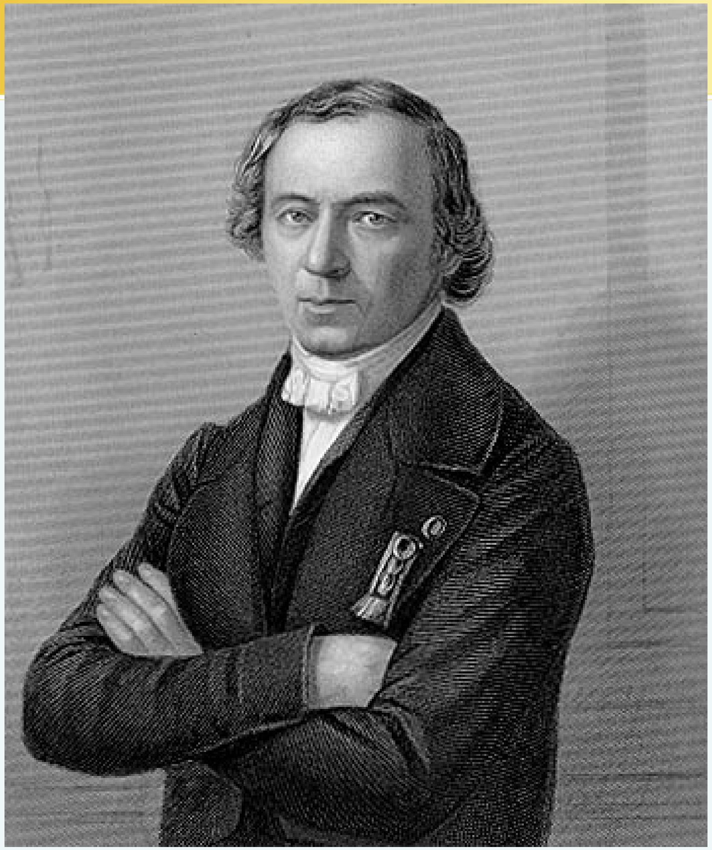
Radical Reactions

Substitution Theory



J. B. Dumas
(1800 -1884)

1838 - chlorination of acetic acid

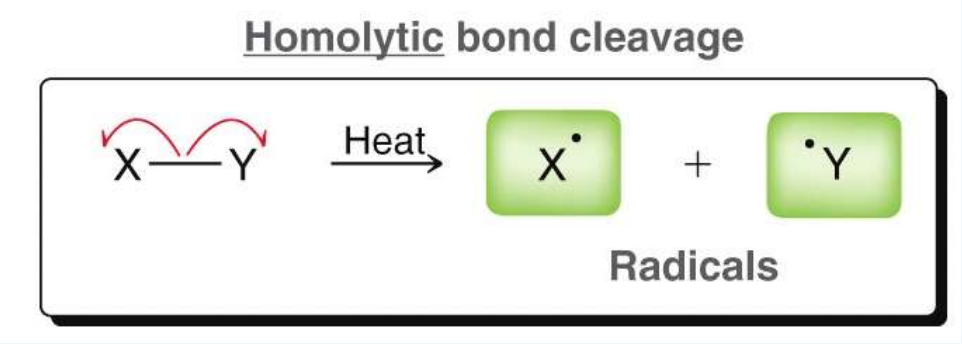
$\underline{C}_4H_4O_2 + Cl_6 = \underline{C}_4HCl_3O_2 + H_3Cl_3$

$\underline{C} = 6, O = 16$

$C_2H_4O_2 + 3Cl_2 = C_2HCl_3O_2 + 3HCl$

11.1 Free Radicals

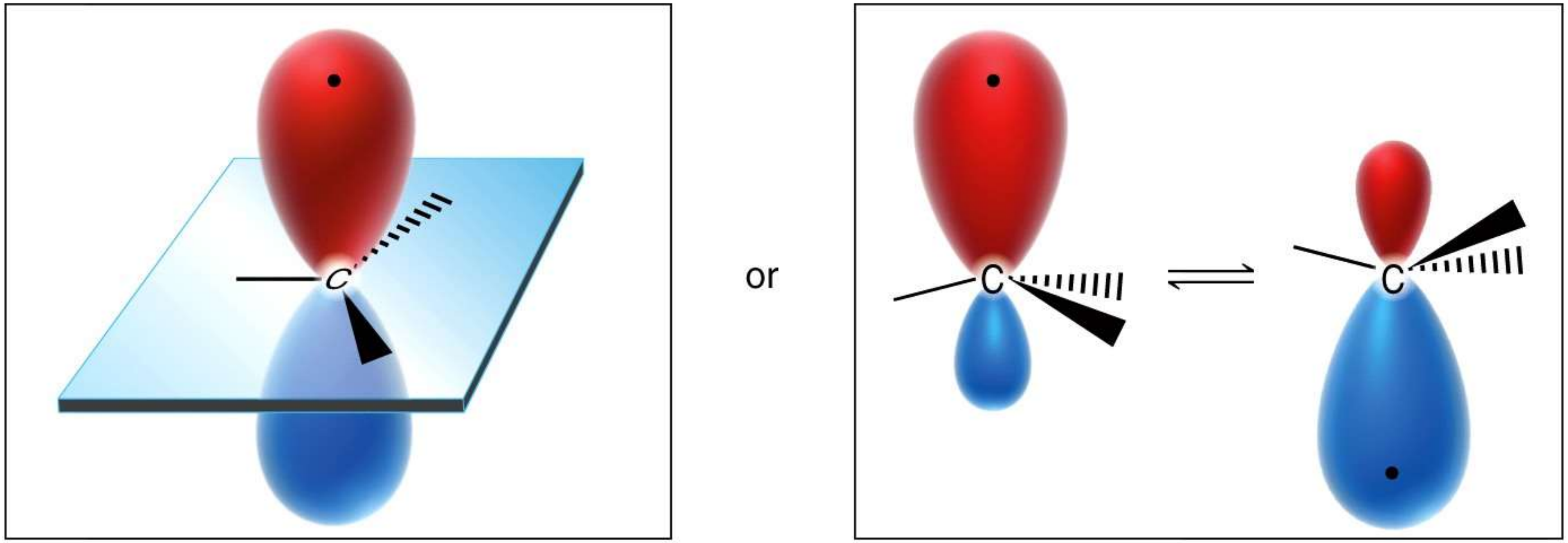
- Free radicals form when bonds break homolytically



- Note the single-barbed or fishhook arrow used to show the electron movement

11.1 Free Radicals

- Free radicals can be thought of as *sp*^{2} hybridized or quickly interconverting *sp*^{3} hybridized

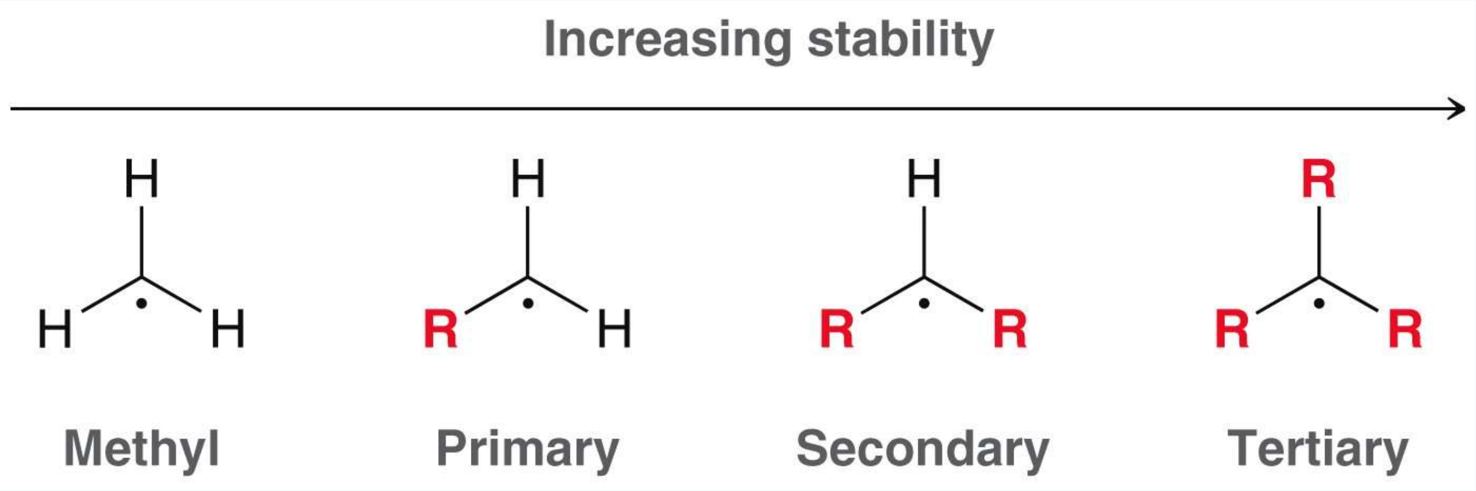


Trigonal planar
sp^2 hybridized

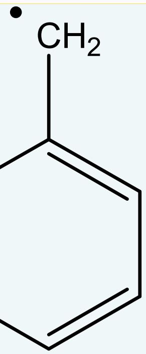
Shallow pyramid
(rapidly inverting)

11.1 Free Radical Stability

- Free radicals do not have a formal charge but are unstable because of an incomplete octet
- Groups that can push (donate) electrons toward the free radical will help to stabilize it. WHY? HOW?
- Consider hyperconjugation

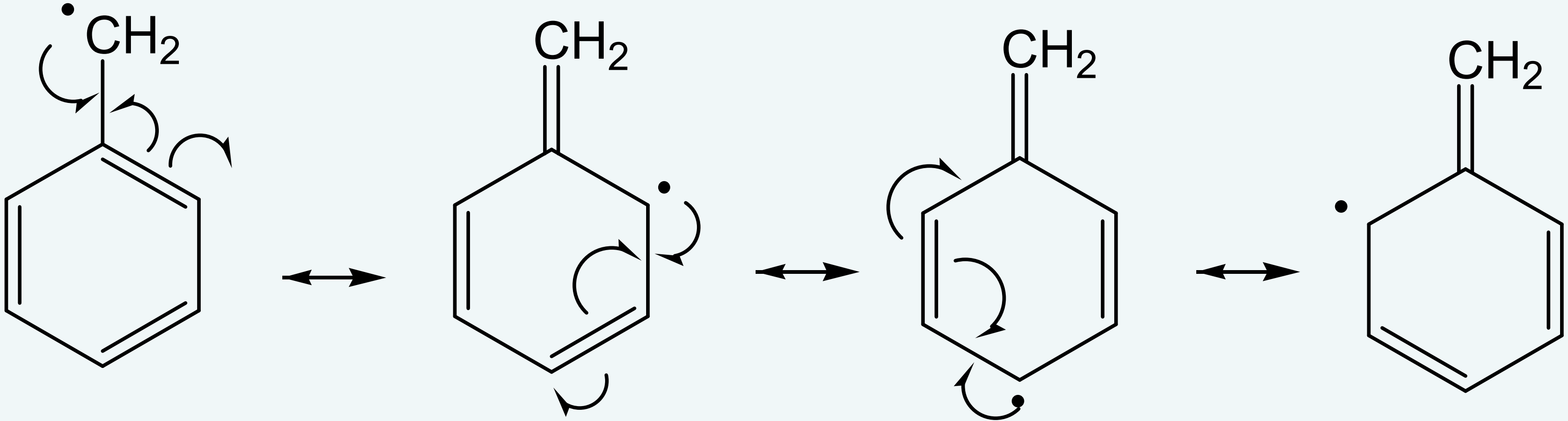


Benzylic radicals



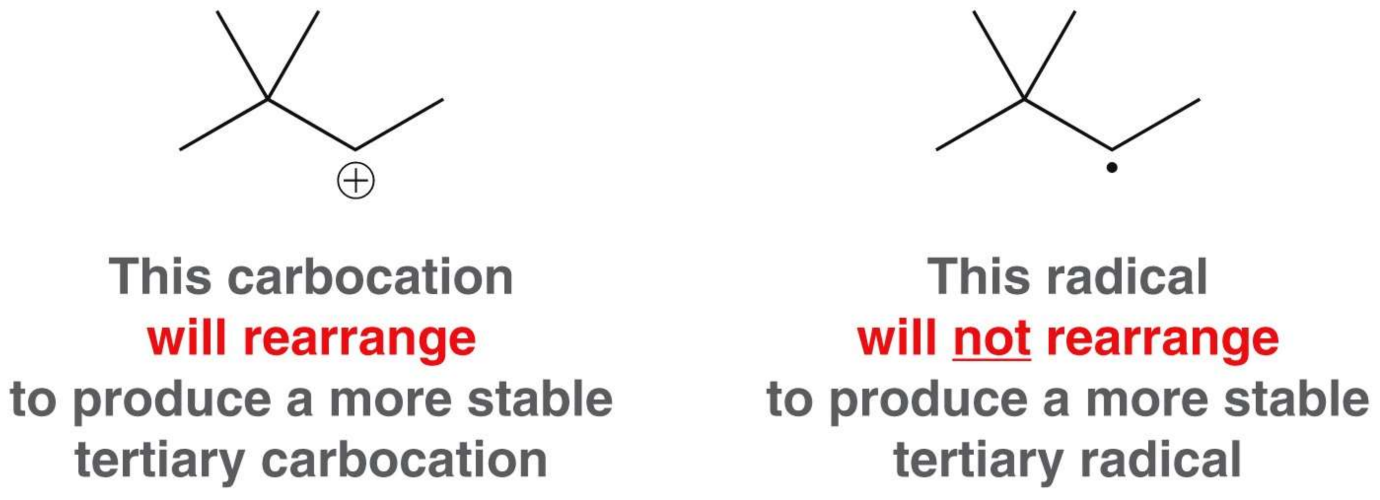
Benzylic radicals

More stable than aliphatic radicals
because of resonance stabilisation



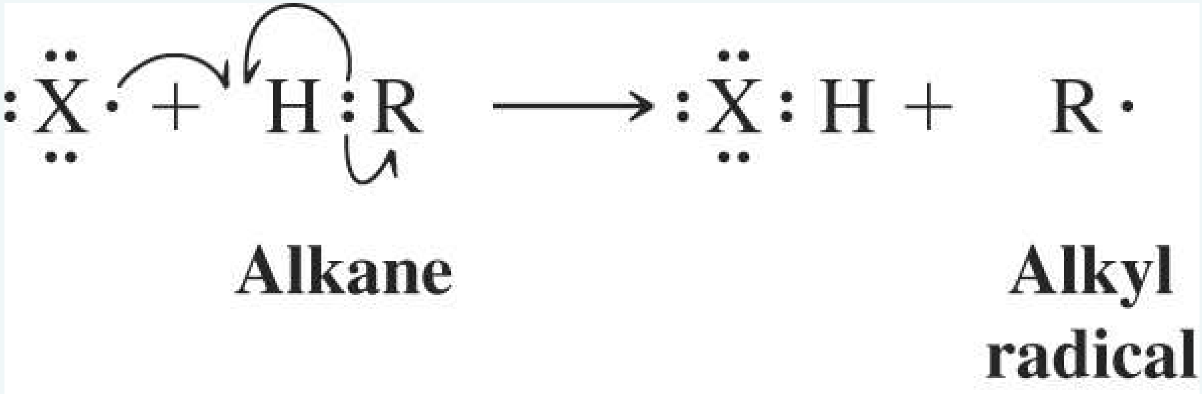
11.2 Radical Electron Movement

- Free radical electron movement is quite different from electron movement in ionic reactions
- For example, free radicals don't undergo rearrangement



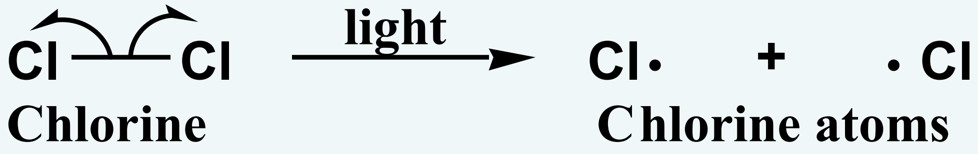
Reactions of Radicals

- Radicals tend to react in ways that lead to pairing of their unpaired electron
  - Hydrogen abstraction is one way a halogen radical can react to pair its unshared electron



Mecanismo

- Um mecanismo radicalar em cadeia
- **Radical:** qualquer espécie química que contém um ou mais elétrons desemparelhados
- Radicais são formados por clivagem homolítica de uma ligação



  - uma seta em forma de anzol é usada para mostrar a mudança na posição de um único elétron

Homolytic Bond Dissociation Energies

- Atoms have higher energy (are less stable) than the molecules they can form
  - The formation of covalent bonds is exothermic
- Breaking covalent bonds requires energy (*i.e.* is endothermic)

$$\mathrm{H{-}H} \longrightarrow \mathrm{H}\cdot + \mathrm{H}\cdot \qquad \Delta H^\circ = +436\ \mathrm{kJ\ mol^{-1}}$$

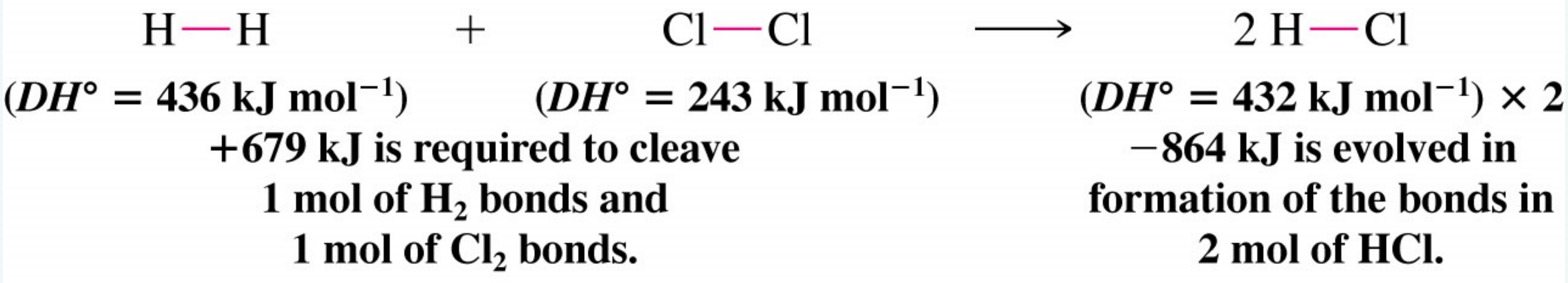
$$\mathrm{Cl{-}Cl} \longrightarrow \mathrm{Cl}\cdot + \mathrm{Cl}\cdot \qquad \Delta H^\circ = +243\ \mathrm{kJ\ mol^{-1}}$$

$$\underset{(DH^\circ = 436\ \mathrm{kJ\ mol^{-1}})}{\mathrm{H{-}H}} \qquad \underset{(DH^\circ = 243\ \mathrm{kJ\ mol^{-1}})}{\mathrm{Cl{-}Cl}}$$

- The homolytic bond dissociation energy is abbreviated *DH^o*

Homolytic Bond Dissociation Energies and Heats of Reaction

- Homolytic Bond Dissociation energies can be used to calculate the enthalpy change (ΔH^o) for a reaction
- DH^o is positive for bond breaking and negative for bond forming
- Example
  - This reaction below is highly exothermic since ΔH^o is a large and negative
  - ΔH^o is not dependant on the mechanism; only the initial and final states of the molecules are considered in determining ΔH^o



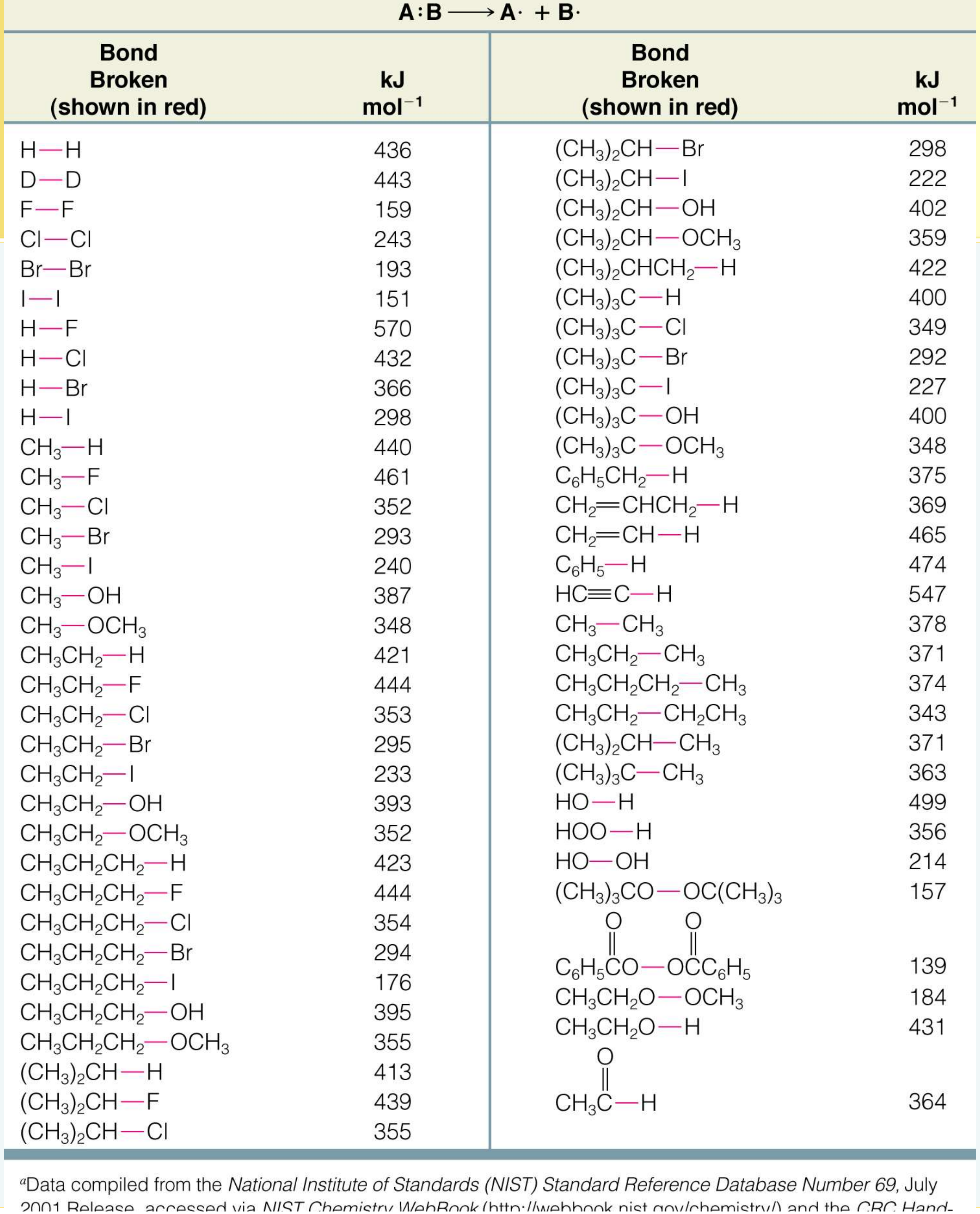
$$\mathrm{H{-}H} \quad + \quad \mathrm{Cl{-}Cl} \longrightarrow 2\ \mathrm{H{-}Cl}$$

(DH° = 436 kJ mol^{-1}) (DH° = 243 kJ mol^{-1}) (DH° = 432 kJ mol^{-1}) × 2

+679 kJ is required to cleave 1 mol of H_2 bonds and 1 mol of Cl_2 bonds.

−864 kJ is evolved in formation of the bonds in 2 mol of HCl.

$$\Delta H^\circ = (-864\ \mathrm{kJ} + 679\ \mathrm{kJ}) = -185\ \mathrm{kJ} \quad \text{for 2 mol HCl produced}$$



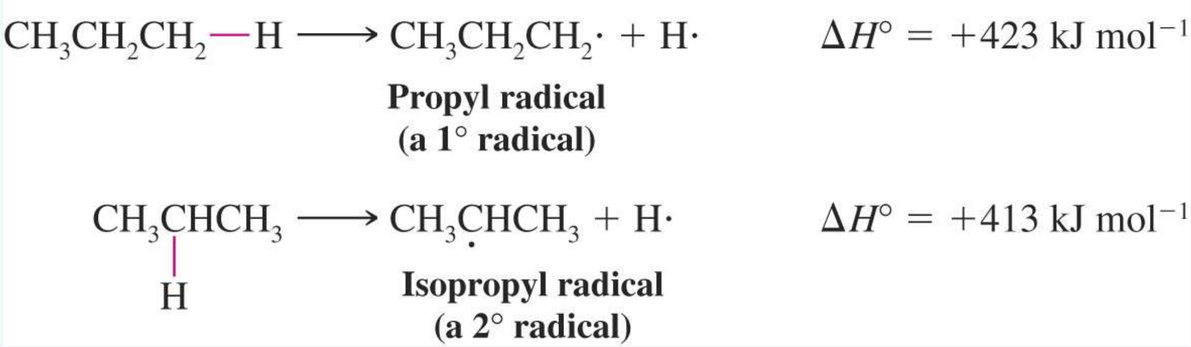
$\mathrm{A{:}B \longrightarrow A\cdot + B\cdot}$

Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}
$\mathrm{H{-}H}$	436	$\mathrm{(CH_3)_2CH{-}Br}$	298
$\mathrm{D{-}D}$	443	$\mathrm{(CH_3)_2CH{-}I}$	222
$\mathrm{F{-}F}$	159	$\mathrm{(CH_3)_2CH{-}OH}$	402
$\mathrm{Cl{-}Cl}$	243	$\mathrm{(CH_3)_2CH{-}OCH_3}$	359
$\mathrm{Br{-}Br}$	193	$\mathrm{(CH_3)_2CHCH_2{-}H}$	422
$\mathrm{I{-}I}$	151	$\mathrm{(CH_3)_3C{-}H}$	400
$\mathrm{H{-}F}$	570	$\mathrm{(CH_3)_3C{-}Cl}$	349
$\mathrm{H{-}Cl}$	432	$\mathrm{(CH_3)_3C{-}Br}$	292
$\mathrm{H{-}Br}$	366	$\mathrm{(CH_3)_3C{-}I}$	227
$\mathrm{H{-}I}$	298	$\mathrm{(CH_3)_3C{-}OH}$	400
$\mathrm{CH_3{-}H}$	440	$\mathrm{(CH_3)_3C{-}OCH_3}$	348
$\mathrm{CH_3{-}F}$	461	$\mathrm{C_6H_5CH_2{-}H}$	375
$\mathrm{CH_3{-}Cl}$	352	$\mathrm{CH_2{=}CHCH_2{-}H}$	369
$\mathrm{CH_3{-}Br}$	293	$\mathrm{CH_2{=}CH{-}H}$	465
$\mathrm{CH_3{-}I}$	240	$\mathrm{C_6H_5{-}H}$	474
$\mathrm{CH_3{-}OH}$	387	$\mathrm{HC{\equiv}C{-}H}$	547
$\mathrm{CH_3{-}OCH_3}$	348	$\mathrm{CH_3{-}CH_3}$	378
$\mathrm{CH_3CH_2{-}H}$	421	$\mathrm{CH_3CH_2{-}CH_3}$	371
$\mathrm{CH_3CH_2{-}F}$	444	$\mathrm{CH_3CH_2CH_2{-}CH_3}$	374
$\mathrm{CH_3CH_2{-}Cl}$	353	$\mathrm{CH_3CH_2{-}CH_2CH_3}$	343
$\mathrm{CH_3CH_2{-}Br}$	295	$\mathrm{(CH_3)_2CH{-}CH_3}$	371
$\mathrm{CH_3CH_2{-}I}$	233	$\mathrm{(CH_3)_3C{-}CH_3}$	363
$\mathrm{CH_3CH_2{-}OH}$	393	$\mathrm{HO{-}H}$	499
$\mathrm{CH_3CH_2{-}OCH_3}$	352	$\mathrm{HOO{-}H}$	356
$\mathrm{CH_3CH_2CH_2{-}H}$	423	$\mathrm{HO{-}OH}$	214
$\mathrm{CH_3CH_2CH_2{-}F}$	444	$\mathrm{(CH_3)_3CO{-}OC(CH_3)_3}$	157
$\mathrm{CH_3CH_2CH_2{-}Cl}$	354	$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}O{-}O\overset{O}{\overset{\|}{C}}C_6H_5}$	139
$\mathrm{CH_3CH_2CH_2{-}Br}$	294	$\mathrm{CH_3CH_2O{-}OCH_3}$	184
$\mathrm{CH_3CH_2CH_2{-}I}$	176	$\mathrm{CH_3CH_2O{-}H}$	431
$\mathrm{CH_3CH_2CH_2{-}OH}$	395	$\mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}H}$	364
$\mathrm{CH_3CH_2CH_2{-}OCH_3}$	355		
$\mathrm{(CH_3)_2CH{-}H}$	413		
$\mathrm{(CH_3)_2CH{-}F}$	439		
$\mathrm{(CH_3)_2CH{-}Cl}$	355		

[a]Data compiled from the *National Institute of Standards (NIST) Standard Reference Database Number 69*, July 2001 Release, accessed via *NIST Chemistry WebBook* (http://webbook.nist.gov/chemistry/) and the *CRC Hand-*

Homolytic Bond Dissociation Energies and the Relative Stabilities of Radicals

- The formation of different radicals from the same starting compound offers a way to estimate relative radical stabilities
  - The propyl radical is less stable than the isopropyl radical



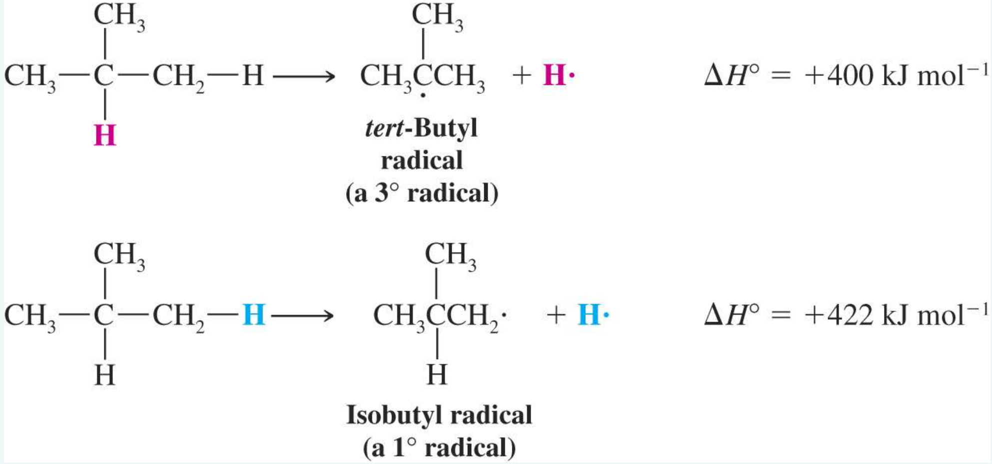
$$CH_3CH_2CH_2{-}H \longrightarrow CH_3CH_2CH_2\cdot + H\cdot \qquad \Delta H^\circ = +423\ \text{kJ mol}^{-1}$$

Propyl radical
(a 1° radical)

$$\underset{\displaystyle H}{CH_3\overset{}{C}HCH_3} \longrightarrow CH_3\underset{\bullet}{C}HCH_3 + H\cdot \qquad \Delta H^\circ = +413\ \text{kJ mol}^{-1}$$

Isopropyl radical
(a 2° radical)

Likewise, the *tert*-butyl radical is more stable than the isobutyl radical



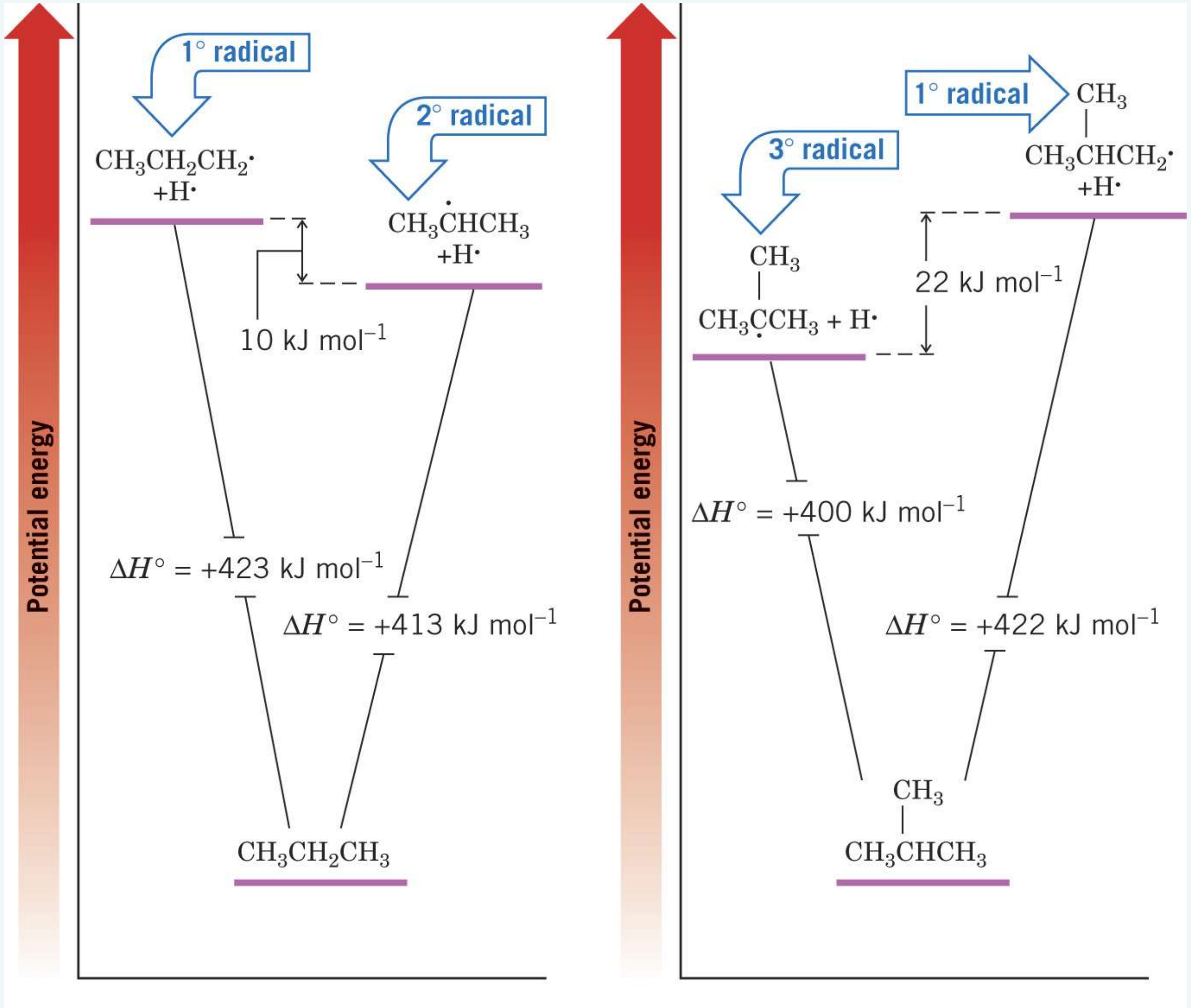
$$CH_3{-}\underset{\displaystyle H}{\overset{\displaystyle CH_3}{C}}{-}CH_2{-}H \longrightarrow CH_3\underset{\bullet}{\overset{\displaystyle CH_3}{C}}CH_3 + H\cdot \qquad \Delta H^\circ = +400\ \text{kJ mol}^{-1}$$

***tert*-Butyl**
radical
(a 3° radical)

$$CH_3{-}\underset{\displaystyle H}{\overset{\displaystyle CH_3}{C}}{-}CH_2{-}H \longrightarrow CH_3\underset{\displaystyle H}{\overset{\displaystyle CH_3}{C}}CH_2\cdot + H\cdot \qquad \Delta H^\circ = +422\ \text{kJ mol}^{-1}$$

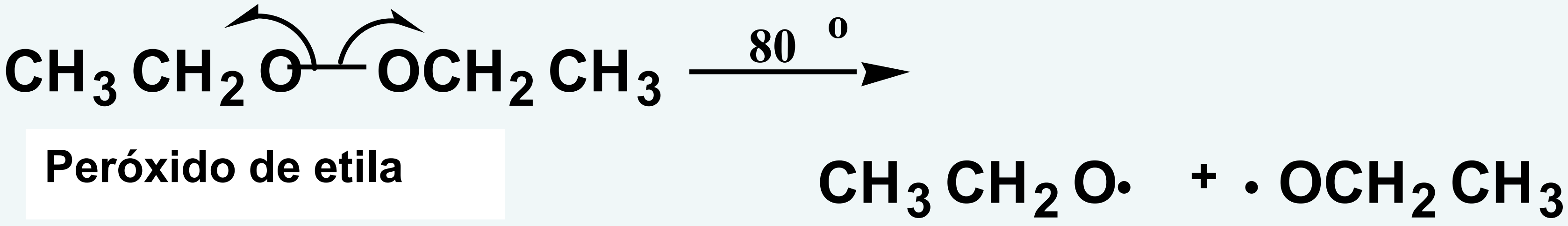
Isobutyl radical
(a 1° radical)

The energy diagrams for these reactions are shown below



(*a*) (*b*)

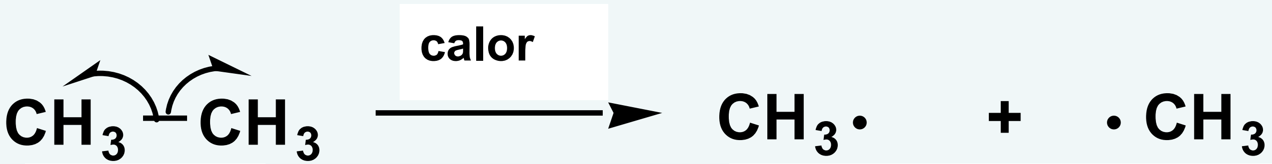
Formação de Radicais



$$CH_3CH_2O{-}OCH_2CH_3 \xrightarrow{80^{o}} CH_3CH_2O\cdot + \cdot OCH_2CH_3$$

Peróxido de etila

Radicais etóxido



$$CH_3{-}CH_3 \xrightarrow{\text{calor}} CH_3\cdot + \cdot CH_3$$

etano

Radicais metílicos

- A ordem de estabilidade dos radicais alquílicos é 3° > 2° > 1° > metila

Mecanismo

- Iniciação da cadeia: passo em uma reação radicalar em cadeia caracterizada pela formação de radicais de compostos não radicalares

Iniciação da cadeia

1. $Cl_2 \xrightarrow[\text{ou luz}]{\text{calor}} Cl\cdot + \cdot Cl$

Mecanismo

- Propagação da cadeia: passo em uma reação radicalar em cadeia caracterizada pela reação de um radical e uma molécula para formar um novo radical

Propagação da cadeia

2. $CH_3CH_3 + Cl\cdot \longrightarrow CH_3CH_2\cdot + HCl$

3. $CH_3CH_2\cdot + Cl_2 \longrightarrow CH_3CH_2Cl + Cl\cdot$

- Comprimento da cadeia, n: o número de vezes no ciclo que o passo de propagação repete-se numa reação em cadeia

Mecanismo

- Terminação da cadeia - passo em uma reação radicalar em cadeia que envolve destruição de radicais

Terminação da cadeia

4. $2\ CH_3CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_3$

5. $CH_3CH_2\cdot + \cdot Cl \longrightarrow CH_3CH_2Cl$

6. $Cl\cdot + \cdot Cl \longrightarrow Cl_2$

Propagação da cadeia

ΔH° (kcal/mol)

Passo 2:

$$\underset{+100}{CH_3CH_3} + Cl\cdot \longrightarrow CH_3CH_2\cdot + \underset{-103}{HCl} \qquad -3$$

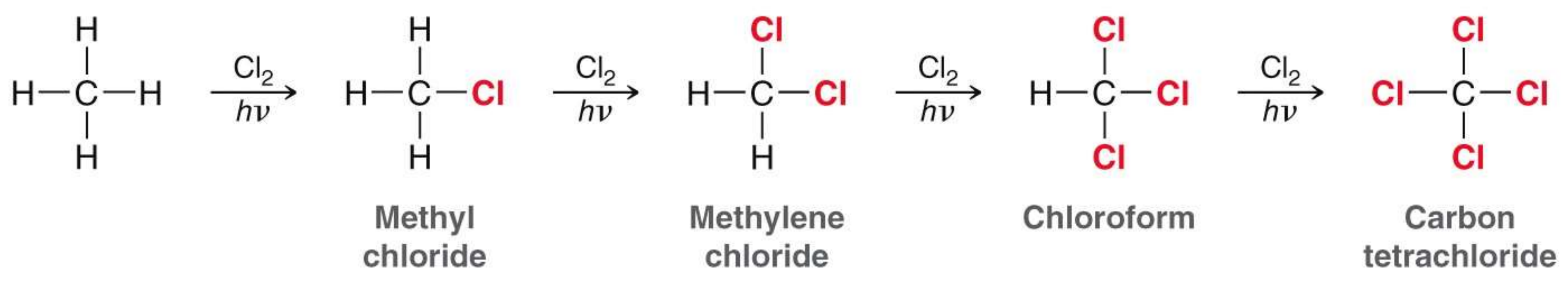
Passo 3:

$$CH_3CH_2\cdot + \underset{+59}{Cl_2} \longrightarrow \underset{-80}{CH_3CH_2Cl} + Cl\cdot \qquad -21$$

$$CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl \qquad -24$$

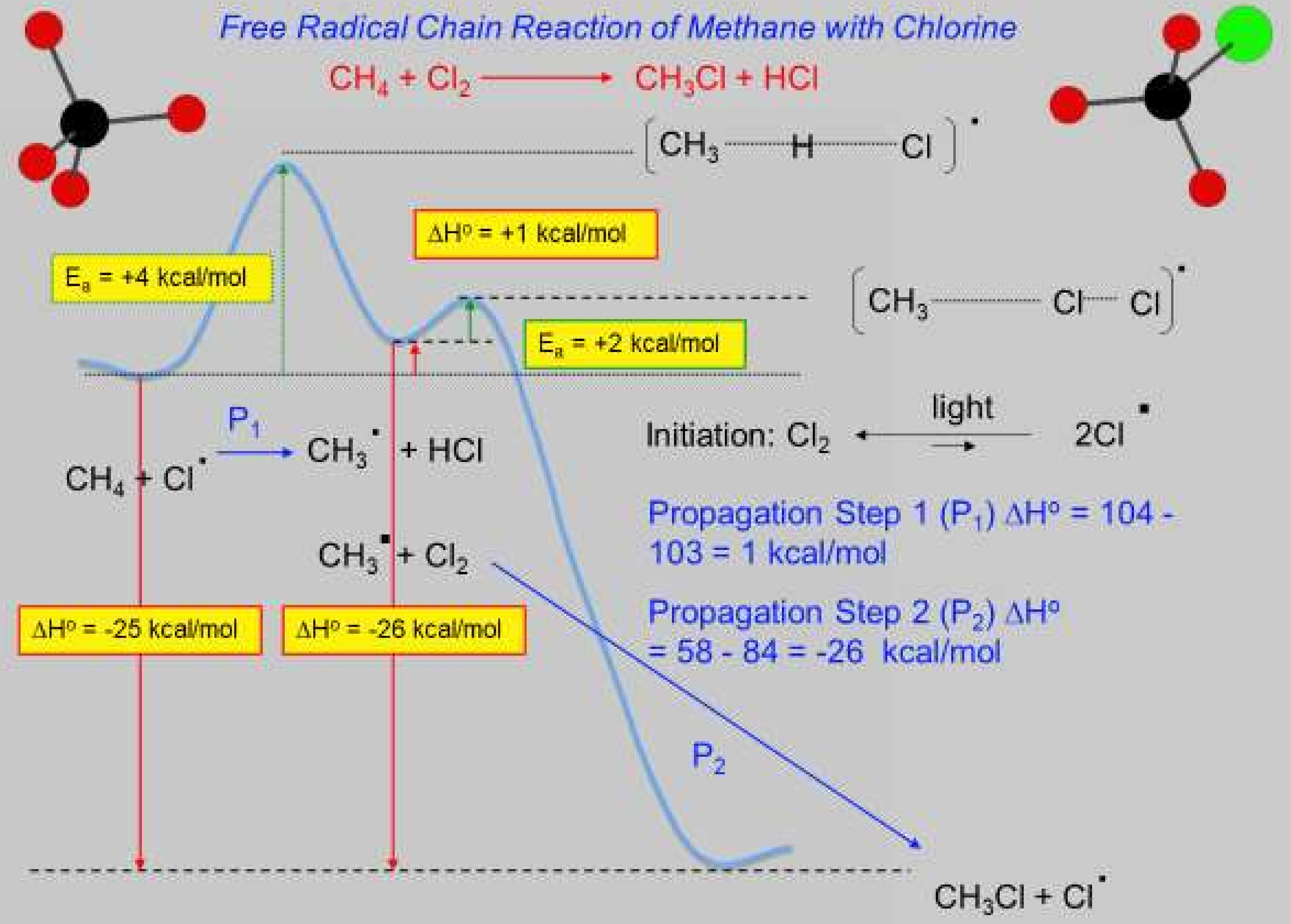
11.3 Chlorination of Methane

- Reactions that have self-sustaining propagation steps are called **chain reactions**
- **Chain reaction:** the products from one step are reactants for a different step in the mechanism
- Polychlorination is difficult to prevent, especially when an excess of Cl_2 is present.



Free Radical Chain Reaction of Methane with Chlorine

$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$



$[CH_3 \cdots H \cdots Cl]^{\bullet}$

ΔH^{o} = +1 kcal/mol

E_a = +4 kcal/mol

$[CH_3 \cdots Cl \cdots Cl]^{\bullet}$

E_a = +2 kcal/mol

$CH_4 + Cl^{\bullet} \xrightarrow{P_1} CH_3^{\bullet} + HCl$

Initiation: $Cl_2 \underset{\longrightarrow}{\overset{\text{light}}{\longleftarrow}} 2Cl^{\bullet}$

Propagation Step 1 (P_1) ΔH^{o} = 104 - 103 = 1 kcal/mol

$CH_3^{\bullet} + Cl_2 \xrightarrow{P_2} CH_3Cl + Cl^{\bullet}$

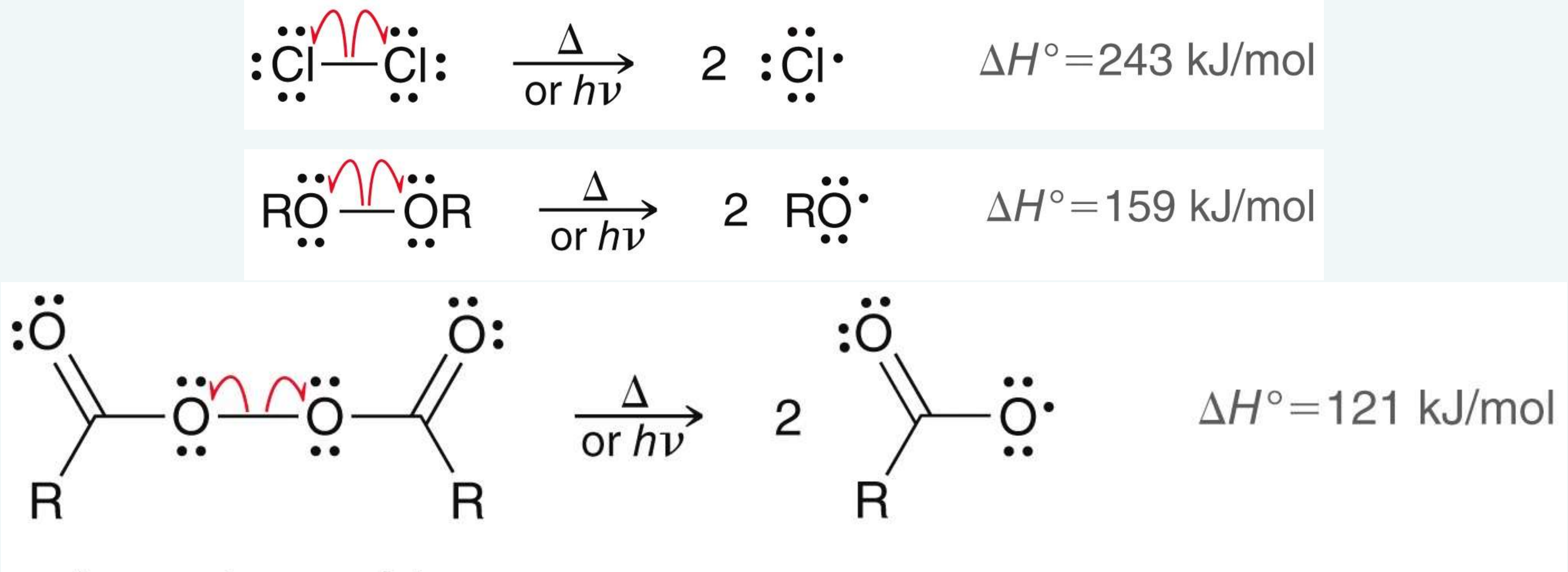
Propagation Step 2 (P_2) ΔH^{o} = 58 - 84 = -26 kcal/mol

ΔH^{o} = -25 kcal/mol

ΔH^{o} = -26 kcal/mol

11.3 Radical Initiators

- An initiator starts a free radical chain reaction

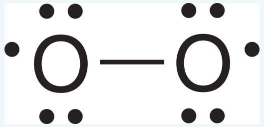


An acyl peroxide

- Which initiator above initiates reactions most readily? WHY?

11.3 Radical Inhibitors

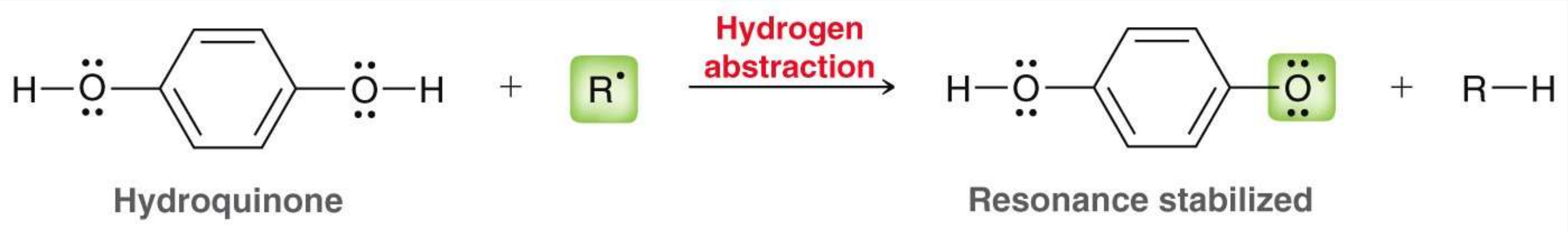
- Inhibitors act in a reaction to scavenge free radicals to stop chain reaction processes
- Oxygen molecules can exist in the form of a diradical, which reacts readily with other radicals. Use arrows to show the process

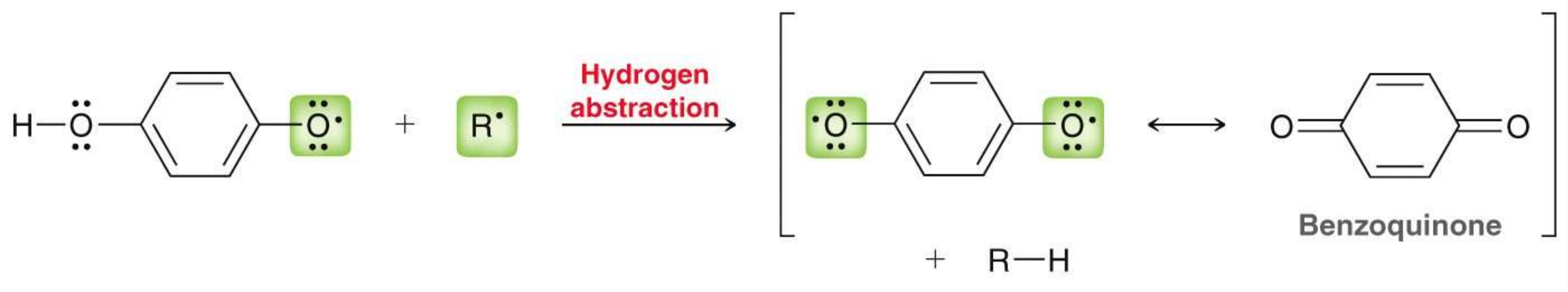


- How can reaction conditions be modified to stop oxygen from inhibiting a desired chain reaction?

11.3 Radical Inhibitors

- Hydroquinone is also often used as a radical inhibitor





Reactivity–Selectivity Principle

- The very reactive chlorine atom will have lower selectivity and attack pretty much any hydrogen available on an alkane
- The less reactive bromine atom will be more selective and tends to react preferentially with the easy targets, i.e. tertiary hydrogens

11.5 Halogenation Regioselectivity

- Which process is least regioselective?

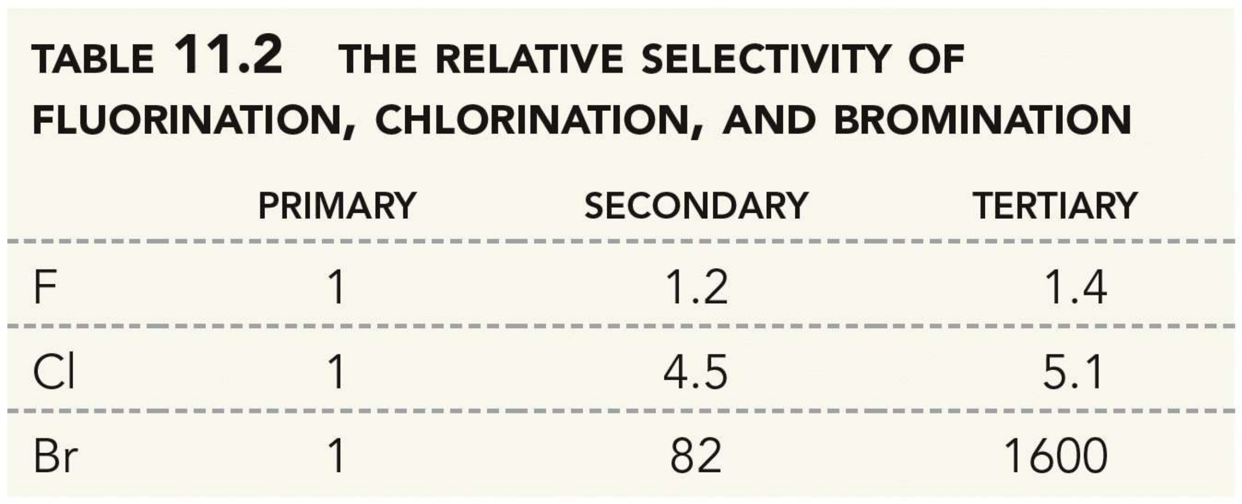
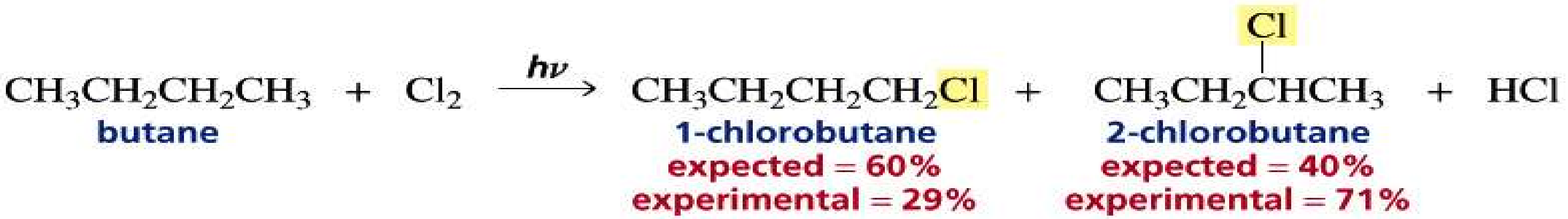


TABLE 11.2 THE RELATIVE SELECTIVITY OF FLUORINATION, CHLORINATION, AND BROMINATION

	PRIMARY	SECONDARY	TERTIARY
F	1	1.2	1.4
Cl	1	4.5	5.1
Br	1	82	1600

Fatores que determinam a distribuição dos produtos…

A etapa determinante da velocidade de toda a reação é a abstração do hidrogênio



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

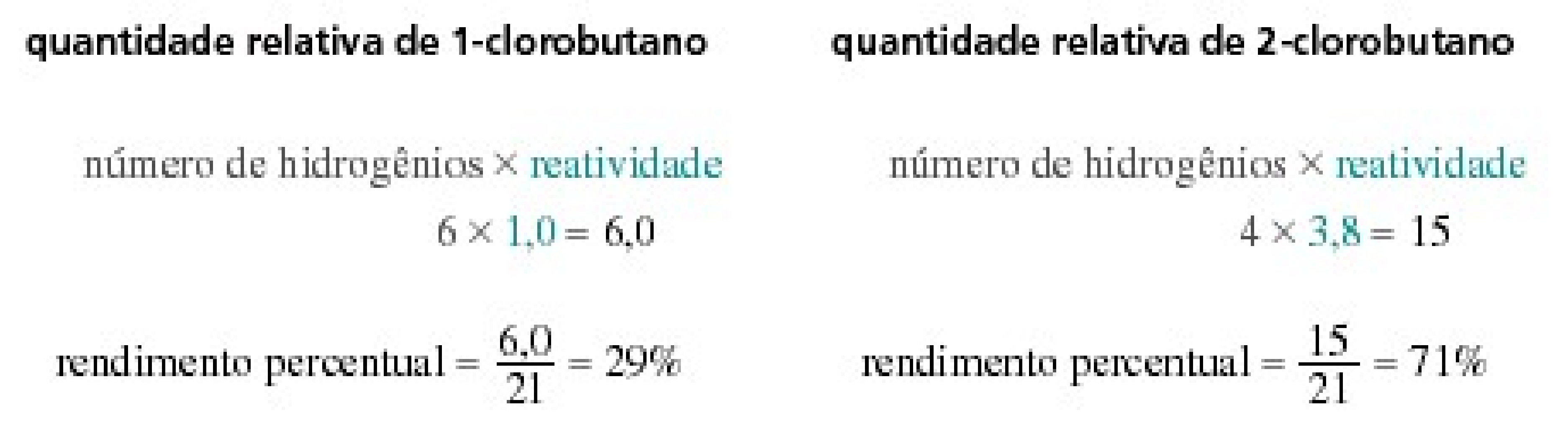
Regioselectivity

Na determinação das quantidades relativas dos produtos obtidos, tanto a *probabilidade* quanto a *reatividade* devem ser consideradas.

Probabilidade: o número de hidrogênios que podem ser abstraídos que levará a formação de um determinado produto.

Reatividade: a velocidade relativa na qual um determinado hidrogênio é abstraído.

Regioselectivity



quantidade relativa de 1-clorobutano

número de hidrogênios × reatividade

$6 \times 1{,}0 = 6{,}0$

$$\text{rendimento percentual} = \frac{6{,}0}{21} = 29\%$$

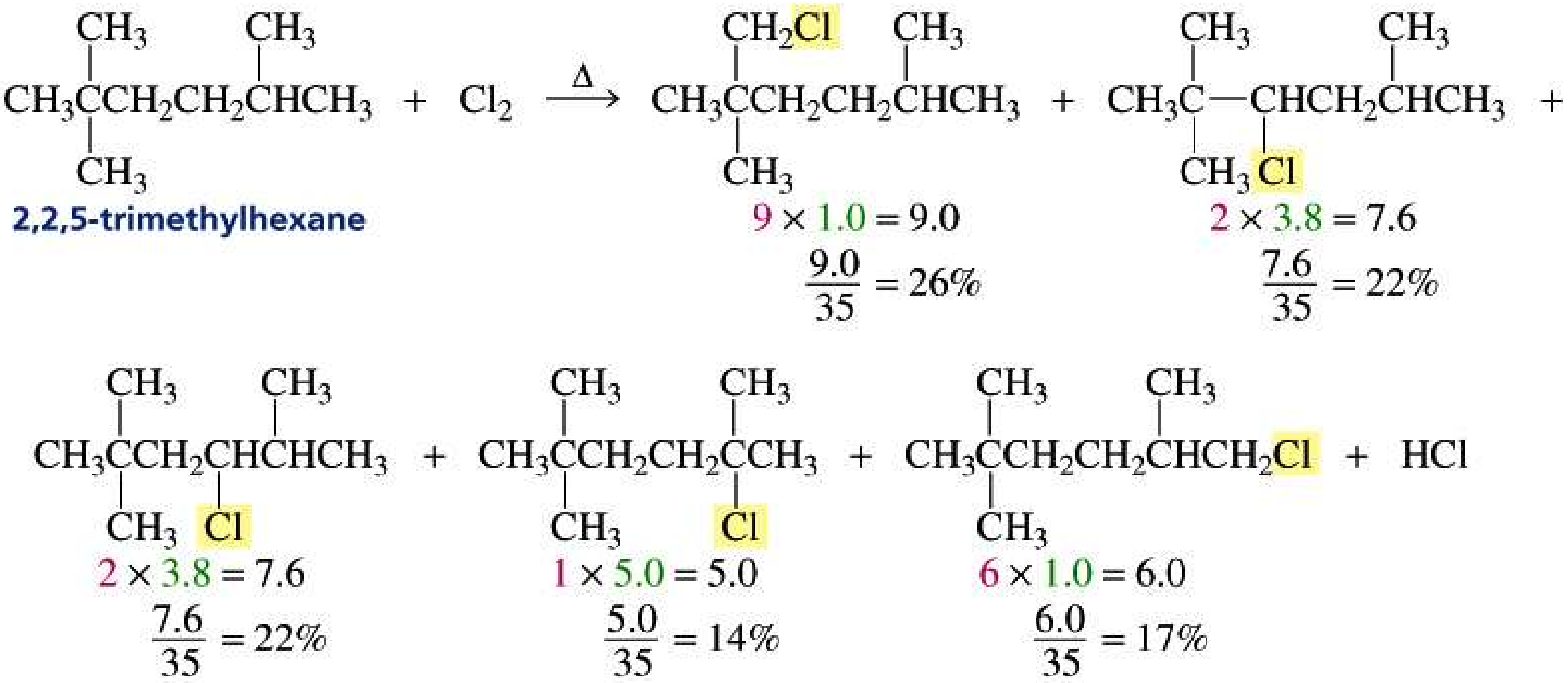
quantidade relativa de 2-clorobutano

número de hidrogênios × reatividade

$4 \times 3{,}8 = 15$

$$\text{rendimento percentual} = \frac{15}{21} = 71\%$$

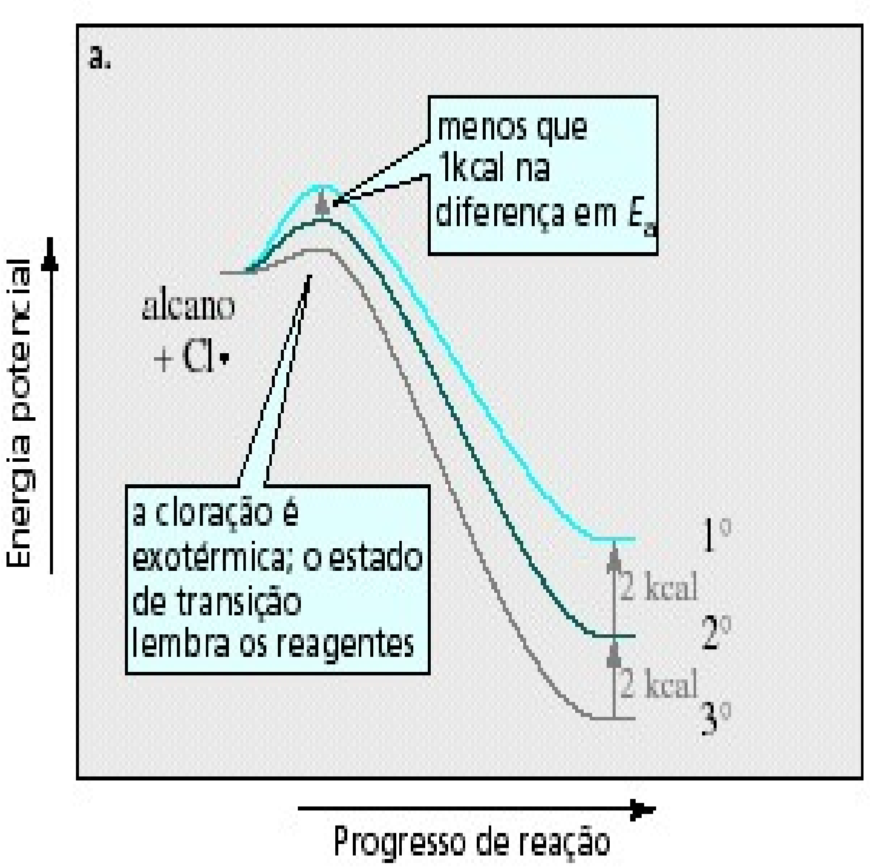
$$CH_3CH_2CH_2CH_3 + Cl_2 \xrightarrow{h\nu} CH_3CH_2CH_2CH_2Cl + CH_3CH_2\overset{\overset{Cl}{|}}{C}HCH_3 + HCl$$


2,2,5-trimethylhexane
Δ
9 × 1.0 = 9.0
9.0/35 = 26%
2 × 3.8 = 7.6
7.6/35 = 22%
2 × 3.8 = 7.6
7.6/35 = 22%
1 × 5.0 = 5.0
5.0/35 = 14%
6 × 1.0 = 6.0
6.0/35 = 17%

Por que as velocidades relativas da formação de radicais são tão diferentes entre o radical bromo e o radical cloro?

Diagrama de reação química

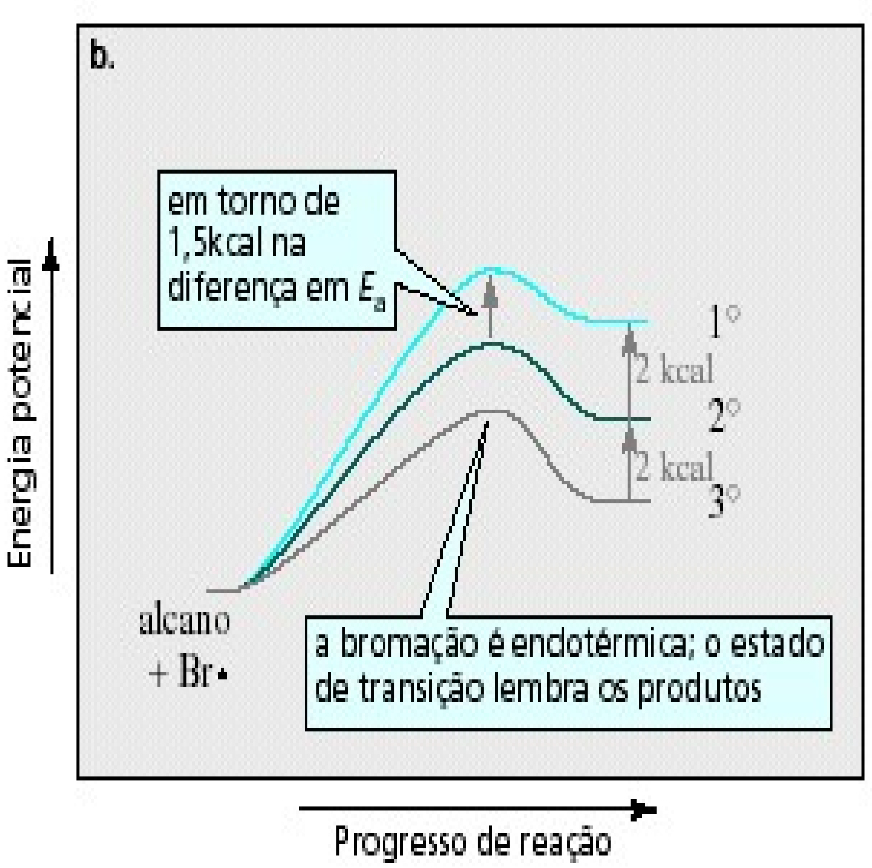
A



menos que 1kcal na diferença em E_a

a cloração é exotérmica; o estado de transição lembra os reagentes

B



em torno de 1,5kcal na diferença em E_a

a bromação é endotérmica; o estado de transição lembra os produtos

Mecanismo = descrição das etapas,
mudanças estruturais ao longo do processo]
de transformação – quebra da lig. Covalente
Formação (diagrama de reação química).

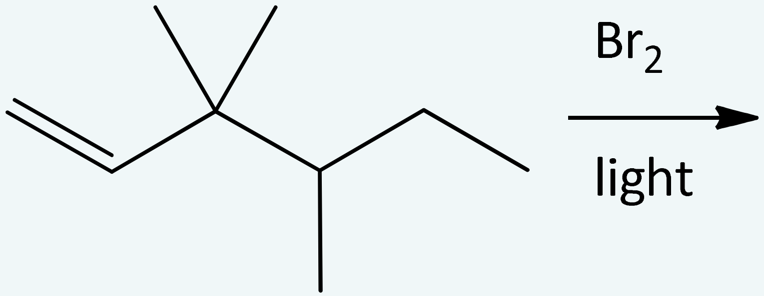
Intermediário – já quebraram ou formaram ligações,
Geralmente, sucedem uma energia de ativação.

Energia de Ativação –
energia para iniciar uma transformação

Estado de transição – estrutura começa a quebrar
Ou formar a ligação, ou tudo ao mesmo tempo.

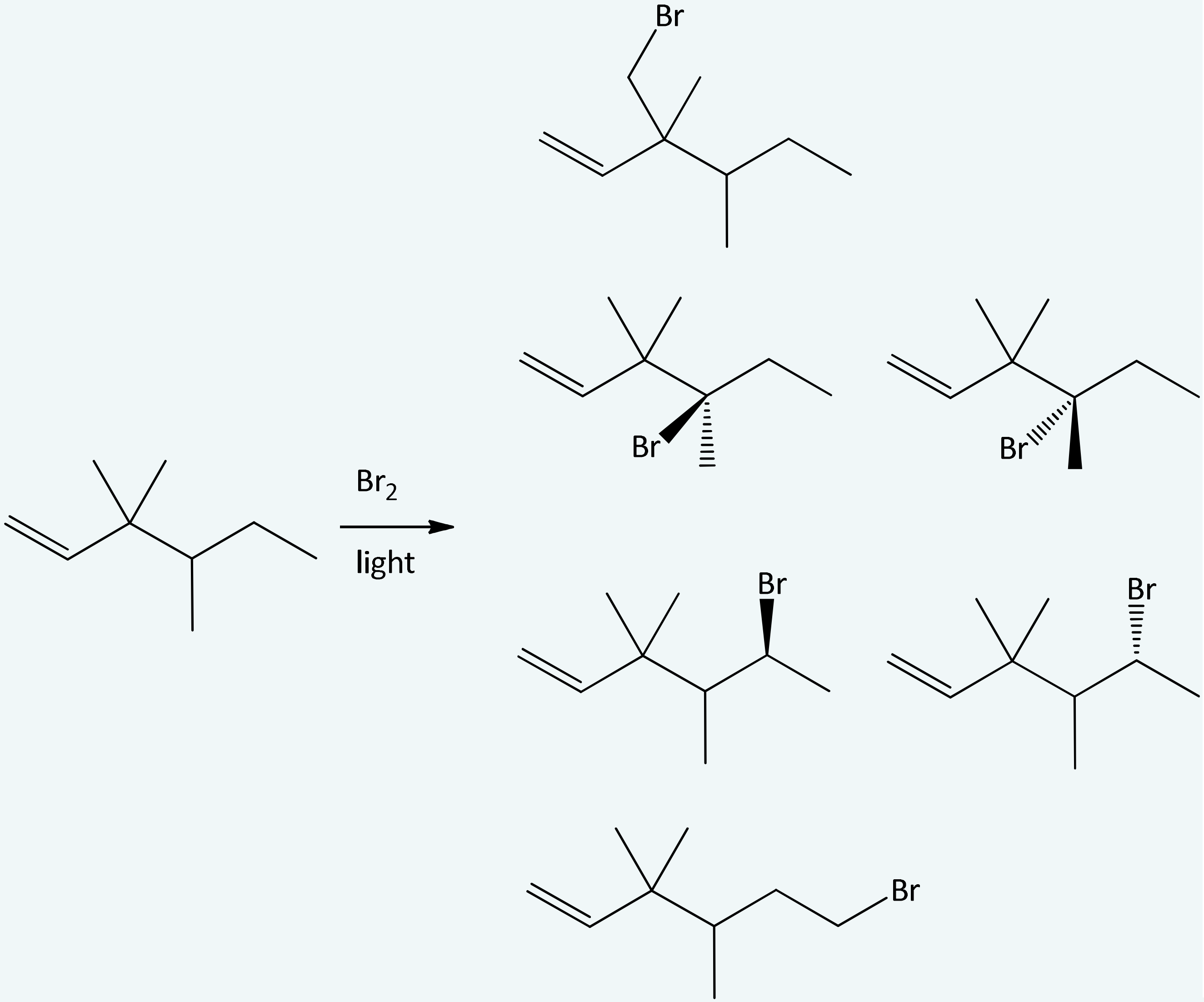
11.5 Halogenation Regioselectivity

- Ignoring possible addition products for now, draw the structure for EVERY possible monobromination product for the reaction below



- Rank the products in order from most major to most minor

11.5 Halogenation Regioselectivity



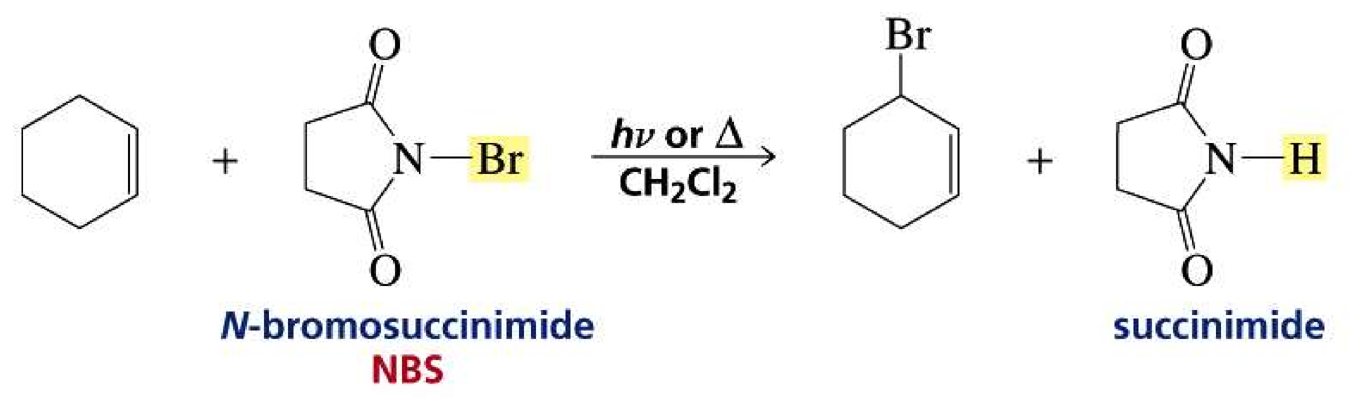
- Second least abundant product
- Most abundant product
- Second most abundant product
- Least abundant product

Radical Substitution of Benzylic and Allylic Hydrogens

- Electrophilic addition can be minimized by maintaining the halogen at a very low concentration
- Under these conditions, halogens can substitute for allylic and benzylic hydrogens

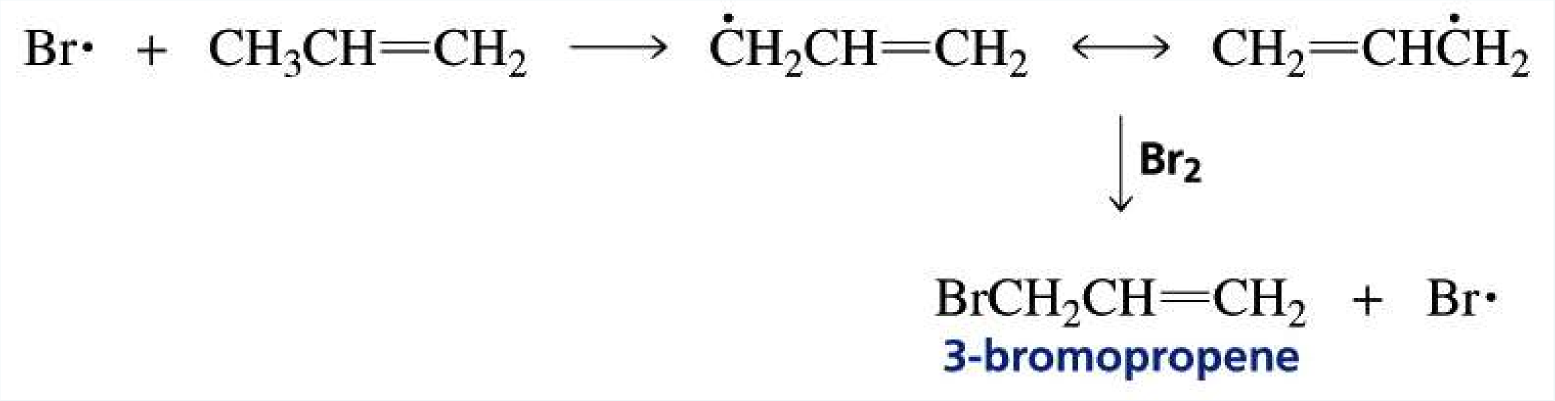
Radical Substitution of Benzylic and Allylic Hydrogens

- *N*-Bromosuccinimide (NBS) is a good reagent for supplying low concentrations of bromine radical



Radical Substitution of Benzylic and Allylic Hydrogens

- When a radical abstracts an allylic or benzylic hydrogen, a radical that is stabilized by resonance is obtained



$$Br\cdot + CH_3CH{=}CH_2 \longrightarrow \dot{C}H_2CH{=}CH_2 \longleftrightarrow CH_2{=}CH\dot{C}H_2$$

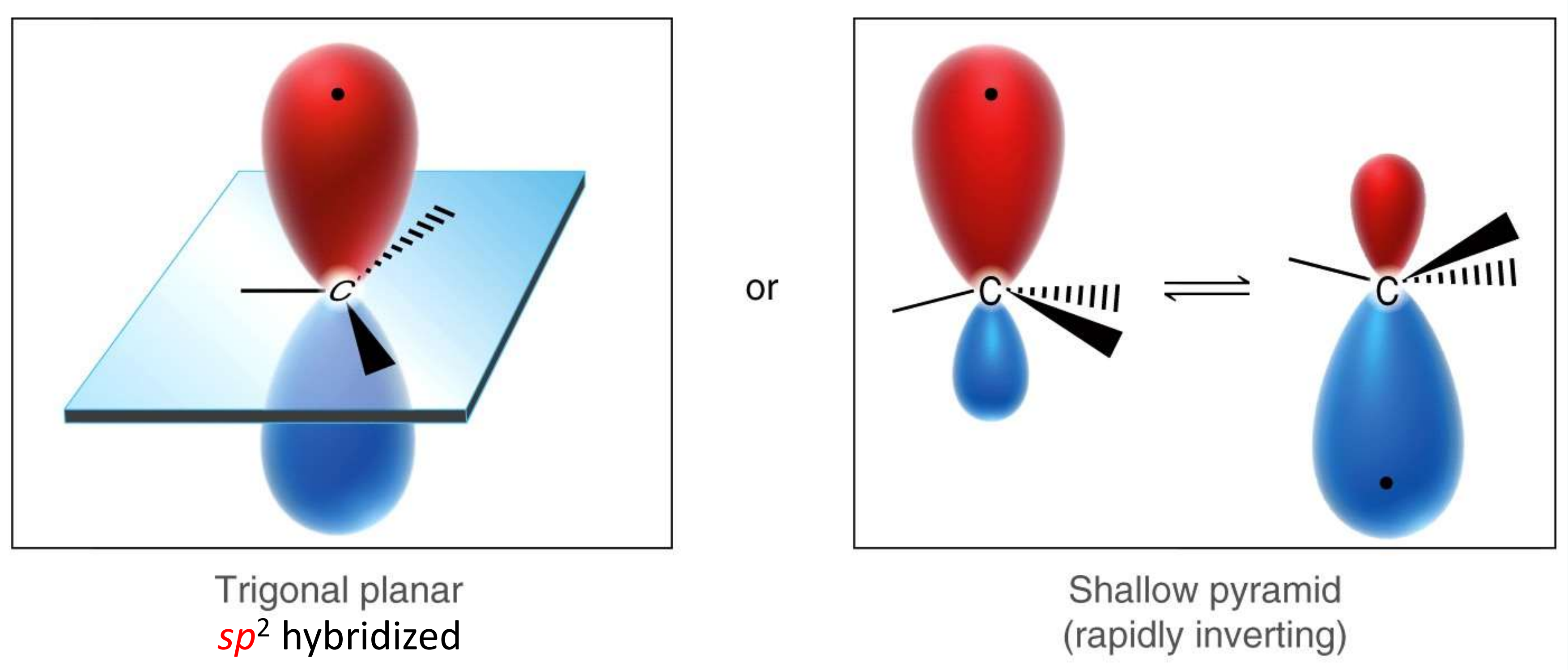
$$\downarrow Br_2$$

$$BrCH_2CH{=}CH_2 + Br\cdot$$

3-bromopropene

11.6 Halogenation Stereochemistry

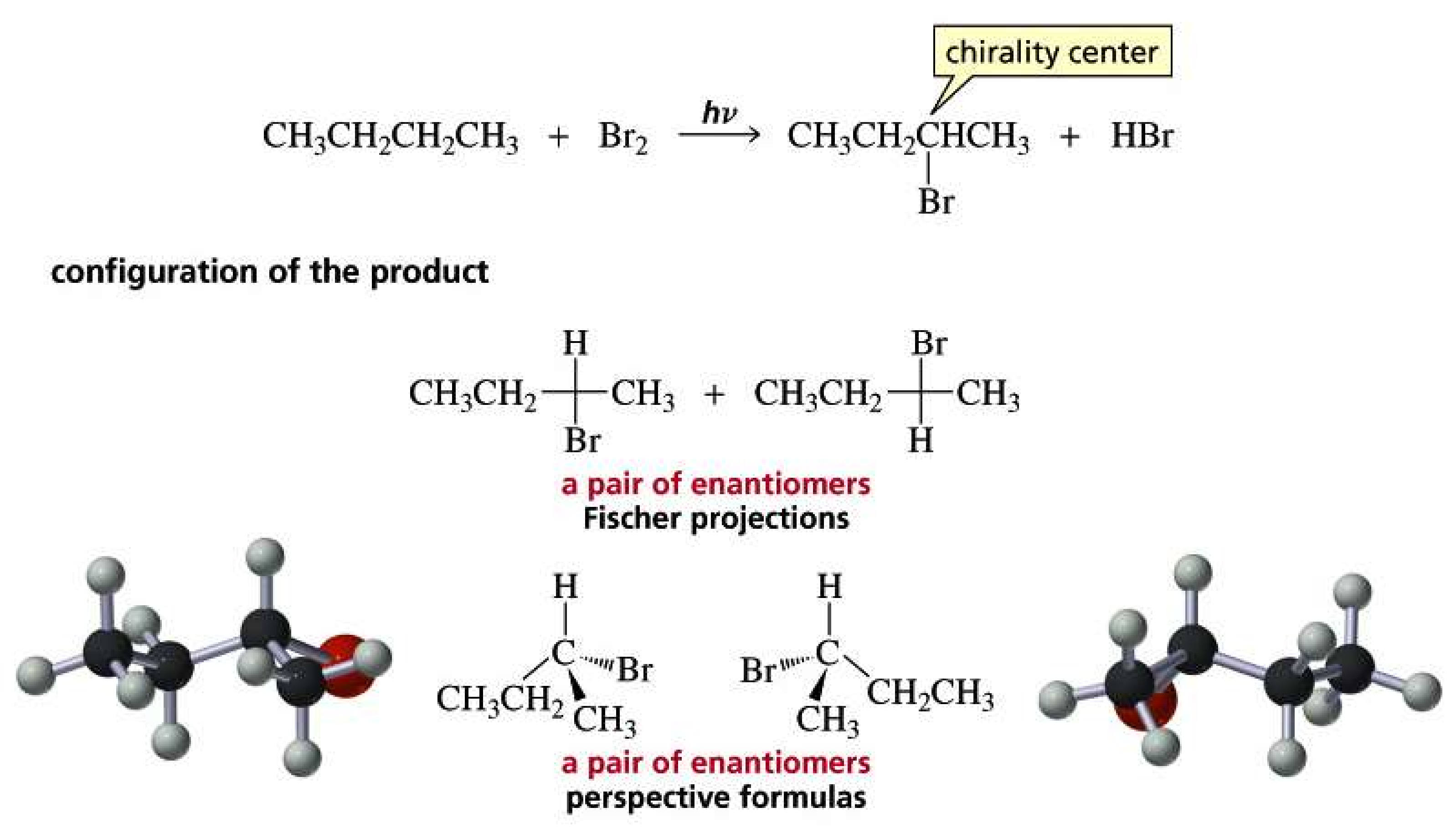
- Whether the free radical carbon is *sp*^{2} or a rapidly interconverting *sp*^{3}, the halogen abstraction will occur on either side of the plane with equal probability



Trigonal planar
sp^2 hybridized

Shallow pyramid
(rapidly inverting)

Stereochemistry of Radical Substitution



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

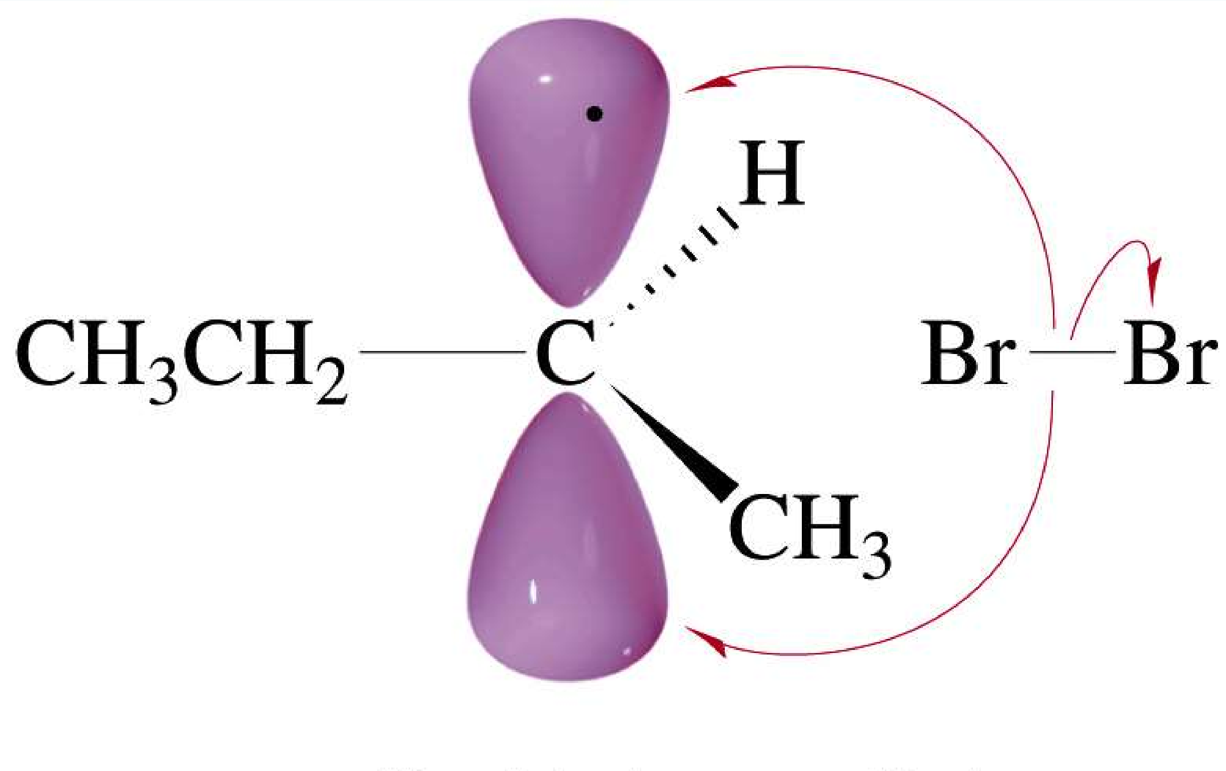
chirality center

configuration of the product

a pair of enantiomers
Fischer projections

a pair of enantiomers
perspective formulas

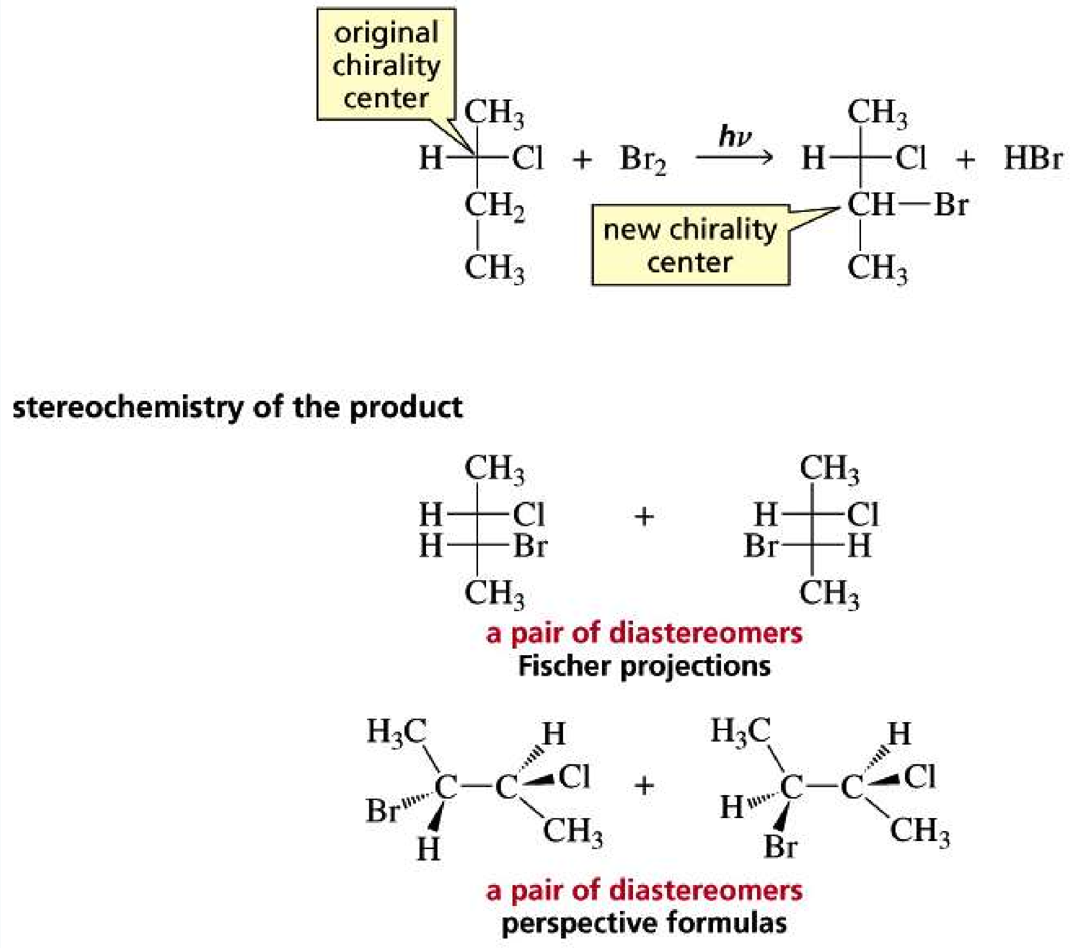
Stereochemistry of Radical Substitution



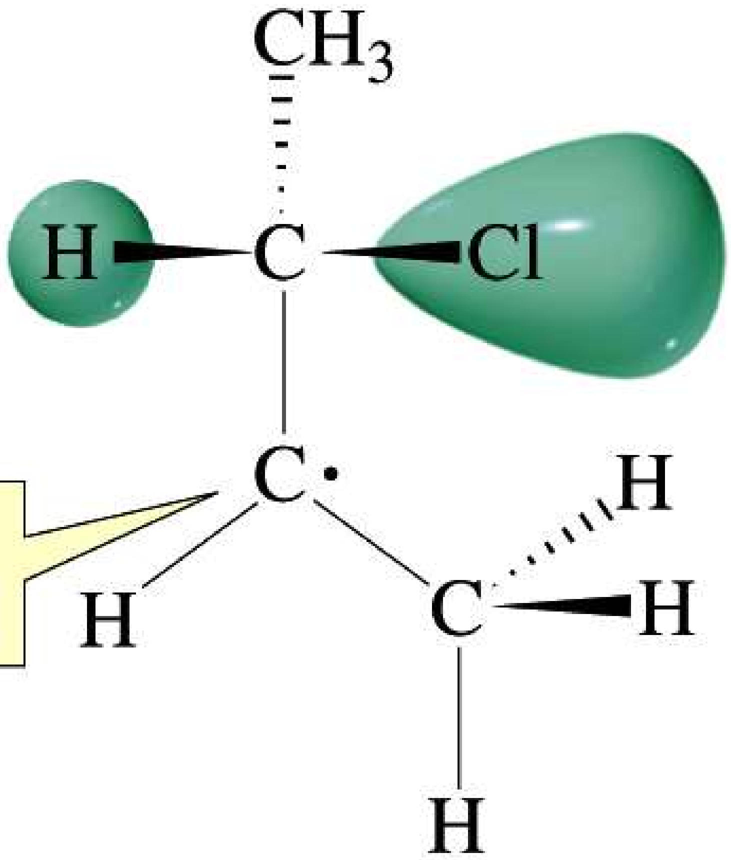
a radical intermediate

Stereochemistry of Radical Substitution

- If a chirality center already exists, it may affect the distribution of products
- A pair of diastereomers will be formed, but in unequal proportions



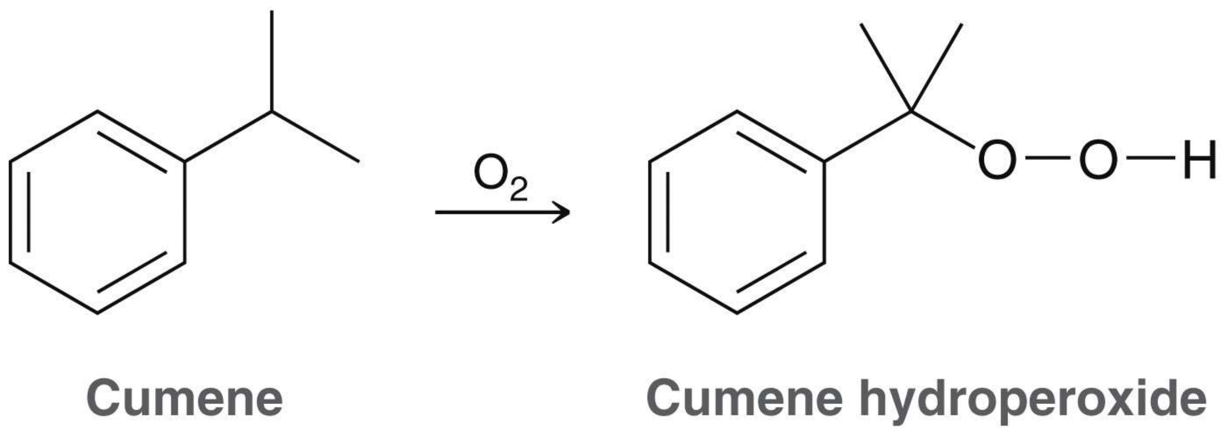
Stereochemistry of Radical Substitution



Br$_2$ has greater access to “the back” of the radical

Autooxidation

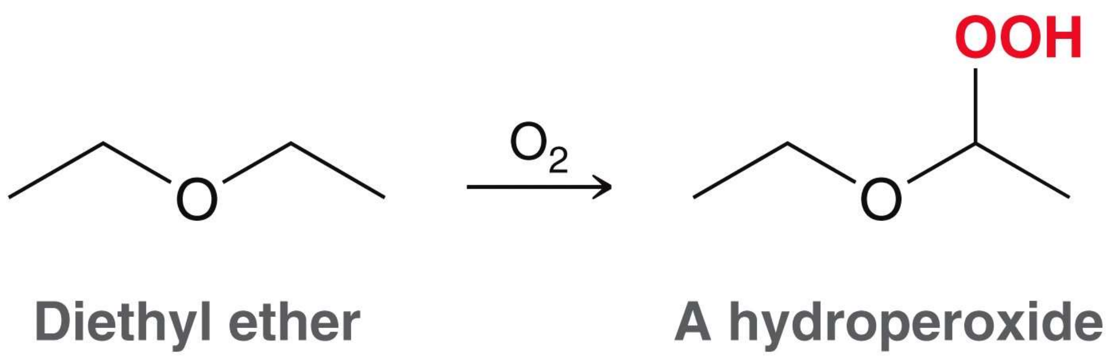
- Autooxidation is the process by which compounds react with molecular oxygen



- The process is generally very slow

Autooxidation

- Some compounds such as ethers are particularly susceptible to autooxidation



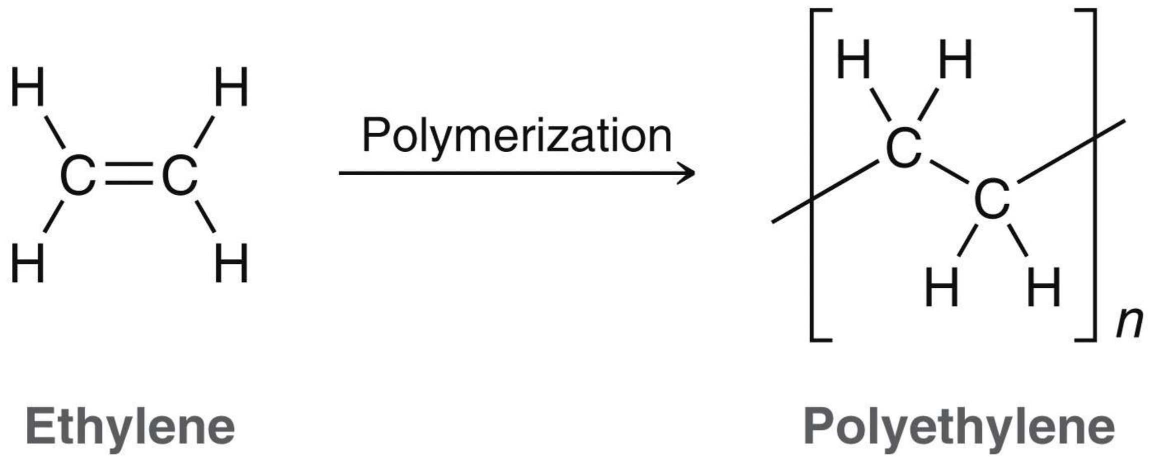
- Because hydroperoxides can be explosive, ethers like diethyl ether must not be stored for long periods of time
- They should be dated and used in a timely fashion

Autooxidation

- Light accelerates the autooxidation process
- Dark containers are often used to store many chemicals such as vitamins
- In the absence of light, autooxidation is usually a slow process
- Compounds that can form a relatively stable C• radical upon H abstraction are especially susceptible to autooxidation. WHY?
- Consider the autooxidation of compounds with allylic or benzylic hydrogen atoms

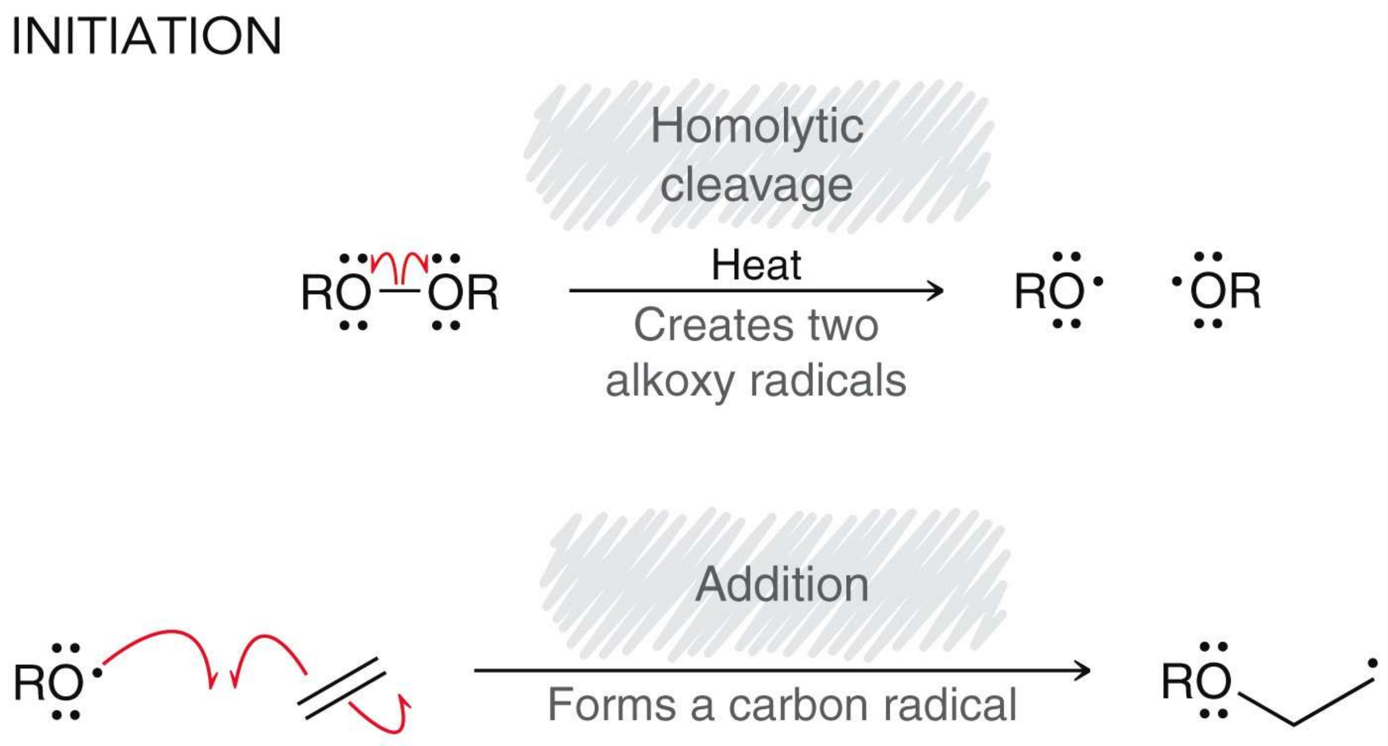
Radical Polymerization

- Free radical conditions are also frequently used to form polymers
- Recall that a polymerization process joins together many small units called monomers in a long chain



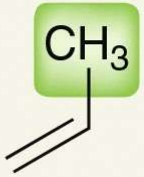
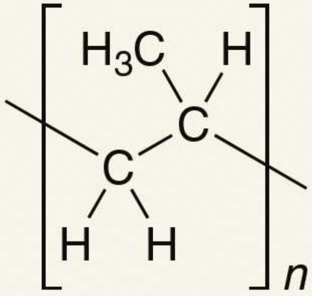
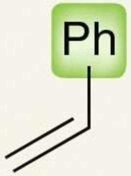
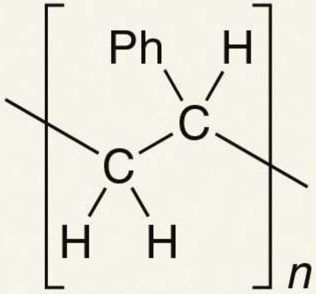
Radical Polymerization

- Radical polymerizations generally proceed through a chain reaction mechanism

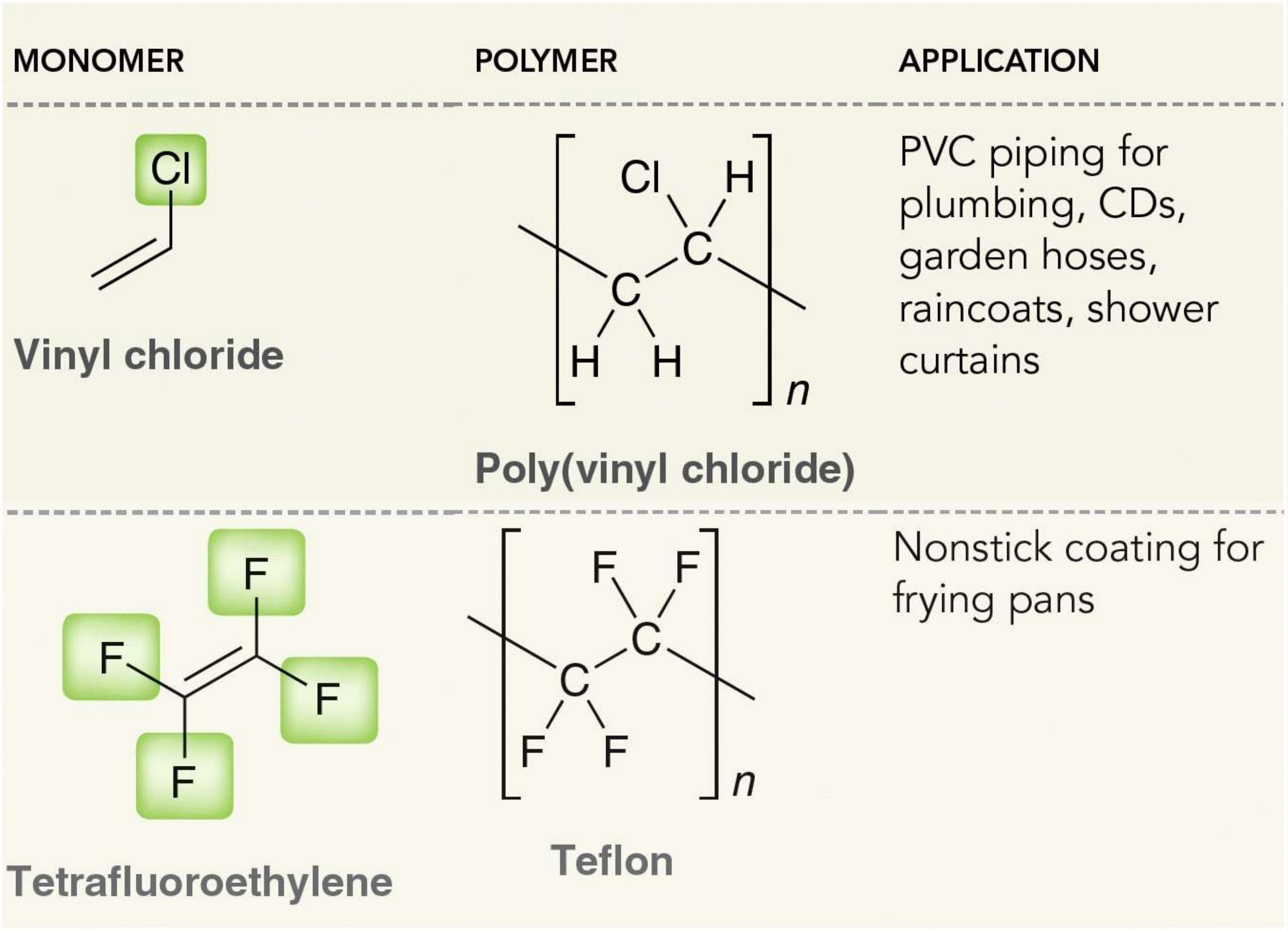


Radical Polymerization

- Many derivatives of ethylene are also polymerized

MONOMER	POLYMER	APPLICATION
 **Propylene**	 **Polypropylene**	Carpet fibers, appliances, car tires
 **Styrene**	 **Polystyrene**	Televisions, radios, Styrofoam

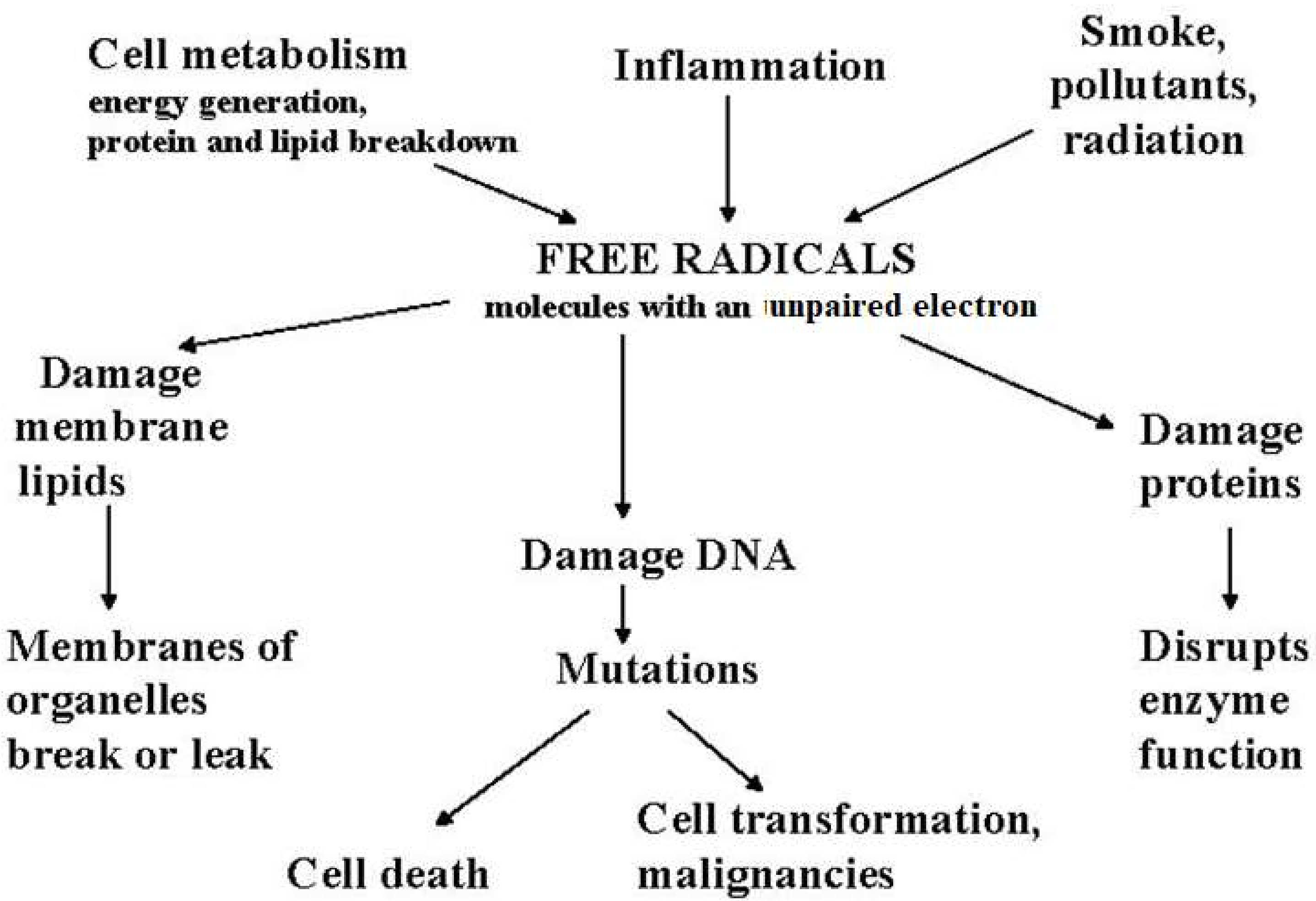
Radical Polymerization



MONOMER	POLYMER	APPLICATION
Vinyl chloride	**Poly(vinyl chloride)**	PVC piping for plumbing, CDs, garden hoses, raincoats, shower curtains
Tetrafluoroethylene	**Teflon**	Nonstick coating for frying pans

Radical Reactions in Biological Systems

Fig. 5.2 – Flow Chart of Free Radical Formation



Cell metabolism
energy generation,
protein and lipid breakdown

Inflammation

Smoke, pollutants, radiation

FREE RADICALS
molecules with an unpaired electron

Damage membrane lipids

Membranes of organelles break or leak

Damage DNA

Mutations

Cell death

Cell transformation, malignancies

Damage proteins

Disrupts enzyme function

Radical Reactions in Biological Systems

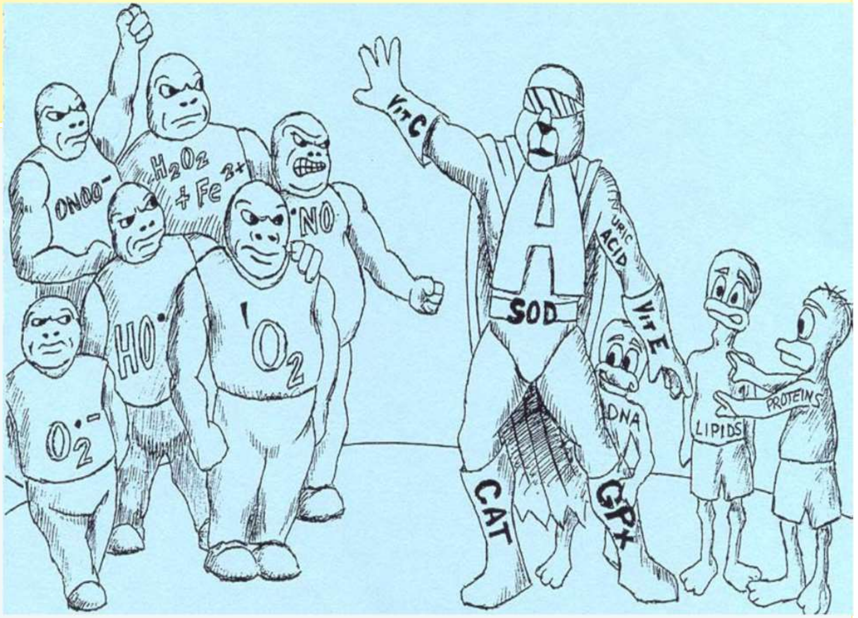
- Can be formed from
    - Oxidative metabolic processes in the mitochondria
    - Irradiation: UV from the sun, X-rays
    - Toxins in bacteria or fungus
    - carcinogens in food

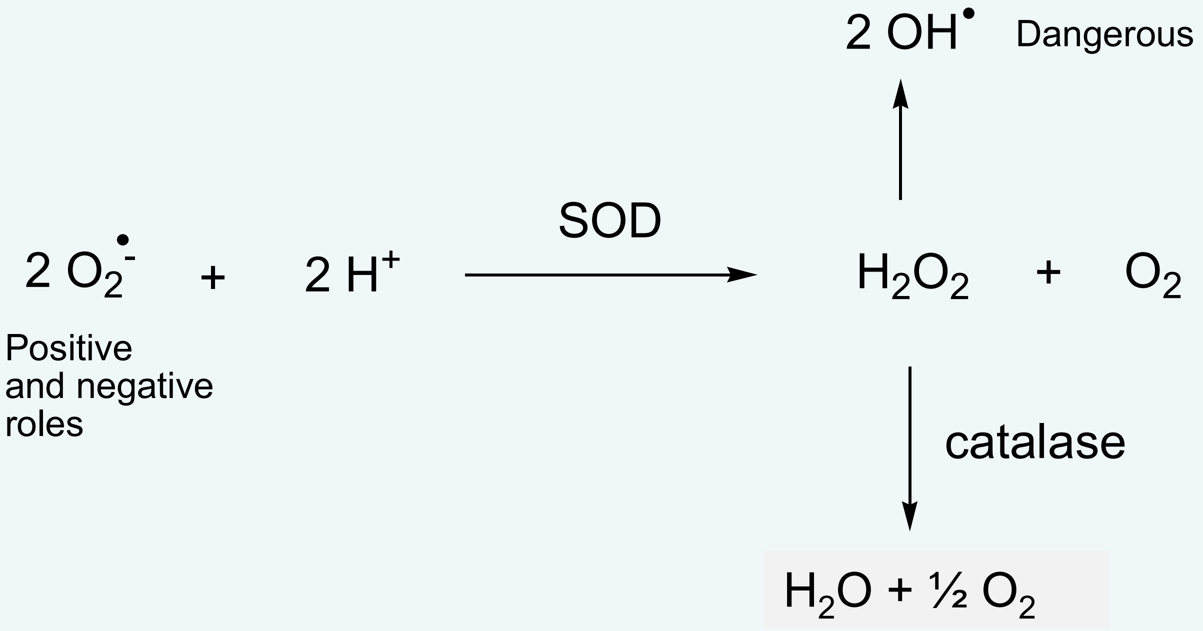
- Some important biological examples:
    - The NO· radical: involved in e.g. blood pressure regulation, stroke, nerve signals
    - The superoxide radical anion $O2\cdot^{-}$ - plays a role in ageing
    - It is formed from oxygen in the body and is formed when molecular oxygen accepts an electron, e.g. from other free radicals
    - Special enzyme for elimination of $O2\cdot^{-}$: Superoxide dismutase (SOD)

Superoxide, SOD and antioxidants

The superoxide $O_2^{\cdot -}$ radical anion plays both positive and negative roles:

- **- participates in the defense against patogens**
- **- plays a role in ageing and oxidative stress**





$2\ OH^{\bullet}$ Dangerous

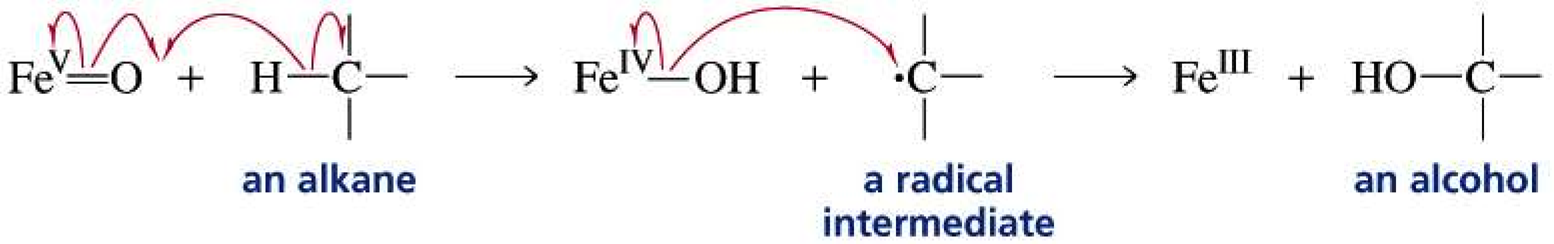
$$2\ O_2^{\bullet -} + 2\ H^+ \xrightarrow{\text{SOD}} H_2O_2 + O_2$$

Positive and negative roles

H_2O_2 → catalase → $H_2O + ½\ O_2$

Radical Reactions in Biological Systems

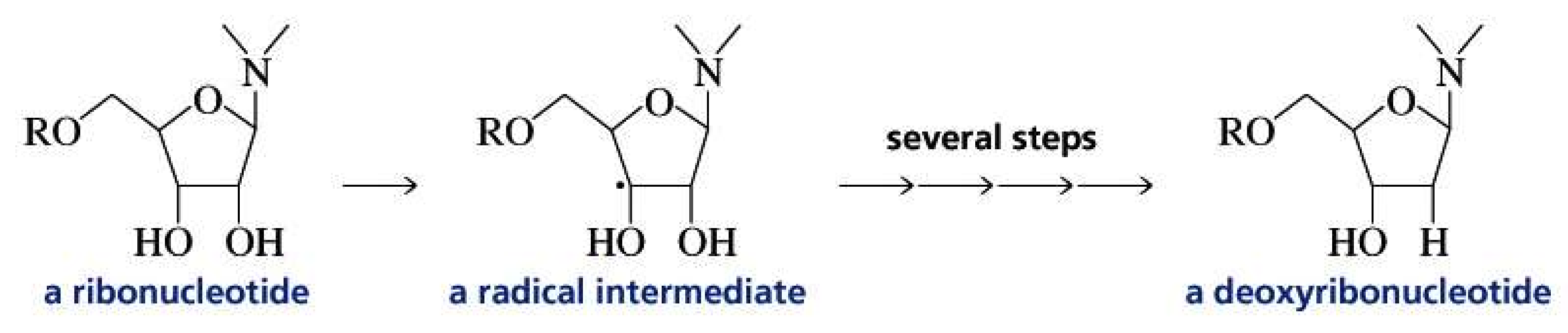
- Alkanes (toxic) are converted to alcohols (nontoxic) in the liver via a radical mechanism



- An iron-containing enzyme, cytochrome P_{450}, catalyzes the reaction

Radical Reactions in Biological Systems

- A radical reaction also is involved in the reduction of a ribonucleotide to a deoxyribonucleotide



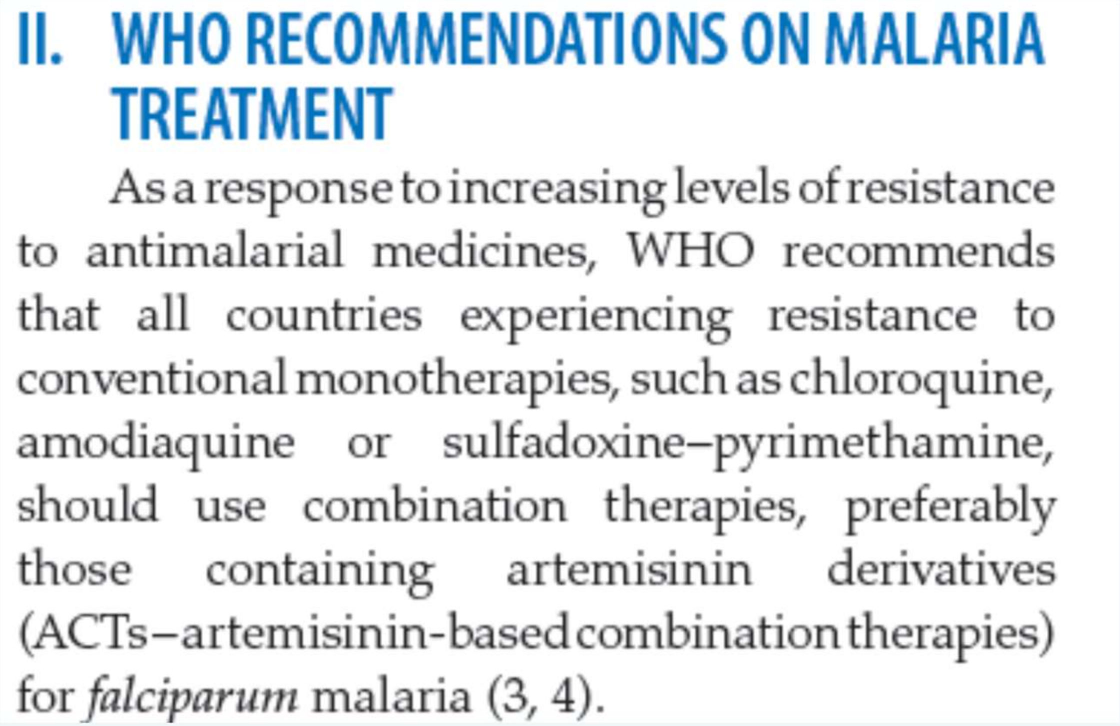
a ribonucleotide a radical intermediate a deoxyribonucleotide

Drugs based on radical reactions

Anti malaria drugs:

World Health Organization

JANUARY 2006 UPDATE

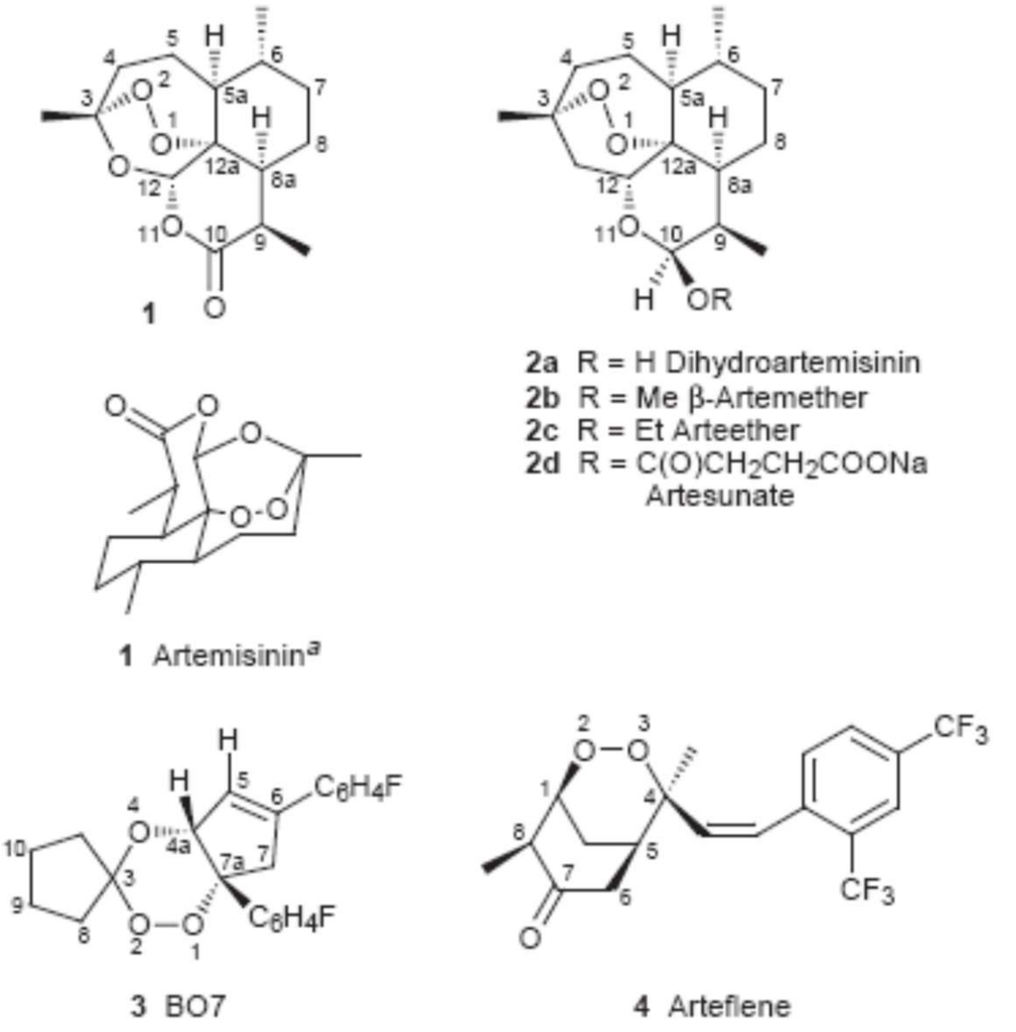


II. WHO RECOMMENDATIONS ON MALARIA TREATMENT

As a response to increasing levels of resistance to antimalarial medicines, WHO recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine–pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs–artemisinin-based combination therapies) for *falciparum* malaria (3, 4).

Drugs based on radical reactions

Anti malaria drugs:
Artemisinin
derivatives:



1

2a R = H Dihydroartemisinin
2b R = Me β-Artemether
2c R = Et Arteether
2d R = C(O)CH$_2$CH$_2$COONa Artesunate

1 Artemisinin[a]

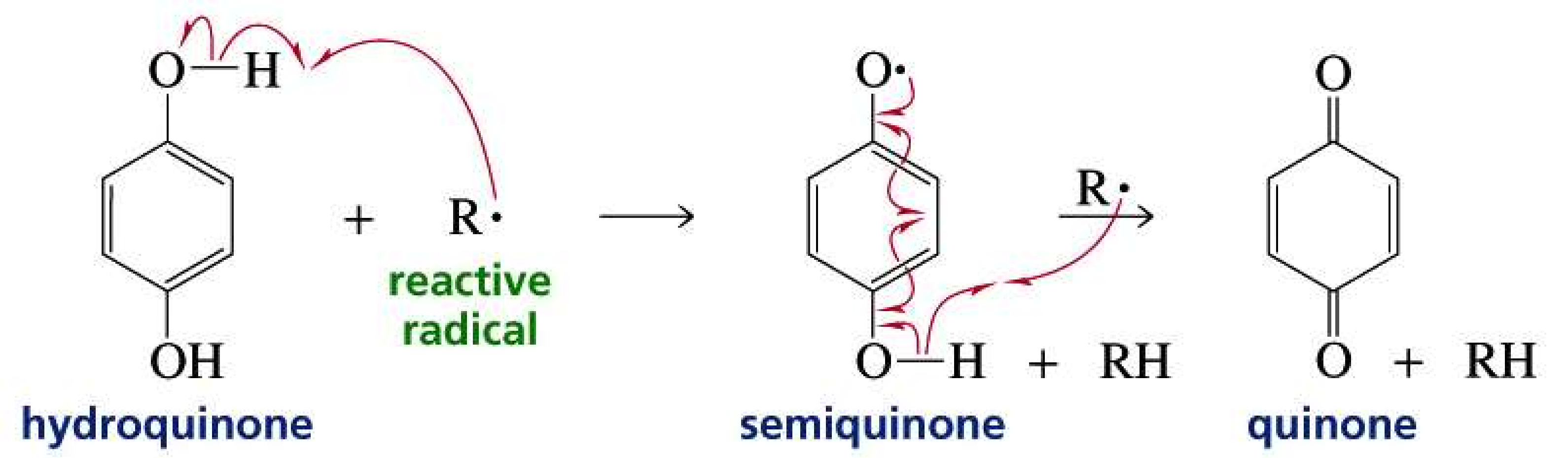
3 BO7

4 Arteflene

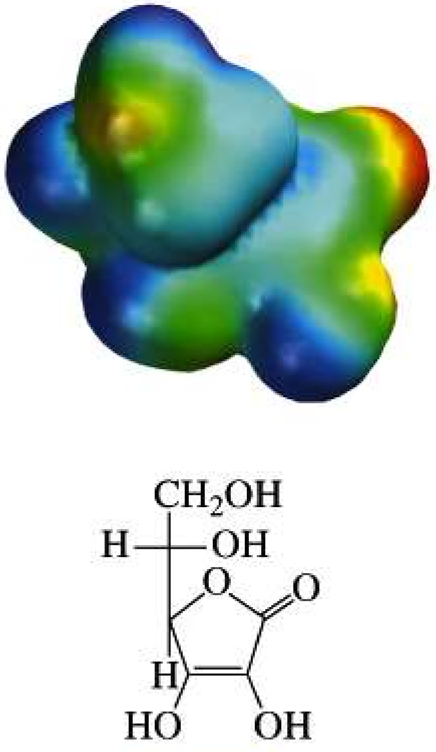
Structure of antimalarial drugs artemisinin, β-artemether, BO7, and arteflene. [a] Two different possible drawings are given for artemisinin.

Radical Reactions in Biological Systems

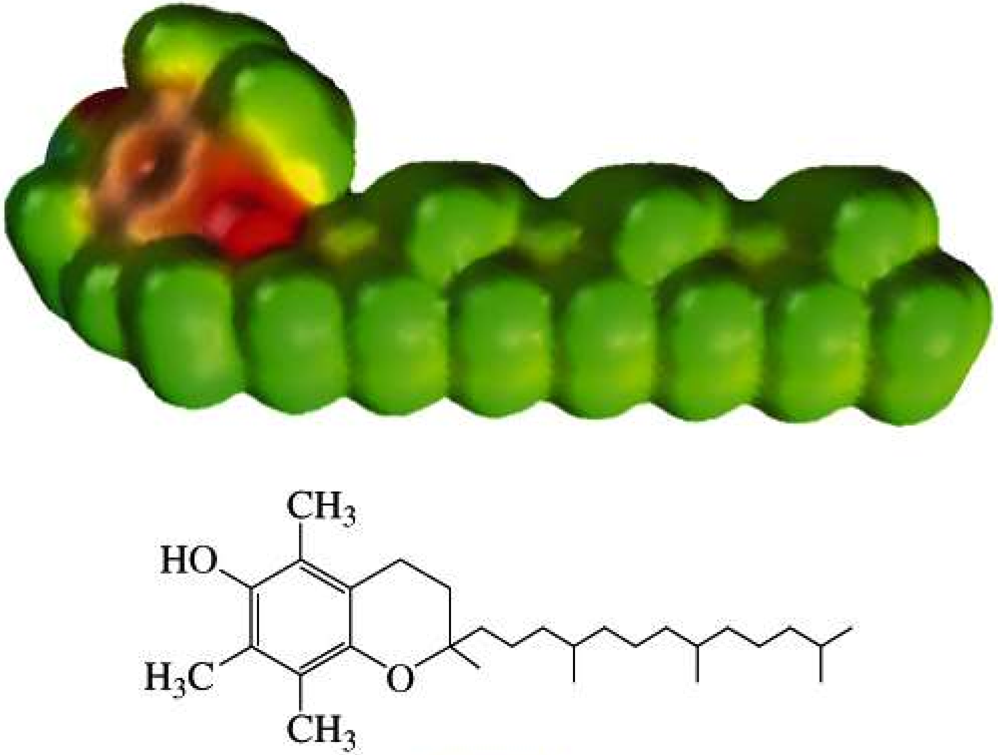
- Protection from radical reaction is possible if a compound is present that reacts with the radical and forms a less reactive radical



Radical Reactions in Biological Systems



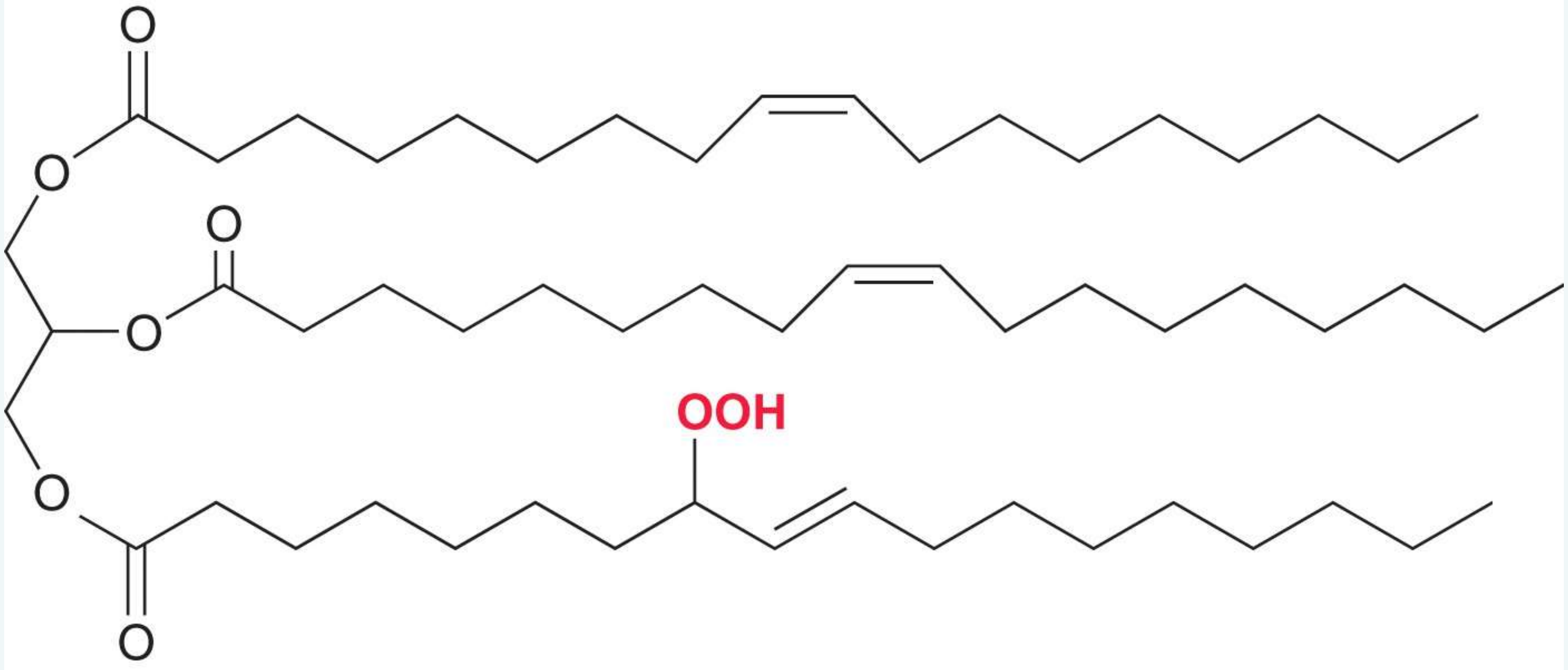
vitamin C
ascorbic acid



vitamin E
α-tocopherol

11.9 Antioxidants

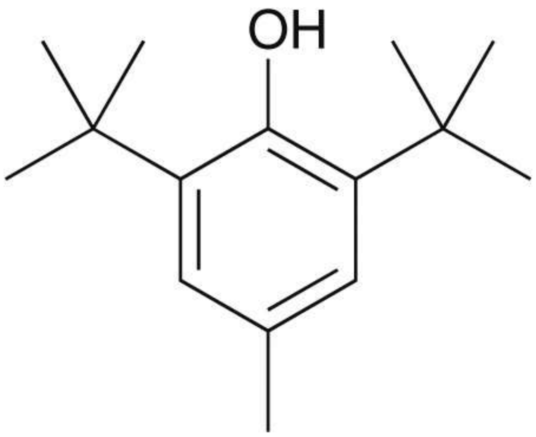
- Triglycerides are important to a healthy diet



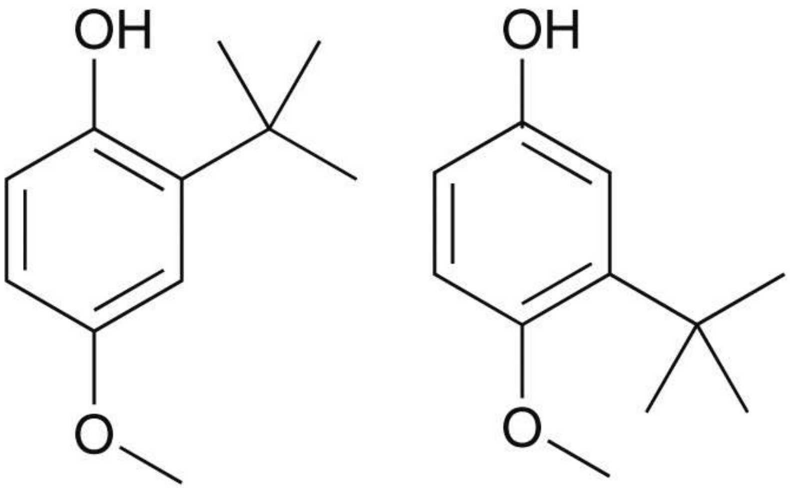
- Autooxidation can occur at the allylic positions causing the food to become rancid and toxic

11.9 Antioxidants

- Foods with unsaturated fatty acids have a short shelf life unless preservatives are used



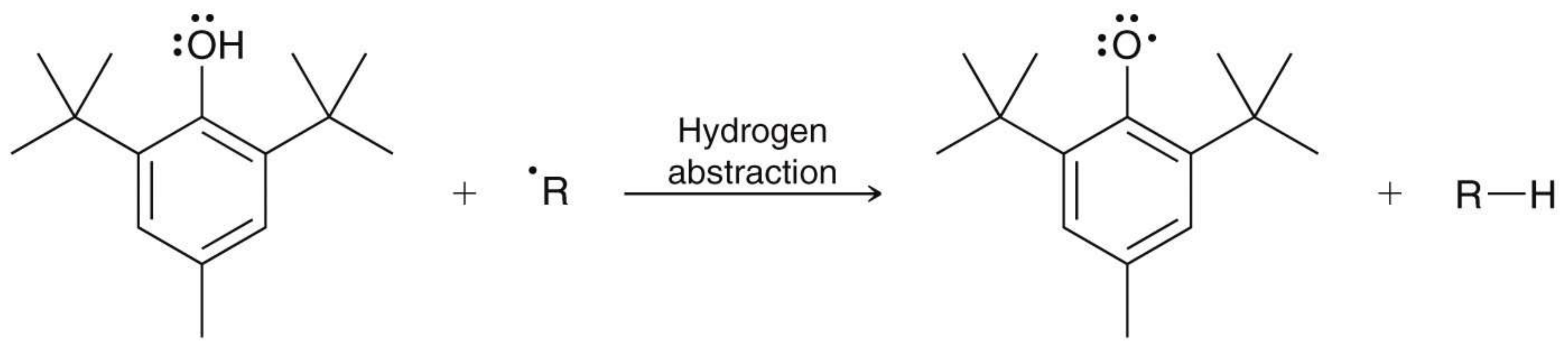
Butylated hydroxytoluene
(BHT)



Butylated hydroxyanisole
(BHA)

11.9 Antioxidants

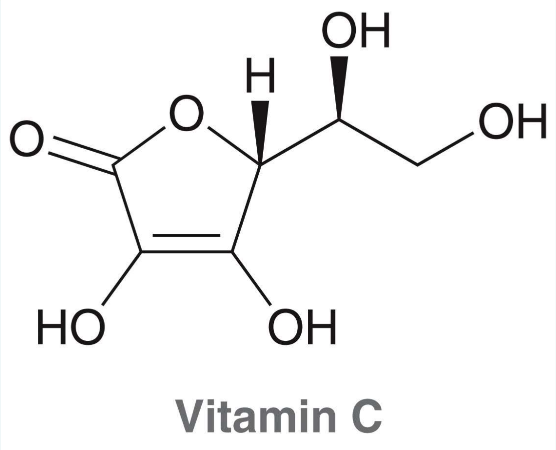
- Preservatives can undergo H abstraction to quench the C• radicals that form in the first step of autooxidation



- One molecule of BHT can prevent thousands of autooxidation reactions by stopping the chain reaction
- How does BHT's structure make it good at taking on a free radical? Consider resonance and sterics

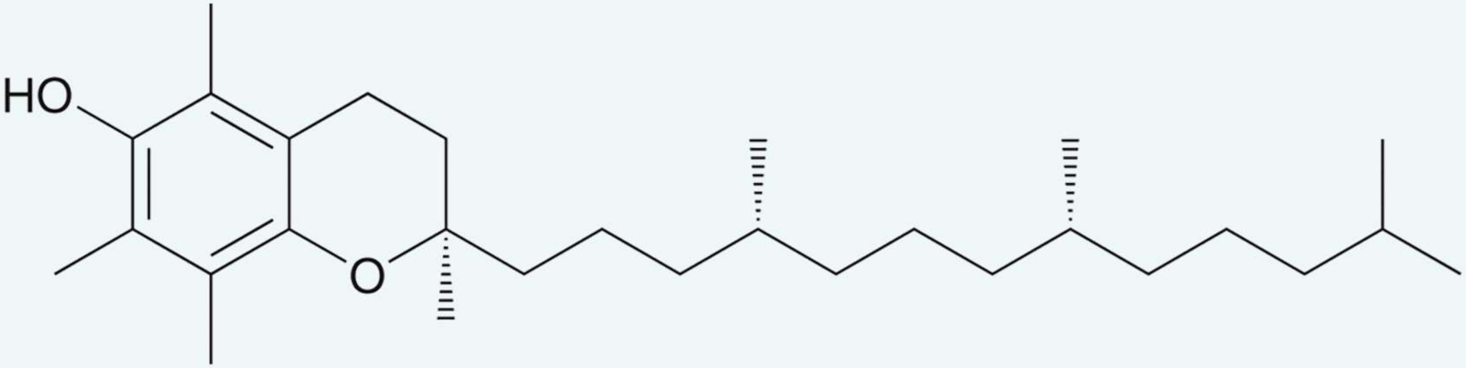
11.9 Natural Antioxidants

- Vitamins C is hydrophilic
- Vitamin E is hydrophobic
- What parts of the body do these vitamins protect?



Vitamin C

- For each vitamin, show its oxidation mechanism, and explain how that protects the body from autooxidation



Vitamin E