Chapter 12

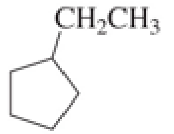
Radicals

- Radicals
- Radical reactions

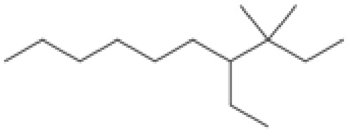
Reactivity of alkanes

- Alkanes are <u>not</u> reactive.
  - a saturated HC
    - <u>no</u> π–bond , <u>no</u> addition rxn
  - σ(C–C) and C–H are non-polar.
    - <u>nowhere</u> for Nu: or E^+ to attack
  - alkanes = paraffins

$CH_3CH_2CH_2CH_3$
butane

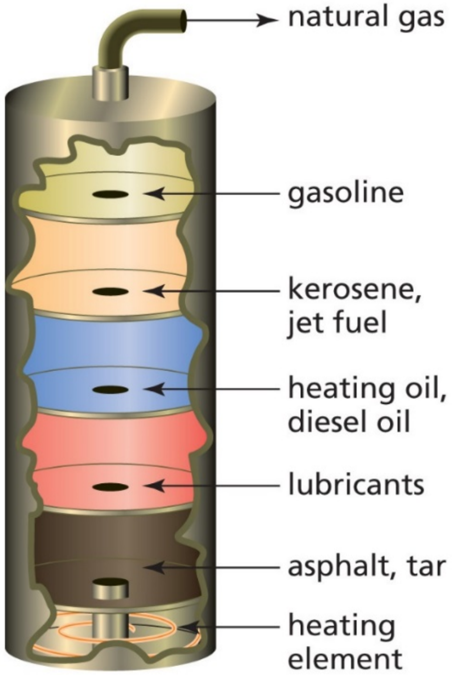


ethylcyclopentane



4-ethyl-3,3-dimethyldecane

- Alkanes are (fossil) fuel. p569
  - LNG, LPG, petroleum
  - combustion rxn
    - 1 of only 2 rxns that alkanes undergo



Chlorination and bromination

- halogenation
  - from alkane to haloalkane
  - why <u>not</u> I or F?

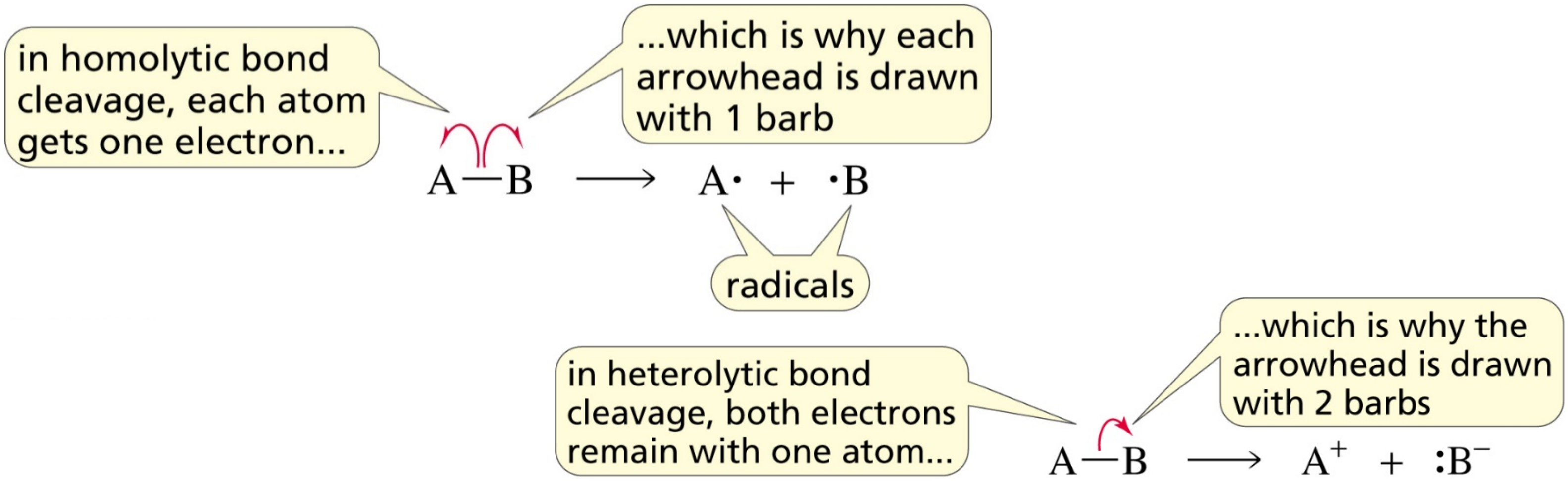
$$CH_4 + Cl_2 \xrightarrow[\text{or } h\nu]{\Delta} CH_3Cl + HCl$$

chloromethane

$$CH_3CH_3 + Br_2 \xrightarrow[\text{or } h\nu]{\Delta} CH_3CH_2Br + HBr$$

bromoethane

- With heat or light, bond breaks
  - to form (free*) radicals (with unpaired electron) *p572
  - thru homolytic cleavage [homolysis]



in homolytic bond cleavage, each atom gets one electron...

...which is why each arrowhead is drawn with 1 barb

$$A{-}B \longrightarrow A\cdot + \cdot B$$

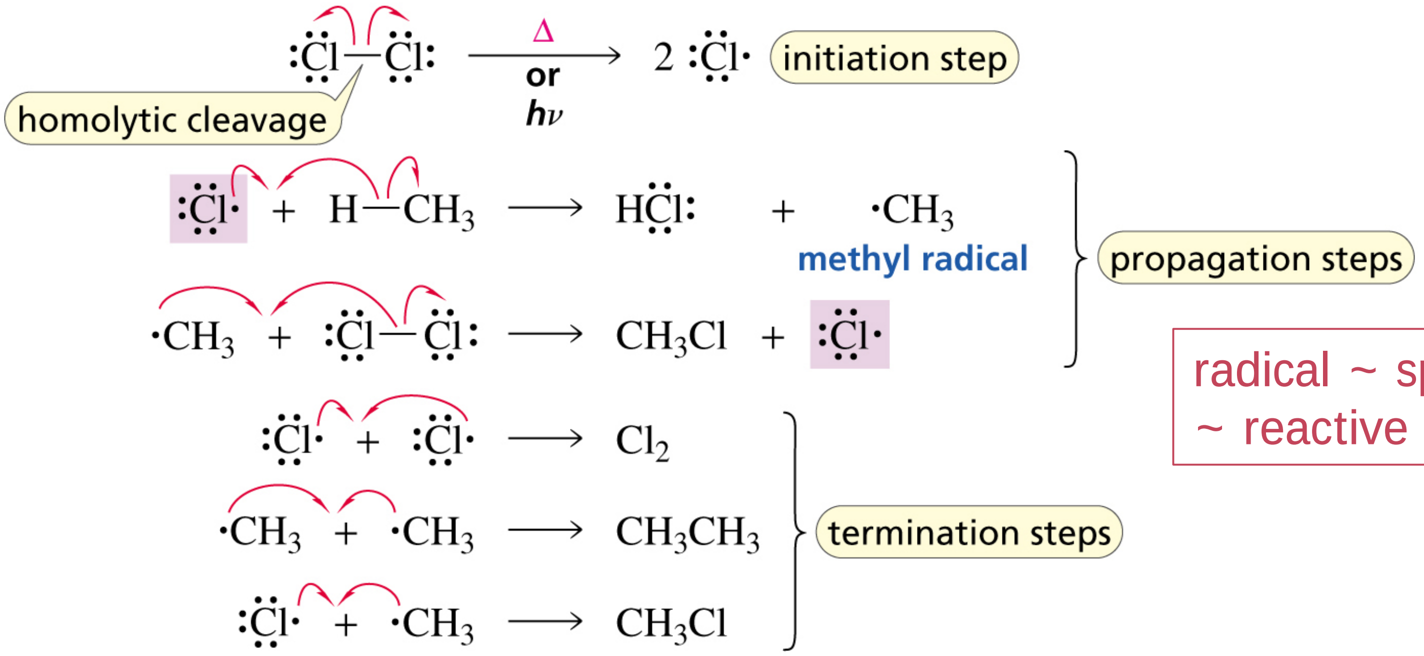
radicals

in heterolytic bond cleavage, both electrons remain with one atom...

...which is why the arrowhead is drawn with 2 barbs

$$A{-}B \longrightarrow A^+ + :B^-$$

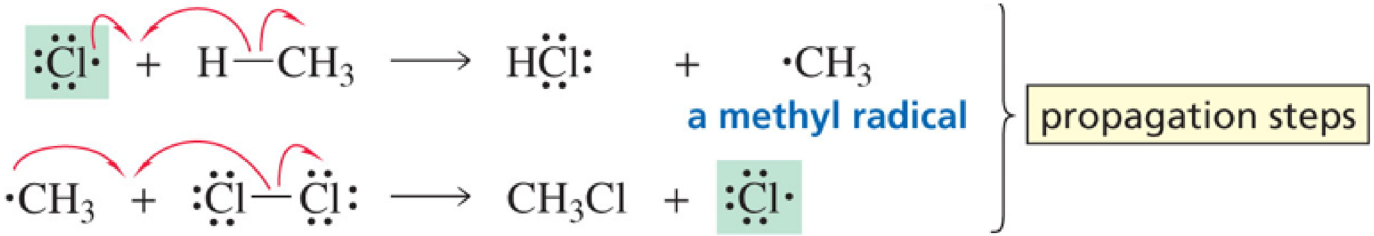
Mechanism



radical ~ specie w/ •
~ reactive ~ octet rule

- 3 steps (of (every) radical reaction)
  - initiation ~ formation of radicals
  - propagation ~ 1-2-1-2-1--- ~ 1 is RDS.
  - termination ~ disappearance of radicals

- Halogenation is ...
  - a (radical) chain reaction
    - repeating propagation steps
  - a radical substitution reaction
    - R–H + X_2 → R–X + HX
- mono- vs di- and tri-substitution



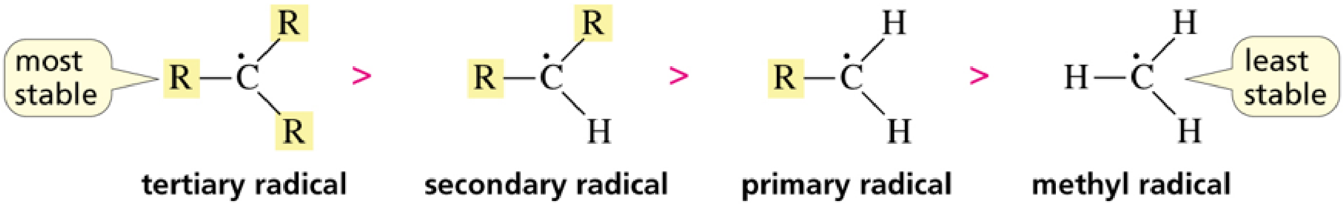
$$Cl\cdot + CH_3Cl \longrightarrow \cdot CH_2Cl + HCl$$

$$\cdot CH_2Cl + Cl_2 \longrightarrow CH_2Cl_2 + Cl\cdot$$

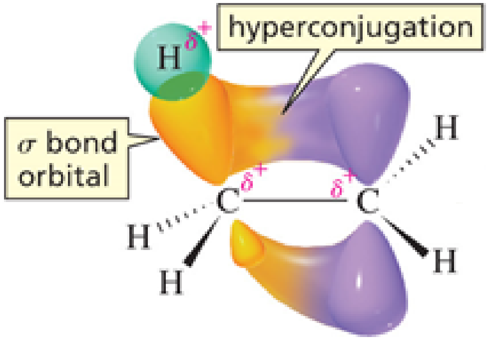
  - how to control (max mono-)?

Stability of radical

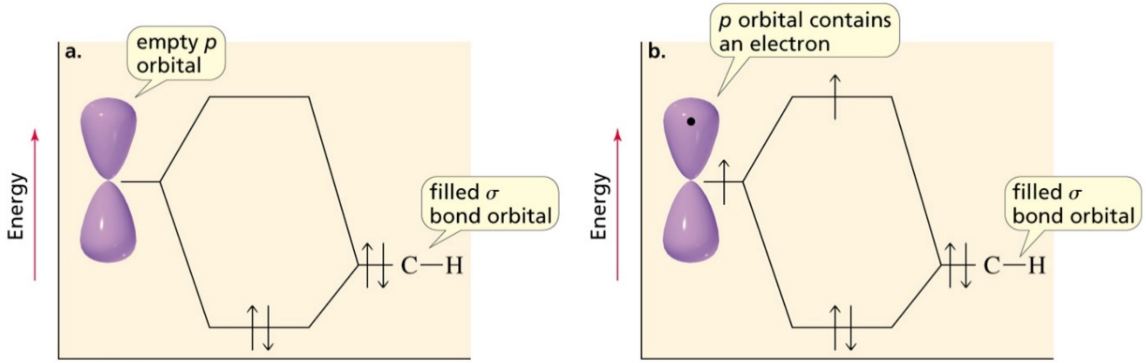
- 3° > 2° > 1° > methyl radical



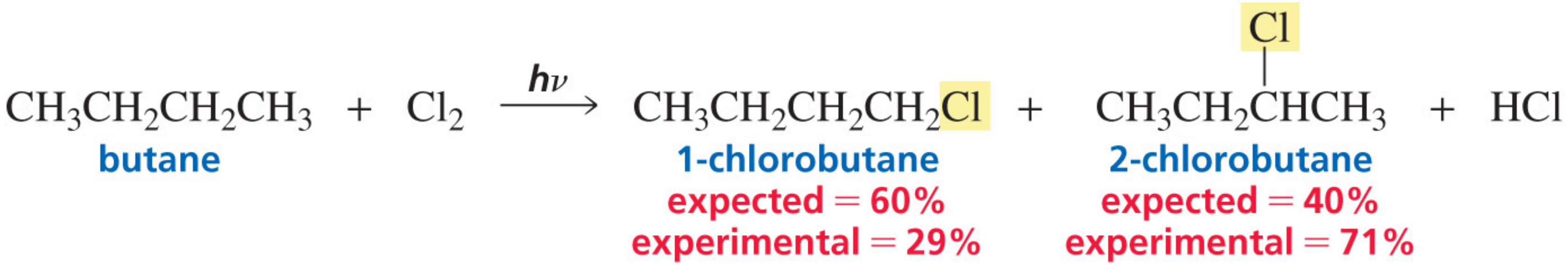
  - due to hyperconjugation
  - difference smaller than in C^+
    - less (stabilizing) overlap
    - 3-e vs 2-e ~ 1 e at AMO



ethyl cation



Distribution of products



$$CH_3CH_2CH_2CH_3 + Cl_2 \xrightarrow{h\nu} CH_3CH_2CH_2CH_2Cl + CH_3CH_2\overset{\overset{Cl}{|}}{C}HCH_3 + HCl$$

- expected (?) 6/4
  ← probability ∝ # of (substitution) sites
- obtained 29/71
  ← probability x reactivity (of site)
  - 29/71 = (6/4) (1/r) → r = 3.8 (times more reactive)
  - why? reactivity ∝ radical stability

	tertiary	>	secondary	>	primary
reactivity	5.0		3.8		1.0

Reactivity-selectivity principle

$$CH_3CH_2CH_2CH_3 + Cl_2 \xrightarrow{h\nu} CH_3CH_2CH_2CH_2Cl + CH_3CH_2\overset{Cl}{C}HCH_3 + HCl$$

butane

1-chlorobutane
expected = 60%
experimental = 29%

2-chlorobutane
expected = 40%
experimental = 71%

relative rates of alkyl radical formation by a chlorine radical at room temperature

tertiary	>	secondary	>	primary
5.0		3.8		1.0

$$CH_3CH_2CH_2CH_3 + Br_2 \xrightarrow{h\nu} CH_3CH_2CH_2CH_2Br + CH_3CH_2\overset{Br}{C}HCH_3 + HBr$$

1-bromobutane
2%

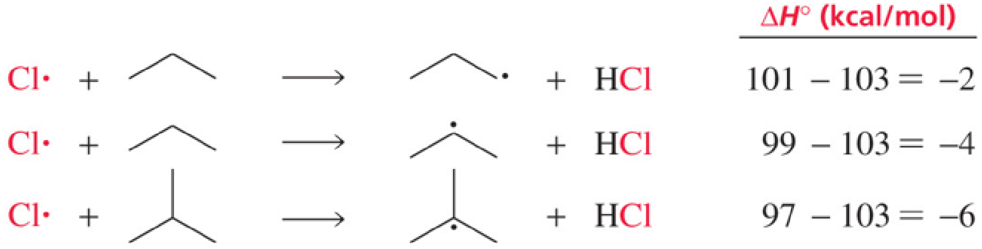
2-bromobutane
98%

relative rates of alkyl radical formation by a bromine radical at 125 °C

tertiary	>	secondary	>	primary
1600		82		1

- A bromine radical is more selective. Why?

- ΔH° = heat in – heat out = DH broken – DH formed
  - DH ~ bond dissociation energy p242 Table 5.1



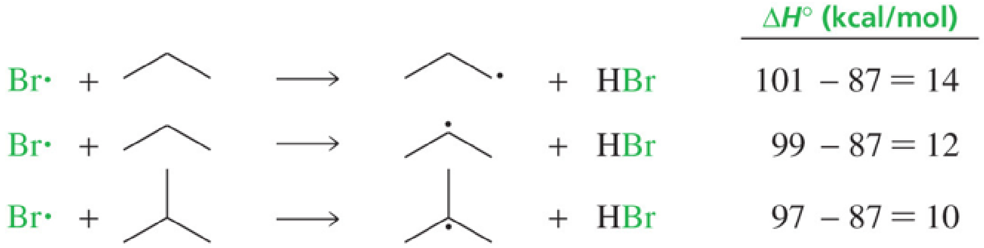
ΔH° (kcal/mol)

$101 - 103 = -2$

$99 - 103 = -4$

$97 - 103 = -6$

exothermic
small and similar E_a
more reactive and less selective



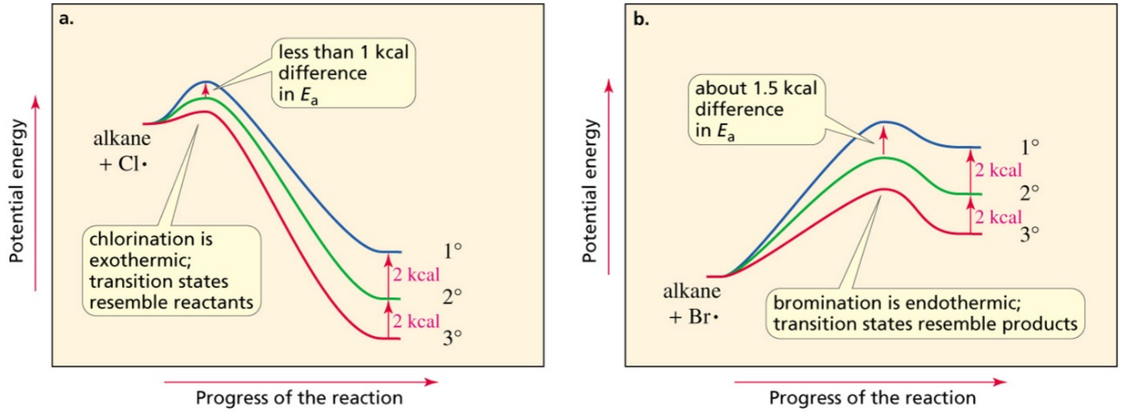
ΔH° (kcal/mol)

$101 - 87 = 14$

$99 - 87 = 12$

$97 - 87 = 10$

endothermic
large and dissimilar E_a
less reactive and more selective

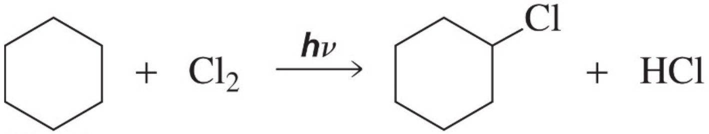


Hammond postulate

- reactivity-selectivity principle [RSP]

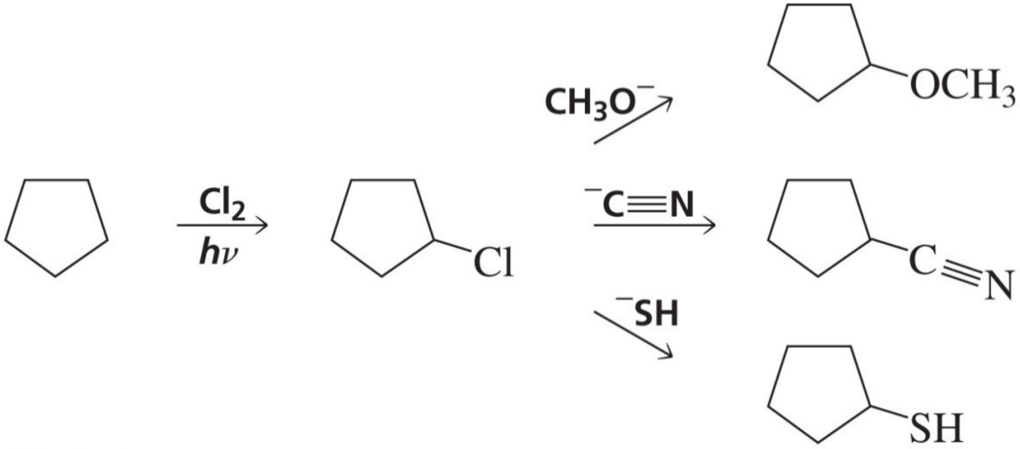
  "A more reactive species will be less selective."

  - rather obsolete ~ too many exceptions
- Br• is less reactive and more selective than Cl• is. (98/2 vs 79/21)
  - Bromination is more controllable and useful.
  - Chlorination is useful when only product.



Halogenation useful?

- Radical chlorination or bromination of alkane
  - is not very useful for RX synthesis
    - not very selective ← isomers and multi-substitution
    - better method? from alkene or ROH
  - is still useful for converting alkane to something



- X is a good leaving group

F• and I•?

- ΔH° of the

first propagation step for monohalogenation

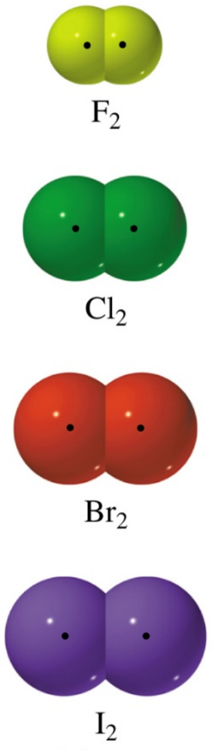
$$\text{F}\cdot + \text{CH}_4 \longrightarrow \cdot\text{CH}_3 + \text{HF} \qquad \Delta H^\circ = 105 - 136 = -31$$

$$\text{Cl}\cdot + \text{CH}_4 \longrightarrow \cdot\text{CH}_3 + \text{HCl} \qquad \Delta H^\circ = 105 - 103 = 2$$

$$\text{Br}\cdot + \text{CH}_4 \longrightarrow \cdot\text{CH}_3 + \text{HBr} \qquad \Delta H^\circ = 105 - 88 = 17$$

$$\text{I}\cdot + \text{CH}_4 \longrightarrow \cdot\text{CH}_3 + \text{HI} \qquad \Delta H^\circ = 105 - 71 = 34$$

  - F• too reactive → explosive
  - I• not reactive → form I_2 not Me•

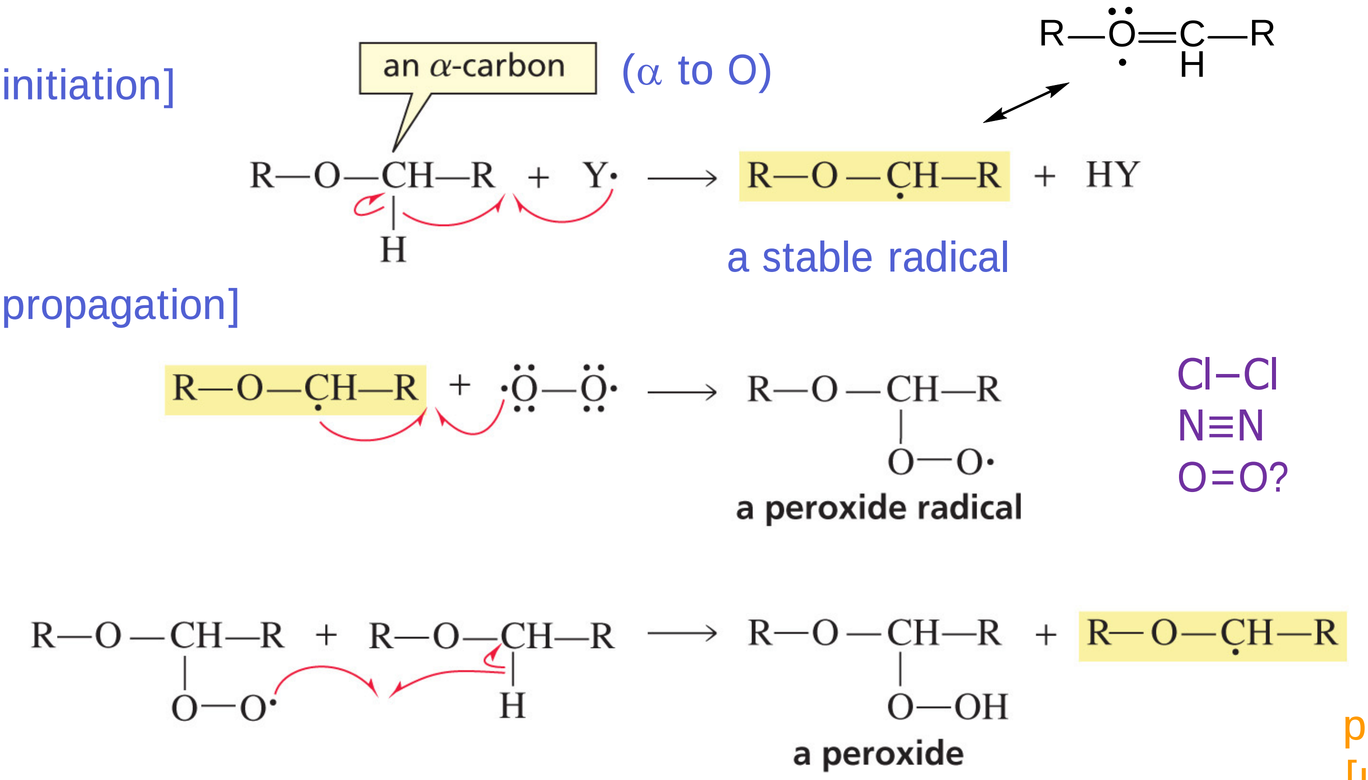


Halogens

Peroxides

- Peroxides are formed from ethers w/ O_2.

[initiation]



an α-carbon

(α to O)

$$\mathrm{R{-}O{-}\underset{\substack{|\\ H}}{C}H{-}R + Y\cdot \longrightarrow R{-}O{-}\underset{\bullet}{C}H{-}R + HY}$$

$$\mathrm{R{-}\overset{\cdot\cdot}{\underset{\cdot}{O}}{=}\underset{H}{C}{-}R}$$

a stable radical

[propagation]

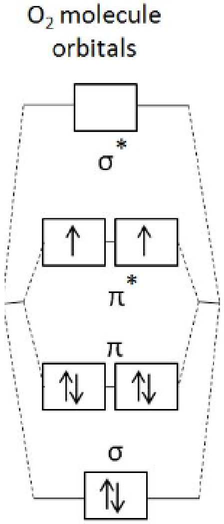
$$\mathrm{R{-}O{-}\underset{\bullet}{C}H{-}R + \cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{-}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}\cdot \longrightarrow R{-}O{-}\underset{\substack{|\\ O{-}O\cdot}}{C}H{-}R}$$

a peroxide radical

$$\mathrm{R{-}O{-}\underset{\substack{|\\ O{-}O\cdot}}{C}H{-}R + R{-}O{-}\underset{\substack{|\\ H}}{C}H{-}R \longrightarrow R{-}O{-}\underset{\substack{|\\ O{-}OH}}{C}H{-}R + R{-}O{-}\underset{\bullet}{C}H{-}R}$$

a peroxide

Cl−Cl
N≡N
O=O?

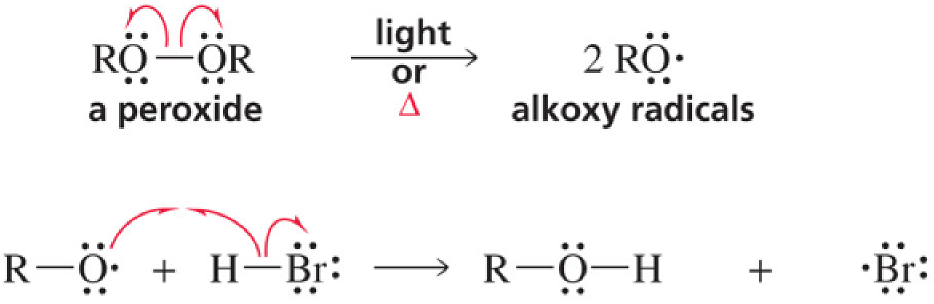


paramagnetic
[unpaired e]
but
bond order = 2
so O ÷ O

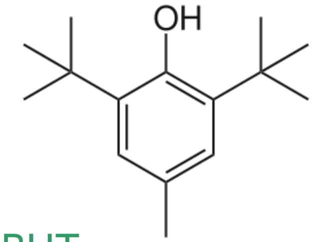
  - explosive!
  - peroxide [ROOR’]; hydroperoxide [ROOH]

- Peroxides are radical initiators.
  - form radicals (by (weak) O–O cleavage)
  - initiate (another) chain reaction

why so weak?

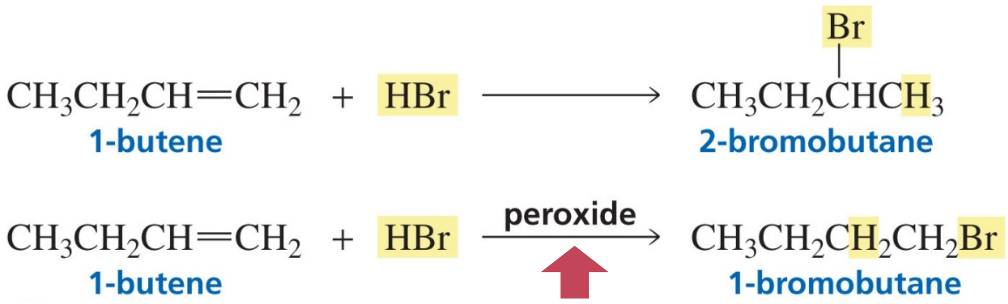


- Ethers are useful solvents,
  but hazardous [explosive with heat or light]!
  - do not heat
  - store w/ stabilizer, and
    purify (immed) before use



BHT
a hindered phenol
a radical scavenger

Addition of • to C=C



$$CH_3CH_2CH{=}CH_2 + HBr \longrightarrow CH_3CH_2\underset{}{\overset{Br}{C}}HCH_3$$

$$CH_3CH_2CH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} CH_3CH_2CH_2CH_2Br$$

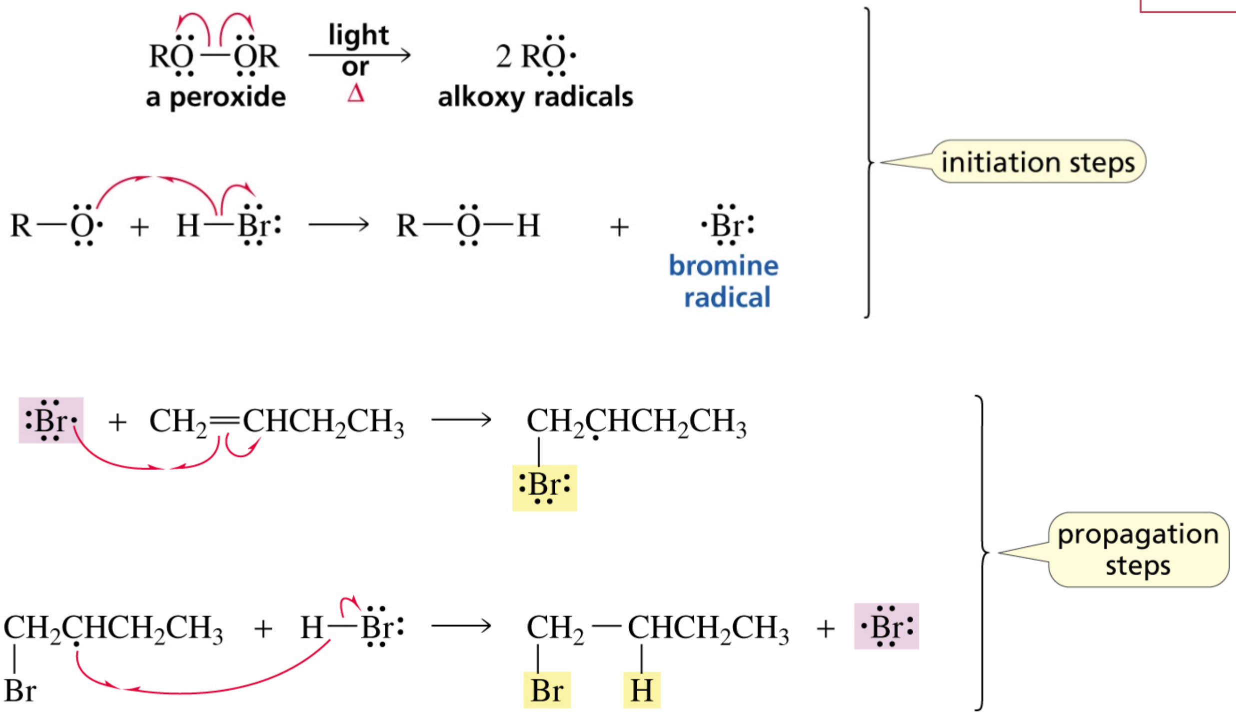
internal

terminal

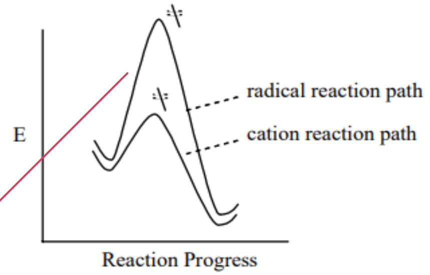
H^+ is the E^+.
more stable 2° C^+
→ internal RX

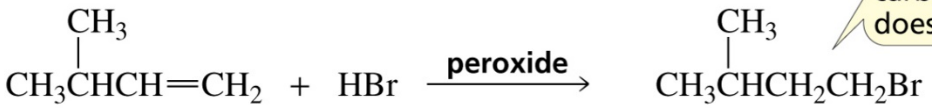
Br• is the E^+.
more stable 2° radical
→ terminal RX

- with peroxide initiator



- radical addition reaction
  - addition of radical electrophile (with one e)
  - need radical initiator (like peroxides)
  - no rearrangement ~ ~~$C\cdot$ vs C^+~~ high-energy TS

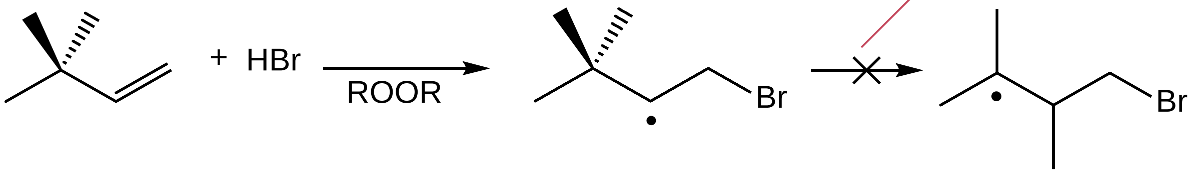




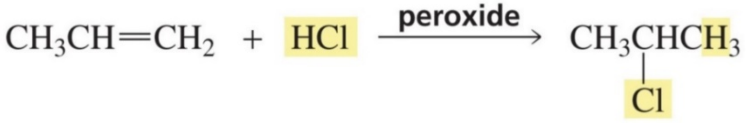
$$CH_3\underset{}{\overset{CH_3}{|}}CHCH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2Br$$

carbon skeleton does not rearrange

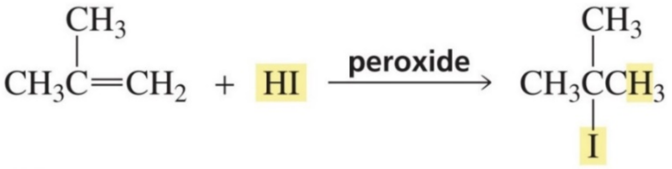
not a good example



- Radical addition only for HBr, not for HCl or HI. Why?



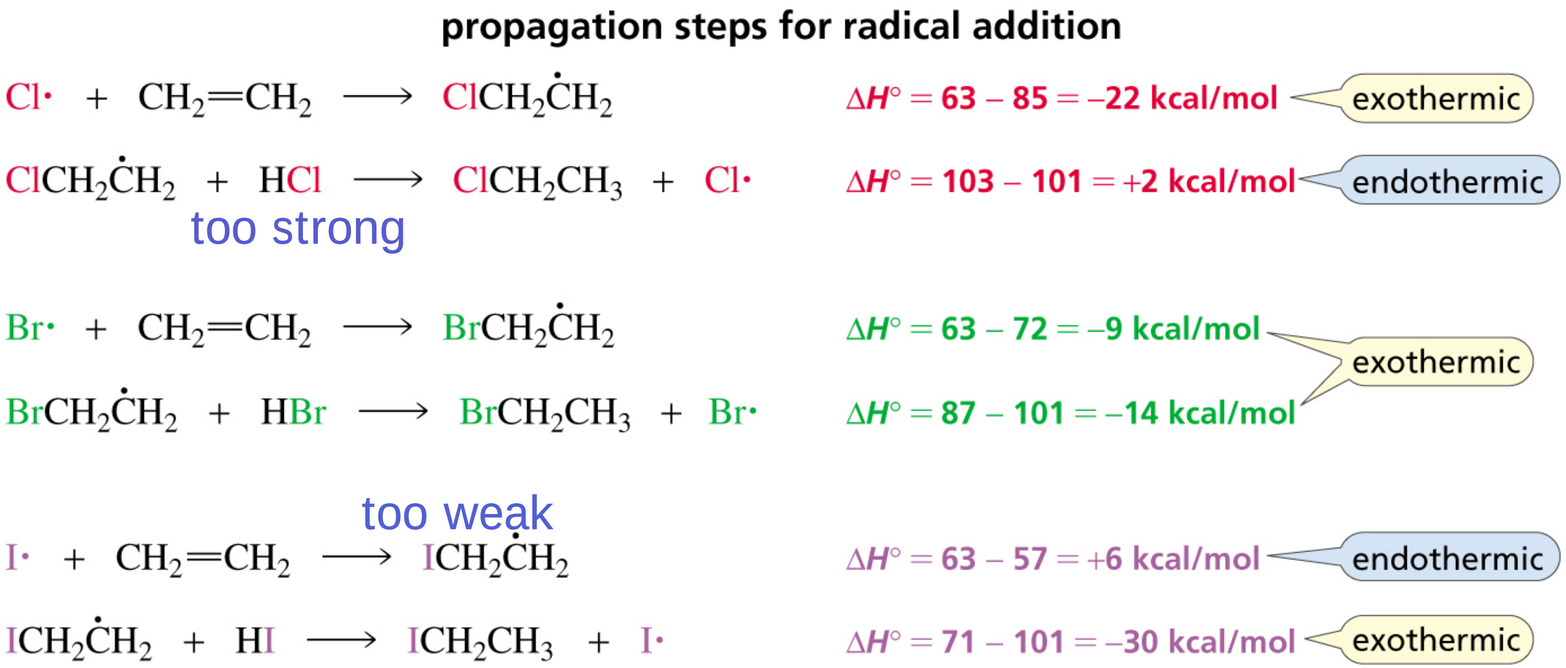
$$CH_3CH{=}CH_2 + HCl \xrightarrow{\text{peroxide}} CH_3\underset{\underset{Cl}{|}}{C}HCH_3$$



$$CH_3\overset{CH_3}{\overset{|}{C}}{=}CH_2 + HI \xrightarrow{\text{peroxide}} CH_3\overset{CH_3}{\overset{|}{\underset{\underset{I}{|}}{C}}}CH_3$$

e-philic additions, not radical

- ΔH° of the



propagation steps for radical addition

$Cl\cdot + CH_2{=}CH_2 \longrightarrow ClCH_2\dot{C}H_2$ $\Delta H^\circ = 63 - 85 = -22$ kcal/mol exothermic

$ClCH_2\dot{C}H_2 + HCl \longrightarrow ClCH_2CH_3 + Cl\cdot$ $\Delta H^\circ = 103 - 101 = +2$ kcal/mol endothermic

too strong

$Br\cdot + CH_2{=}CH_2 \longrightarrow BrCH_2\dot{C}H_2$ $\Delta H^\circ = 63 - 72 = -9$ kcal/mol

$BrCH_2\dot{C}H_2 + HBr \longrightarrow BrCH_2CH_3 + Br\cdot$ $\Delta H^\circ = 87 - 101 = -14$ kcal/mol

exothermic

too weak

$I\cdot + CH_2{=}CH_2 \longrightarrow ICH_2\dot{C}H_2$ $\Delta H^\circ = 63 - 57 = +6$ kcal/mol endothermic

$ICH_2\dot{C}H_2 + HI \longrightarrow ICH_2CH_3 + I\cdot$ $\Delta H^\circ = 71 - 101 = -30$ kcal/mol exothermic

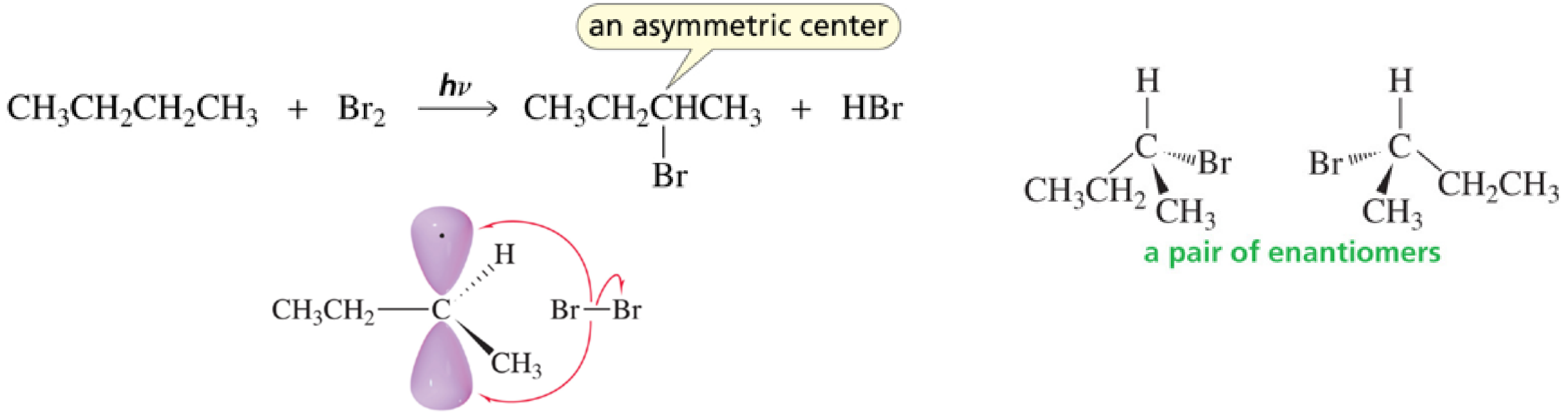
  - Both propag'n steps have to be exothermic

    ← to compete w/ terminations, which are always exothermic (with forming bonds only).

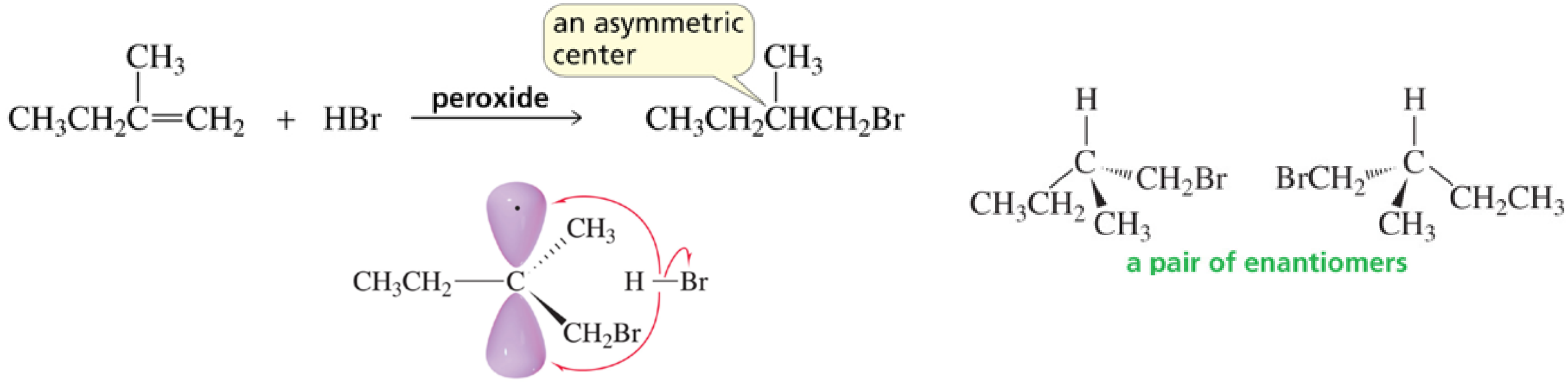
  - If not, no chain rxn, and goes to ionic, even with a peroxide.

Stereochemistry

- Radical substit'n and add'n rxns are not stereospecific.
  → Racemates form.



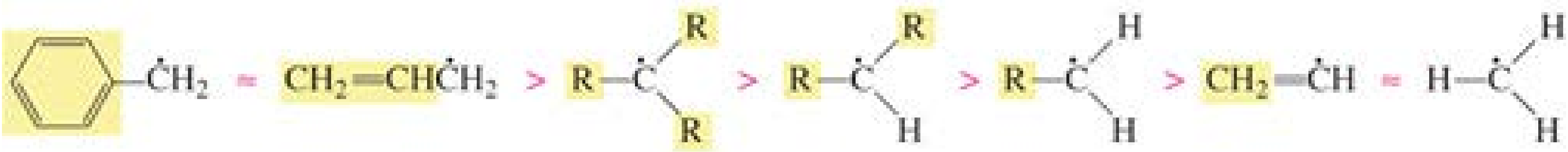
$$CH_3CH_2CH_2CH_3 + Br_2 \xrightarrow{h\nu} CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 + HBr$$



$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 + HBr \xrightarrow{\text{peroxide}} CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br$$

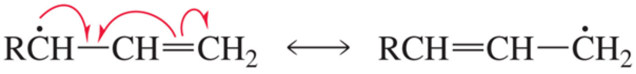
Allylic and benzylic

- A&B radicals are very stable.

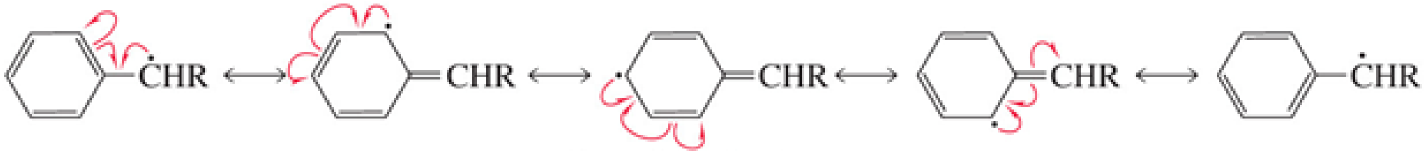


$$C_6H_5\dot{C}H_2 = CH_2{=}CH\dot{C}H_2 > R_3\dot{C} > R_2\dot{C}H > R\dot{C}H_2 > CH_2{=}\dot{C}H = H_3\dot{C}$$

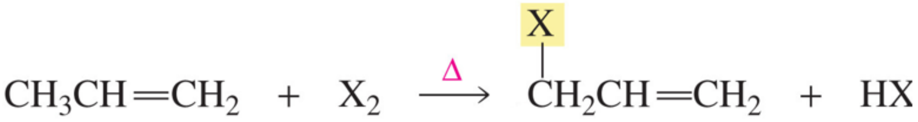
  - 1° but more stable than 3° due to



$$R\dot{C}H{-}CH{=}CH_2 \longleftrightarrow RCH{=}CH{-}\dot{C}H_2$$

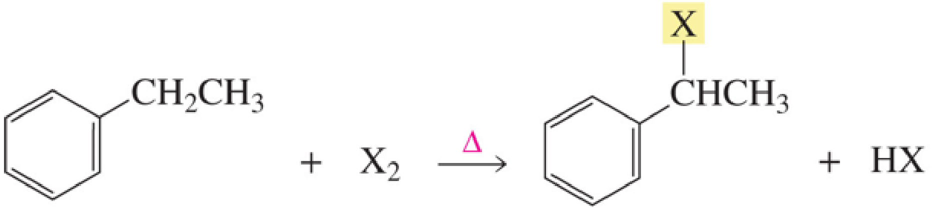


- A&B positions are reactive.



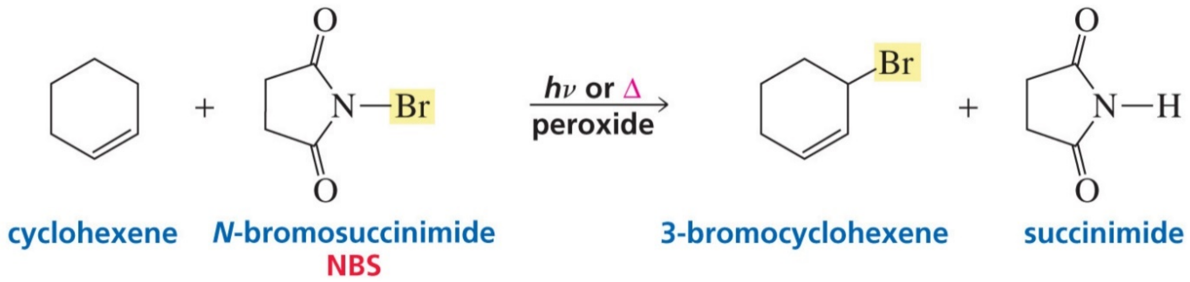
$$CH_3CH{=}CH_2 + X_2 \xrightarrow{\Delta} \overset{X}{C}H_2CH{=}CH_2 + HX$$

Substit’n on allylic competes w/ add’n to =. To favor substit’n use NBS



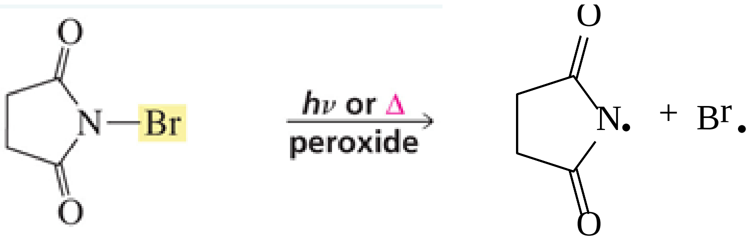
(X = Cl or Br)

Using NBS for bromin’n of allylic C



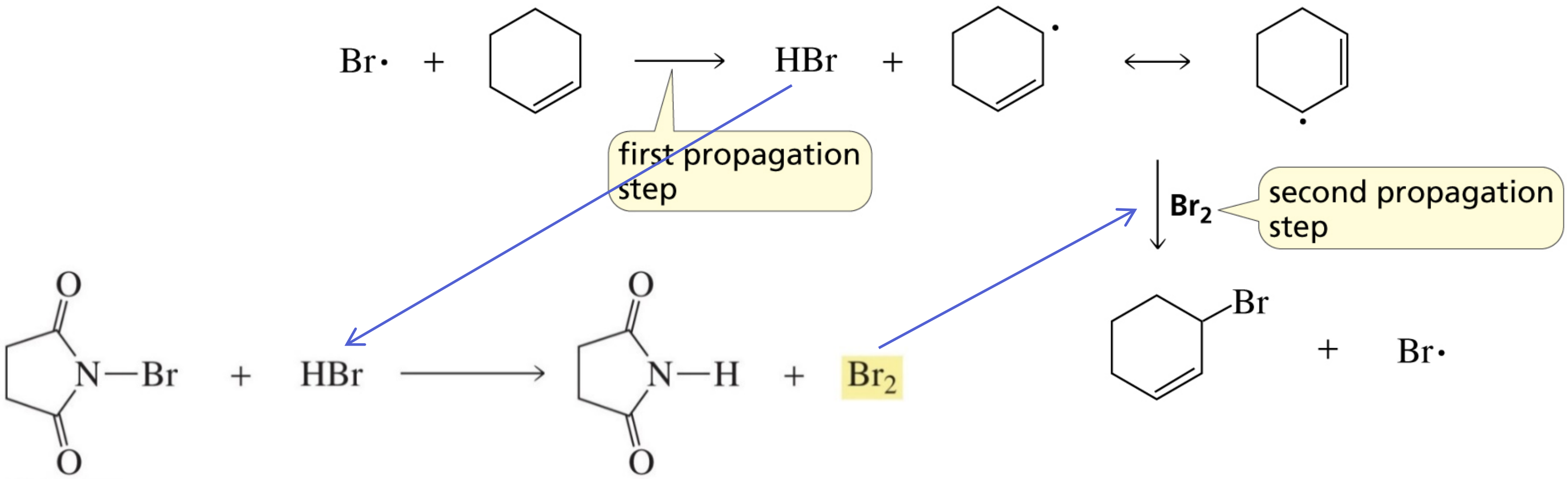
not Br-cx

- mechanism
  - initiation

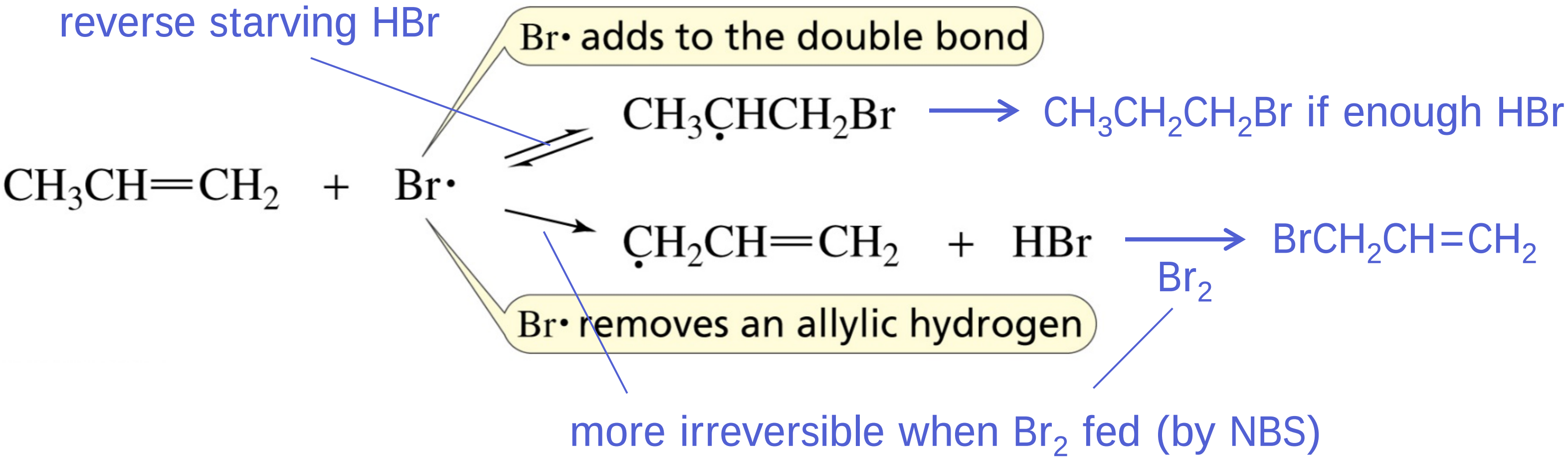


HBr and Br_2 generated during rxn ~ low conc’n
If in high conc’n? add’n

  - propagation ~ 2 steps



- competition betw substit’n and addition



reverse starving HBr

Br• adds to the double bond

$$CH_3CH{=}CH_2 + Br\cdot \rightleftharpoons CH_3\underset{\bullet}{C}HCH_2Br \longrightarrow CH_3CH_2CH_2Br$$

$CH_3CH_2CH_2Br$ if enough HBr

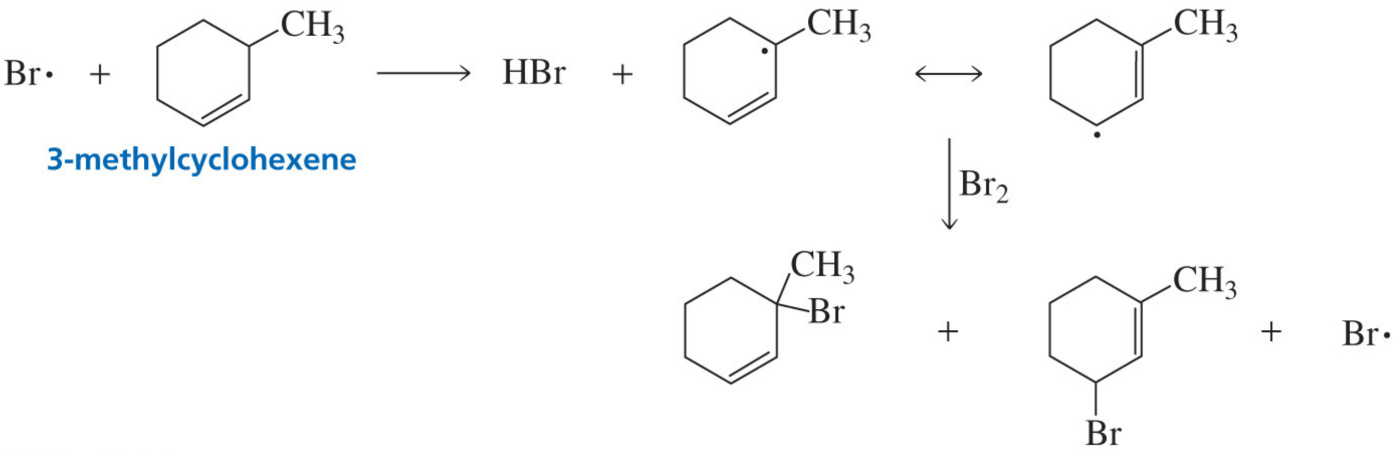
$$CH_3CH{=}CH_2 + Br\cdot \longrightarrow \underset{\bullet}{C}H_2CH{=}CH_2 + HBr \xrightarrow[Br_2]{} BrCH_2CH{=}CH_2$$

Br• removes an allylic hydrogen

more irreversible when Br_2 fed (by NBS)

- NBS enables the substitution on allylic position by keeping the conc’n of HBr low.

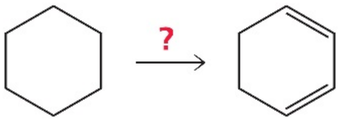
- Only 1 product, if 1-resonance radical.
- If not

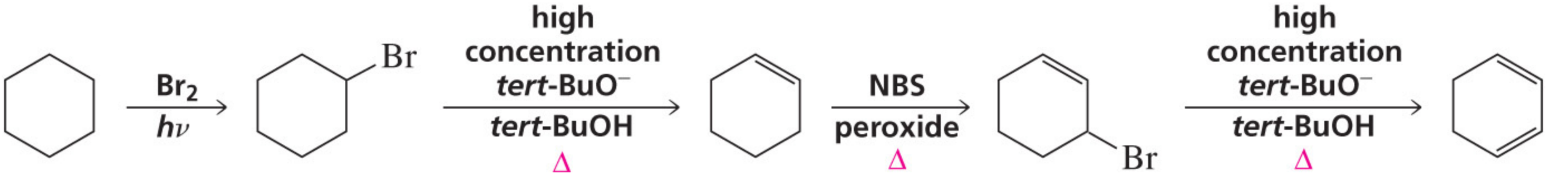


- Prob 20 ~ # of stereoisomers?
  - Look up Chapter 4, stereochemistry
- Prob 20b ~ kinetic and thermodynamic control
  - Look up §8.13, addition to conj diene

Synthetic strategy

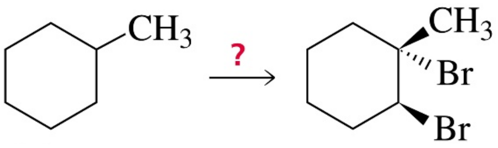
- Ex 2

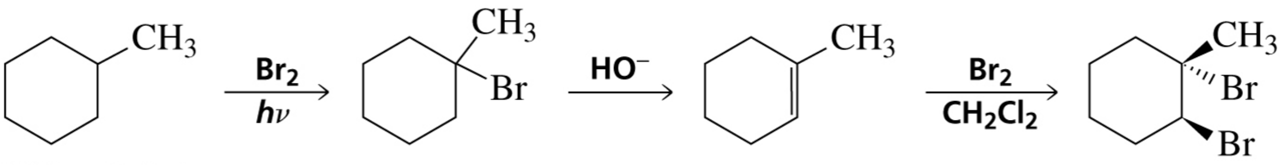




E2 avoiding S_N

- Ex 3

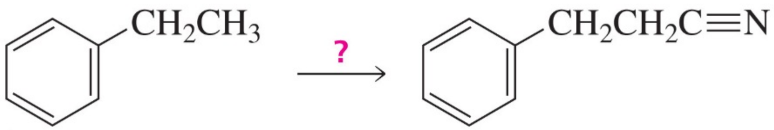




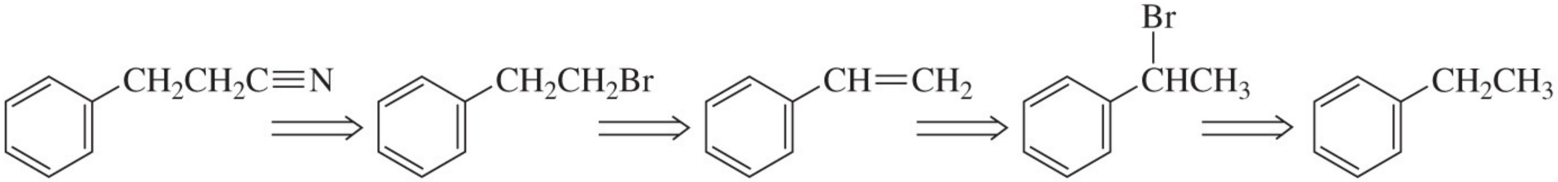
small B: → Zaitsev

anti addition

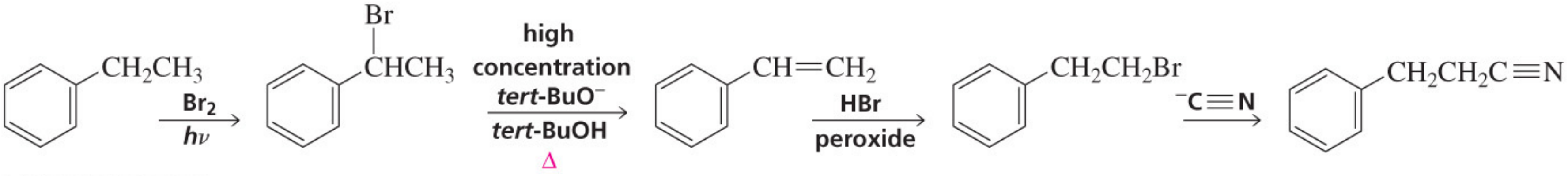
- Ex 4



  - retrosynthetic analysis

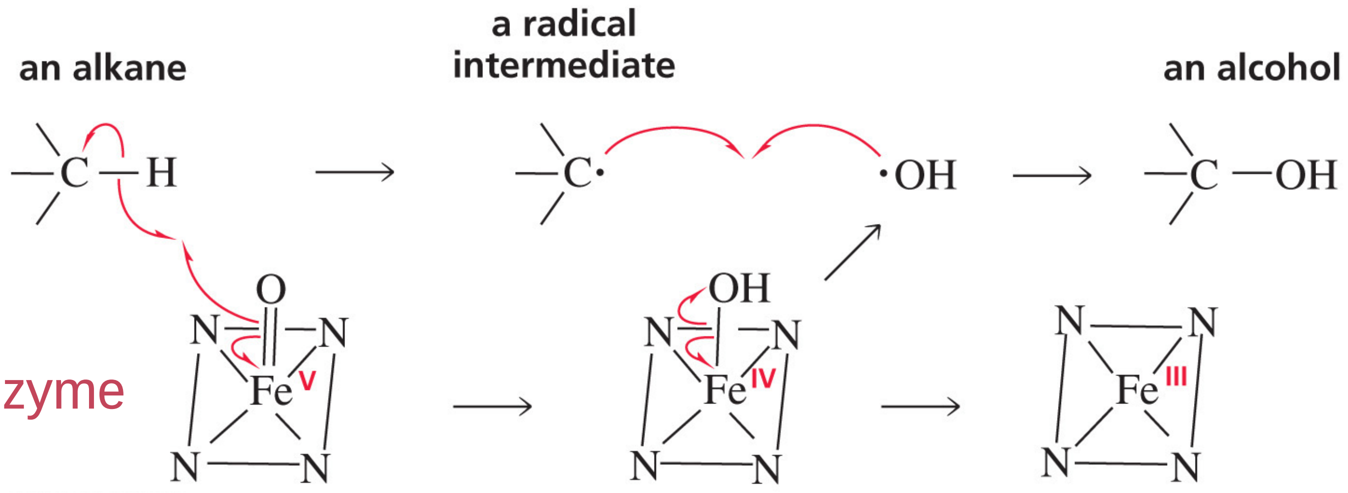


  - synthesis



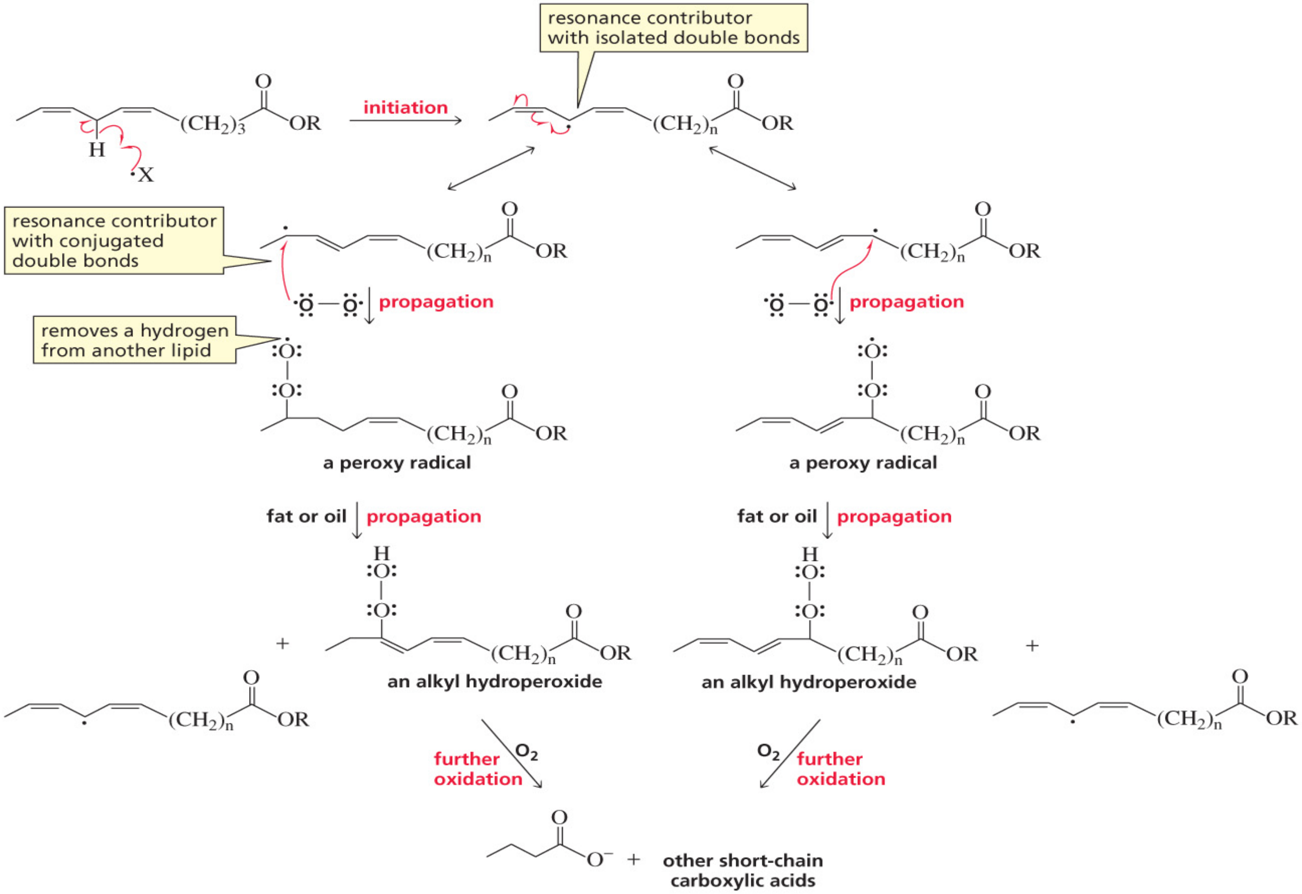
Radical rxns in biological systems

- at the active site of enzyme
  - radical formed by the interaction of alkane with metal ion (of enzyme) (not by heat or light)
  - example: Liver detoxicates RH to ROH (soluble, excretable)



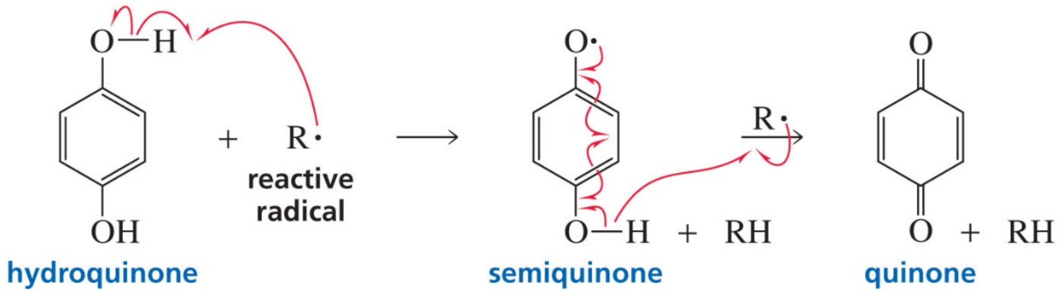
enzyme

- (radical) oxidation of oils and fats by O_2
  - similar to ether case
    - stable radical → peroxy radical → chain rxn to other fat molecule

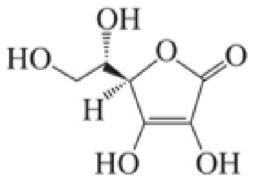


Radical inhibitor

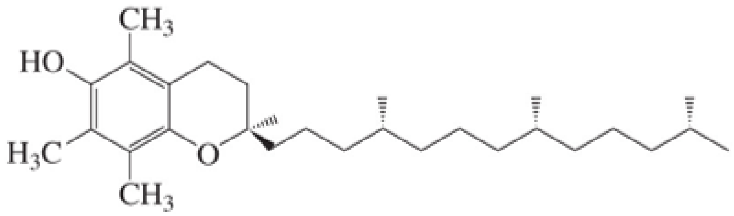
- stops [destroy] radical



- in living cells and cell membranes
  - (radical) oxidation is ‘aging’
  - anti-aging ~ inhibiting radicals in cells
    - vitamin C ~ water-soluble radical inhibitor [antioxidants] in cells
    - vitamin E ~ fat-soluble ~ works in cell membrane



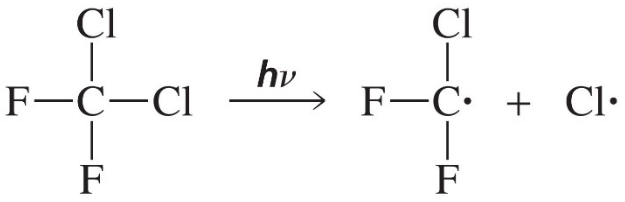
vitamin C
ascorbic acid



vitamin E
α-tocopherol

Depletion of ozone in stratosphere

- by CFCs



$$\mathrm{F{-}\underset{\displaystyle F}{\overset{\displaystyle Cl}{C}}{-}Cl} \xrightarrow{h\nu} \mathrm{F{-}\underset{\displaystyle F}{\overset{\displaystyle Cl}{C}}\cdot} + \mathrm{Cl}\cdot$$

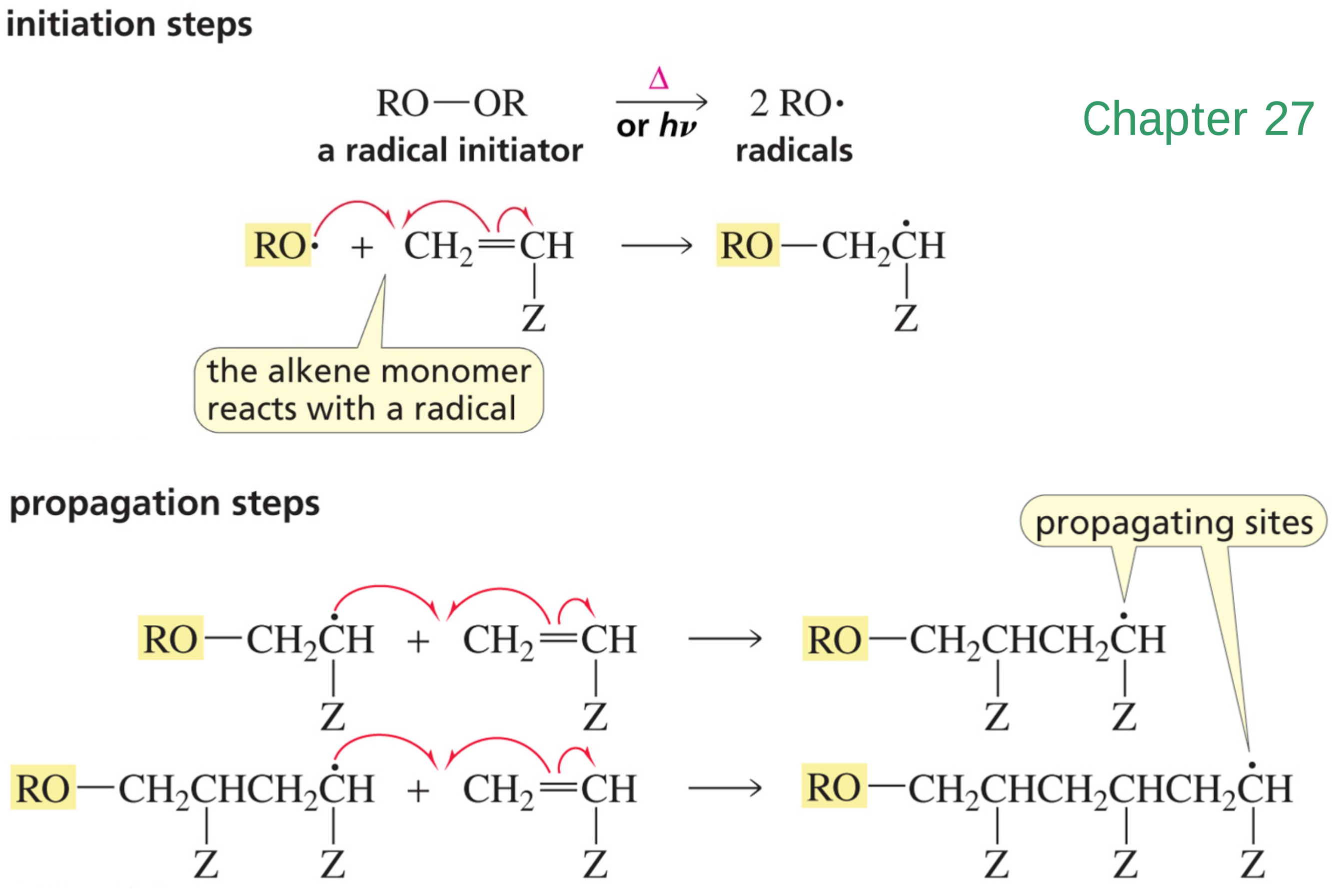
- a radical reaction ~ chain rxn

$$\mathrm{Cl}\cdot + \mathrm{O_3} \longrightarrow \mathrm{ClO}\cdot + \mathrm{O_2}$$

$$\mathrm{ClO}\cdot + \mathrm{O_3} \longrightarrow \cdot\mathrm{ClO_2} + \mathrm{O_2}$$

$$\cdot\mathrm{ClO_2} \longrightarrow \mathrm{Cl}\cdot + \mathrm{O_2}$$

Radical chain polymerization



Chapter 27

Z = Cl ~ PVC
Z = Ph ~ PS
Z = COOR ~ acrylates

Summary

- halogenation substitution (to alkane)
  - Cl and Br
  - reactivity-selectivity
- ether explosion through peroxide
- addition (to =)
  - with peroxide
  - HBr only
- benzylic, allylic
- allylic substitution with NBS
- radical initiator and inhibitor