Radicals – Part 1

Explain This Observation...

Consider: A mixture of Br₂ and an alkane...

Predict: No pi bonds, therefore no reaction

Observation:

Questions: • Mechanism?
  • Why reaction occurs at 3° carbon?
Mechanism

Colorless Red

So mechanism begins with Br₂ absorbs $h \nu$

• Causes electronic excitation of lone pair electron to $\sigma^*$ orbital

• Weakens $\sigma$ bond

Unpaired electron = free radical

Homolytic cleavage = even distribution of bond electrons

Photolysis (photo = light; lysis = destruction) = reaction via light

Radical Fates

Now that I have a radical, what do I do with it?

• How do radicals react?

• What is a radical's motivation?

Radicals react in ways to

... reduce or resolve their electron deficiency.

... become more stable.

Three common ways in which radicals react: The Radical Fates.
Radical Fates
Radicals desire to become more stable.

Radical desires one electron to fill octet.
Electron can be provided by ________________________________.

Radical Fate #1: Add to a pi bond
• Trade pi bond (weaker) for sigma bond (stronger)

Alternate possibility: Why not?

Radical Fates
Radicals desire to become more stable.

Radical desires one electron to fill octet.
Electron can be provided by ________________________________.

Radical Fate #2: Atom transfer
• Usually trades weaker sigma bond for stronger sigma bond
Radical Fates
Radicals desire to become more stable.

Radical desires one electron to fill octet.
Electron can be provided by ________________________________.

Radical Fate #3: Radical combination
• Driven by completing two open octets, and by gaining a sigma bond

Fact: Radical mechanism steps generally have low \( \Delta G^\ddagger \)
• Therefore one formed, radicals react quickly
• [radicals] never becomes very high
• Metaphor: Finding a friend (common) versus finding your soul mate (one-of-a-kind)

Conclusion: Radical combination is common uncommon event

Back to the Radical Halogenation Mechanism...
Our mechanism so far...

What happens next? Three radical fates...
• Add to a pi bond – no pi bond present
• Atom transfer – possible
• Radical combination – possible but unlikely

What atom does Br steal?

Overall reaction is...
Therefore next mechanism step is...
Radical Halogenation Mechanism

Our mechanism so far...

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{Br} \quad \text{Br} \\
\text{Br} \quad \text{H} \rightarrow 2 \cdot \text{Br}^* \\
\text{CH}_3 \quad \text{Br} \quad \text{H} \rightarrow \text{CH}_3 \\
\text{H} \quad \text{Br} \quad \text{H} \\
\end{align*}
\]

Why not...

\[
\begin{align*}
\text{H} \quad \text{Br} \\
\text{H} \quad \text{H} \quad \text{Br} \\
\text{CH}_2 \quad \text{Br} \\
\end{align*}
\]

When choosing between two potential products of a mechanism step, we generally choose ____________________________.

Radical Structure and Stability

**Structure:**

- *sp*\(^3\) carbon
- *sp*\(^2\) carbon

**Pyramidal** versus **Trigonal planar**

Which repels more strongly? One nonbonded electron Two bonded electrons

**Stability**

- Central electron-deficient carbon, like a carbocation
- So do radicals have same stability trends as carbocations?
Radical Stability: Degree of Substitution

Carbocations:

Methyl 1° 2° 3°

Increasing number of electron-donating groups
Increasing stability

Radicals:

Methyl 1° 2° 3°

Increasing number of electron-donating groups
Increasing stability

Radical Stability: Pi Bond Resonance

Carbocations:

Resonance hybrids

Radicals:

Conclusion

• A radical does not gain resonance stabilization from adjacent pi bond.
### Radical Stability: Lone Pair Resonance

#### Resonance hybrid

**Carbocations:**
\[
\text{H}_2\text{C} \quad \overset{\circ}{} \quad \overset{\circ}{\text{H}} \quad \overset{\circ}{\text{O}} \quad \leftrightarrow \quad \text{H}_2\text{C} \quad \overset{\bullet}{\circ} \quad \overset{\circ}{\text{H}} \quad \overset{\circ}{\text{O}}
\]

**Radicals:**
\[
\text{H}_2\text{C} \quad \overset{\circ}{} \quad \overset{\circ}{\text{H}} \quad \overset{\circ}{\text{O}} \quad \leftrightarrow \quad \text{H}_2\text{C} \quad \overset{\bullet}{\circ} \quad \overset{\circ}{\text{H}} \quad \overset{\circ}{\text{O}}
\]

### Conclusion

- A radical does not gain resonance stabilization from adjacent lone pair.

### FAQ: Radical Rearrangement?

**Fact:** Carbocations may rearrange.

**Question:** Do radicals rearrange?

**Answer:** Radical rearrangement is likely possible never occurs.
Radical Halogenation Mechanism

Our mechanism so far...

\[
\text{\textbf{Br} Br} \quad \text{hv or heat} \quad 2 \text{\textbf{Br} +} \]

\[
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{Br} + \text{H Br}
\]

Last step:

\[
\text{CH}_3 \quad \text{Three ways} \quad \text{CH}_3
\]

What is the final step of the mechanism?

Addition to a pi bond – no pi bond present.

Atom transfer –

Br-Br bond weaker than Br-H bond.

Radical combination –

Radical combination unlikely due to low concentration of radicals.
**Radical Halogenation Mechanism**

Complete mechanism:

\[ \text{Br}_2 \xrightarrow{h\nu \text{ or heat}} 2 \cdot \text{Br} \cdot \]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[ \text{CH}_3 \\
\text{Br} \quad \text{Br} \\
\text{CH}_3 \\
\]

\[ + \quad \text{Br} \cdot \]

Chain reaction: A reaction whose mechanism includes one or more steps that are repeated indefinitely, until the chain is terminated.

One photon yields (in principle) many molecules of product.

**Chain Reaction Mechanism Steps**

Initiation (I) – starts chain

\[ \text{Br}_2 \xrightarrow{h\nu \text{ or heat}} 2 \cdot \text{Br} \cdot \]

Propagation (P) – continues chain

radicals \rightarrow radicals

Termination (T) – ends chain

radicals \rightarrow no radicals
Radicals – Part 2

\[ \text{F} \quad \text{Cl} \quad + \quad \text{O}_3 \quad \rightarrow \quad \cdot \cdot \cdot \cdot \]

Radicals – Part 1 Summary

Free radical halogenation:

- Mechanism:
  \[ \text{CH}_3 \quad \text{Br} \quad \text{Br} \quad \text{hv} \quad \text{or heat} \quad \rightarrow \quad 2 \cdot \text{Br} \]

- Radical: Has unpaired electron
  - Radical fates:
    - Add to pi bond
    - Atom transfer
    - Radical combination

- Radical stability:
  - Methyl < 1° < 2° < 3°
  - Pi bond resonance
  - Lone pair resonance
**Radicals – Part 1 Summary**

**Mechanism:**

\[
\text{Br} + \text{Br} \xrightarrow{h\nu \text{ or heat}} 2 \cdot \text{Br}^-
\]

\[
\text{CH}_3 + \text{Br} \xrightarrow{h\nu \text{ or heat}} \text{CH}_3\text{Br} + \text{H} - \text{Br}
\]

**Chain reaction:** A reaction whose mechanism includes one or more steps that are repeated indefinitely, until the chain is terminated.

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**Can Other Halogens Be Used?**

**Highly selective**

\[
\text{CH}_3 \xrightarrow{h\nu \text{ or heat}} \text{Br}_2 \rightarrow \text{CH}_3\text{Br}
\]

**Less selective**

\[
\text{CH}_3 \xrightarrow{h\nu \text{ or heat}} \text{Cl}_2 \rightarrow \text{CH}_3\text{Cl} + \text{Cl} - \text{Cl}
\]

**Nonselective**

\[
\text{CH}_3 \xrightarrow{h\nu \text{ or heat}} \text{I}_2 \rightarrow \text{No reaction}
\]

\[
\text{CH}_3 \xrightarrow{h\nu \text{ or heat}} \text{F}_2 \rightarrow \text{Nonselective}
\]
More on Addition of HBr to Alkenes and Alkynes

Recall:

\[
\ce{H2C=CH2 + HBr -> H2C=CHBr}
\]

Markovnikov addition

But it’s not quite that simple...

\[
\ce{H2C=CH2 + HBr -> H2C-CHBr + H2C=CH2}
\]

Mixture

Kharasch, Mayo (1933): • Impurity = peroxide R-O-O-R
  • Adding peroxide causes 100% anti-Markovnikov addition

\[
\ce{H2C=CH2 + HBr + HO- -> H2C-CHBr + H2O}
\]

Anti-Markovnikov is major product

“Peroxide effect” observed for HBr only

More on Addition of HBr to Alkenes and Alkynes

Mechanism?

• Kharasch and Mayo show it to be a radical chain reaction
  • Radical addition to pi bond gives most stable radical

\[
\ce{H2C=CH2 + Br \rightarrow H2C-CHBr}
\]

comes from

versus

When choosing between two potential products of a mechanism step, we generally choose

Conclusion: Which adds to pi bond first? \( \ce{Br^+} \) \( \ce{H^-} \)
More on Addition of HBr to Alkenes and Alkynes

Mechanism? Radical chain = initiate then propagate

**Initiation:**
\[ \text{HO} - \text{OH} \rightarrow 2 \text{HO}^+ \]
Weak bond

**Propagation:** Generate Br•

Add to make most stable radical

Last step = termination propagation

Chain continues

H-X Addition Reactions Orientation Summary

Markovnikov versus Anti-Markovnikov?

Markovnikov  Anti-Markovnikov

Markovnikov  Anti-Markovnikov

Markovnikov  Anti-Markovnikov

Markovnikov  Anti-Markovnikov

Markovnikov  Anti-Markovnikov
**Dioxygen and Metabolites – Biological Oxidation**

**Molecular Structure of Dioxygen (O₂)**

- **Lewis theory predicts:** \( = \)
  - Dioxygen does not have a double bond.
  - *Simple Lewis theory gets it wrong.*
- **Quantum mechanics predicts:** \( = \)
  - Dioxygen is a diradical.
  - *Quantum mechanics gets it right.*

**Organisms bathed in O₂, a diradical. Is this a problem?**

- **O₂ is less reactive than most radicals**
- **Electron "leaks" from normal mitochondrial metabolic pathways**
- **Superoxide** • A radical anion
  - \( = \)
- **Hydrogen peroxide**
  - \( = \)
- **Hydroxyl radical** • Very aggressive radical
  - • Can attack DNA, lipids, proteins, etc.
  - \( = \)
Dioxygen and Metabolites – Biological Oxidation

Potential for damage to biological structures...

Phospholipid bilayer
- Contains fatty acid alkenes
- Susceptible to attack by HO•

Resonance stabilization

Fatty acid alkenes

Radical chain continues

Dioxygen and Metabolites – Biological Oxidation

Phospholipid cross-linking can lead to...
- ...membranes less flexible, distorted, and damaged
- ...reduced solubility lipid → plaque in arteries → atherosclerosis

Biological defenses against radicals: Antioxidants
- Radical scavenger enzymes
- Nonenzymatic defenses

Example: Superoxide dismutase (SOD)

Lipids susceptible to attack by HO• because ____________________________

Therefore an efficient antioxidant has ________________________________

Resonance contributors
- Reduces reactivity
- Slows chain propagation
Dioxygen and Metabolites – Biological Oxidation

Lipophilic (Hydrophobic) Antioxidants

α-Tocopherol *Main component of vitamin E*

Ubiquinone (coenzyme Q)

Carotenes *β-Carotene is shown*

Dioxygen and Metabolites – Biological Oxidation

Lipophobic (Hydrophilic) Antioxidants

Ascorbate (vitamin C)

Uric acid
Chlorofluorocarbons and Ozone Depletion

Ozone ($O_3$)
- Hazardous at ground level (ozonolysis!)
- Protects against high-energy solar UV in ozone layer (few ppm $O_3$ at 15-35 km altitude)

$$2O_3 \overset{hv}{\rightarrow} 3O_2$$

Chlorofluorocarbons (CFCs)
- Used as refrigerants, spray can propellants, etc.
- Low chemical reactivity $\rightarrow$ atmospheric half-life typically 50-100 years
- Released in atmosphere; not removed until stratosphere (8-50 km altitude)
- Crutzen, Rowland, and Molina implicate CFCs in ozone depletion

Montreal Protocol (1987)
- Agreement to phase out manufacture and release of CFCs and related substances
- Atmosphere will fully recover by 2070
- Nobel Prize in Chemistry 1995 (www.nobelprize.org)
Chlorofluorocarbons and Ozone Depletion

Mechanism (simplified):

\[
\text{Freon 12}
\]

\[
\begin{align*}
\text{Cl} & \text{Cl} \quad \text{F} \quad \text{F} \\
\text{h} \nu & \rightarrow \text{Cl} \text{Cl} \quad \text{Cl} + \cdot \text{Cl} \\
\text{Cl} + \text{O} & \rightarrow \text{ClO} + \cdot \text{O} \\
2 \text{Cl} + \cdot \text{O} & \rightarrow \text{ClO} + \text{Cl} + \cdot \text{O} \\
\text{ClO} + \cdot \text{O} & \rightarrow \cdot \text{Cl} + \text{O} \\
\text{Cl} & \text{Cl} \quad \text{F} \quad \text{F} \\
\end{align*}
\]

Chain reaction: On average one Cl radical destroys $\sim 10^4$ O$_3$ before termination

Nitric Oxide -- NO!

Gaseous radical and air pollutant

- Presence in high altitude exhaust implicated in ozone destruction

Physiological effects

- Important for signaling between nerve cells in brain
- Endogenous antibacterial/antiparasitic
- Relaxes blood vessel wall smooth muscle (vasodilation)

Short lived: $\text{in vivo}$ half-life $\sim 10$ seconds

Nobel Prize in Medicine 1998: Furchgott, Murad, and Ignarro (UCLA)
End Exam 2 Coverage