u>solvent</u> acts as nucleophile! (solvent = H_2O or ROH)
⇨ the less basic a species is, the less nucleophilic it is too

▪ common: H_2SO_4 / H_2O, H_3PO_4 / H_2O, H_2SO_4 / MeOH, *etc.*

▪ Not HX: Cl^-, Br^- = good Nu's ⇨ get hydrohalogenation

(21)

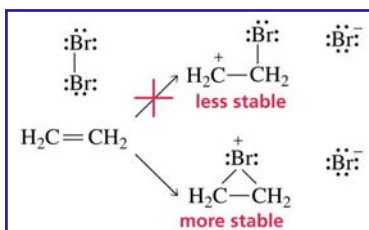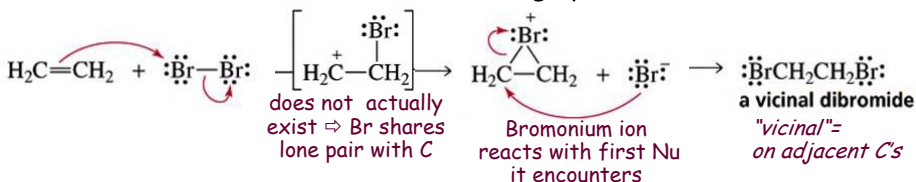
4.7 Addition of halogens: "halogenation"

NET RESULT: Add X-X across the C=C bond ⇨ vicinal dihalide product

MECHANISM: polarizable X–X acts as δ^+X–Xδ^-
1.) C=C bond attacks "X+" ⇨ cyclic *halonium ion* intermediate
2.) nucleophile (X⁻) attacks halonium ion
    ⇨ X ends up bonded to the more highly substituted C

$$H_2C=CH_2 + :\ddot{Br}-\ddot{Br}: \longrightarrow \left[\overset{:\ddot{Br}:}{\underset{}{H_2\overset{+}{C}-CH_2}} \right] \rightarrow \overset{:\overset{+}{Br}:}{H_2C-CH_2} + :\ddot{Br}:^- \rightarrow :\ddot{Br}CH_2CH_2\ddot{Br}:$$

does not actually
exist ⇨ Br shares
lone pair with C

Bromonium ion
reacts with first Nu
it encounters

a vicinal dibromide
"vicinal"=
on adjacent C's

▪ Imagine it as if C+ forms 1ˢᵗ *(but not true!)*
  & then C+ shares adjacent X's lone pair

⇨ Result: no atoms have open valence!
             much more stable than a C+!

Thus: NO carbocation intermediate
       ∴ rearrangements do NOT occur.

less stable

more stable

(22)

Some details about halogenation of alkenes

▪ **Can we use all the halogens to prepare vicinal dihalides from alkenes?**
    NO: Cl_2 & Br_2 are the only synthetically useful halogens
        F_2 is too reactive (explosive reaction → too dangerous)
        I_2 rxn thermo. unfavourable (diiodide products unstable)

▪ **Halonium ions are reactive intermediates** (but much more stable than C+)
        react with whichever Nu they encounter first
        THUS: **be sure <u>Nu of interest</u> is most conc. Nu present**

    THIS AFFECTS OUR CHOICE OF SOLVENT:
    ▪ **If want a vicinal dihalide:** use non-nucleophilic solvent *e.g.,* CH_2Cl_2
                        only Nu the halonium ion sees is X^- anion

    ▪ **If we use a nucleophilic solvent:** *e.g.,* water
            solvent will be Nu present in highest concentration!
            → solvent reacts with halonium ion intermediate
            → **useful route to vicinally heterodisubstituted compounds**,
                such as "halohydrins" (next slide)

(23)

Addition of Halogens in the Presence of Water:
"Halohydrin" formation (cmpd with vicinal X & OH)

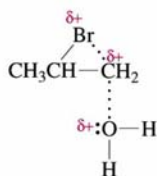**Why does the Nu attack the more substituted C?**
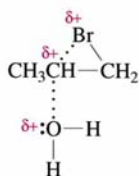
more stable transition state

less stable transition state

Resembles the more
stable carbocation
(but true C+ isn't formed...)

Regiochemistry:
the OH ends up on the more highly substituted C
(as usual: <u>electrophile</u> bonds
  to the C with more H's on it)

(24)

What products would these reaction conditions yield?

Ask yourself:
  1) **What is the electrophile?** — *π-bond attacks E's δ⁺ atom…*
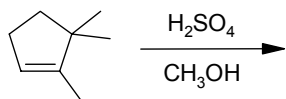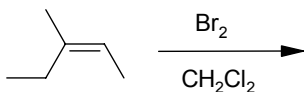   *…& E ends up on least substituted C*
  2) **Does a carbocation result?** → *If yes: form most stable cation possible*
     • *1st: via regiochemistry of E addition*
     • *2nd: via rearrangement(s)*

  3) **What is the nucleophile?** → *Nu reacts with electrophilic carbon*
     (of highest concentration) *(be sure to check if solvent is nucleophilic!)*

Br_2

CH_2Cl_2

H_2SO_4

CH_3OH

(25)

ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read: rest of Ch.2

Practice: drawing cyclohexane & ring flipping

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Next 3 slides:

Kinetics / thermodynamics review

see Bruice section 3.7

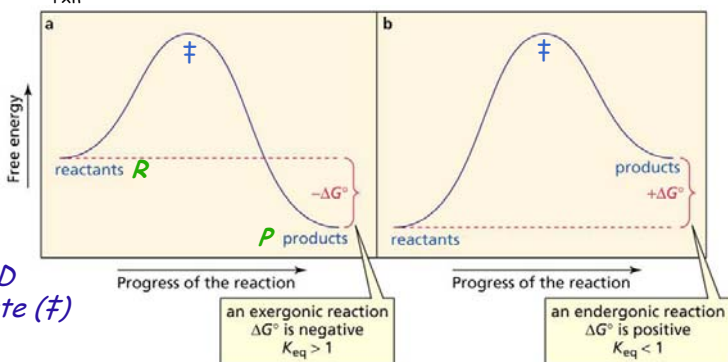## 3.7 Thermodynamics and kinetics: REVIEW

THERMODYNAMICS

▪ recall: $\Delta G^o = \Delta H^o - T\Delta S^o$
   and $\Delta G^o = -RT\ln K_{eq}$

So: what will our rxn mixture be like when it reaches EQUILIBRIUM:
- large, negative ΔG^o_{rxn}: product-favoured
- large, positive ΔG^o_{rxn}: reactant-favoured

▪ Enthalpy relates to stabilization due to bonds ΔH^o *estimated using bond energies (formed – broken...)*
▪ Entropy relates to disorder ΔS^o *estimated by comparing degree of movement (P – R)*

Fig.3.3 Reaction coordinate diagrams:
show free E of reactants, products, AND transition state (‡)

a

‡

Free energy

reactants R

$-\Delta G^o$

P products

Progress of the reaction

an exergonic reaction
ΔG^o is negative
$K_{eq} > 1$

b

‡

products

$+\Delta G^o$

reactants

Progress of the reaction

an endergonic reaction
ΔG^o is positive
$K_{eq} < 1$

KINETICS: rxn rate depends on temperature, because of E barrier

Reaction rate = (rate constant) x (concentration dependence)
   1st order: rate = k[reactant]
   2nd order: rate = k[reactant]^2 *or* rate = k[reactant A][reactant B]
   depends on the reaction's mechanism…

Activation energy, E_a: also depends on the mechanism!
▪ E needed to reach ‡ (some bonds *partially* broken, others forming…)
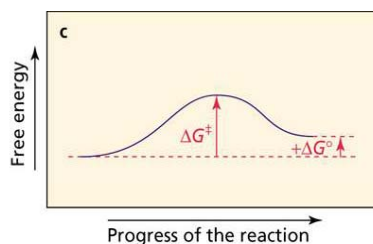▪ E of collided reactants must exceed E_a for rxn to occur
      Arrhenius' equation: $k = Ae^{-E_a/RT}$
      • E_a is a purely enthalpic quantity:
         considers bond strengths only
      • the A term includes entropic factors

To include entropic factors in one term:
      "**free energy of activation**", $\Delta G^{\ddagger}$
         $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$

(29)
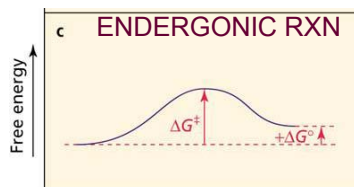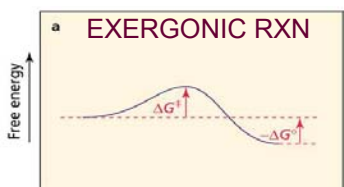
Why this information is useful to an organic chemist

Because rxn rates depend on "getting over the energy barrier":
      ▪ anything that stabilizes rxn's transition state will make rxn faster
      ▪ choose solvent that interacts better with ‡ ⇨ lower ‡'s E ⇨ ↓ $\Delta G^{\ddagger}$

If both the forward & reverse rxns are "thermally accessible":
      ▪ system can reach equilibrium (steady state with rate$_{fwd}$= rate$_{rev}$)

IMPORTANT: Composition of rxn mixture AT EQUILIBRIUM
depends on relative thermodynamic stabilities of reactants *vs.* products.
**At equilibrium, the more stable species will dominate.** *WHY?*
▪ Consider an exergonic rxn: products more stable than reactants
      IMPLIES: lower activation barrier for fwd rxn *vs.* reverse rxn
            ⇨ rate constants: $k_{fwd} > k_{rev}$
            ⇨ rate faster in forward direction until build up large [product]
            ⇨ by the time rate$_{fwd}$ = rate$_{rev}$, have more products than reactants

(30)

Extra example: C+ rearrangements

(31)

Many intermediate C+s ⇨ may get many products

major   +   I   +   H

Major

Minor
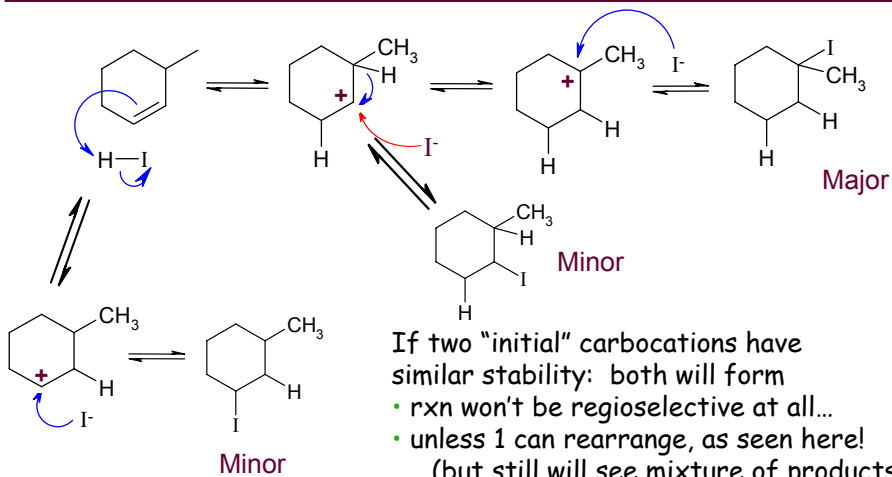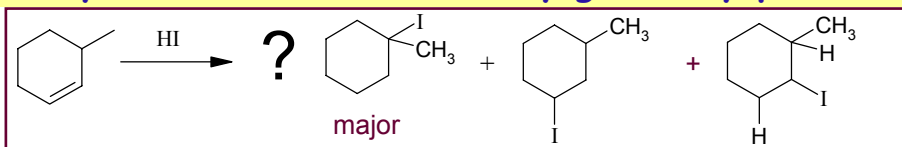
If two "initial" carbocations have
similar stability: both will form
• rxn won't be regioselective at all…
• unless 1 can rearrange, as seen here!
    (but still will see mixture of products)

Minor

(32)