Chapter 14
Mass Spectrometry

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Mass Spectrometry (MS)

- An analytical technique for measuring the mass-to-charge ratio (\(m/z\)) of ions in the gas phase.
  - Mass spectrometry is our most valuable analytical tool for determining accurate molecular masses.
  - Also can give information about structure.
  - Proteins can now be sequenced by MS.
Mass Spectrometry (MS)

- Schematic of an electron ionization mass spectrometer (EI-MS).
A mass spectrometer is designed to do three things

- Convert neutral atoms or molecules into a beam of positive (or rarely negative) ions.
- Separate the ions on the basis of their mass-to-charge ($m/z$) ratio.
- Measure the relative abundance of each ion.
A Mass Spectrometer

Electron Ionization MS

- In the ionization chamber, the sample is bombarded with a beam of high-energy electrons.
- Collisions between these electrons and the sample result in loss of electrons from sample molecules and formation of positive ions.

\[ \text{Molecular ion (a radical cation)} \]
Molecular Ion

- **Molecular ion (M):** A radical cation formed by removal of a single electron from a parent molecule in a mass spectrometer.

- For our purposes, it does not matter which electron is lost; radical cation character is delocalized throughout the molecule; therefore, we write the molecular formula of the parent molecule in brackets with
  - a plus sign to show that it is a cation.
  - a dot to show that it has an odd number of electrons.
Mass Spectrum

- **Mass spectrum**: A plot of the relative abundance of ions versus their mass-to-charge ratio.
- **Base peak**: The most abundant peak.
  - Assigned an arbitrary intensity of 100.
- The relative abundance of all other ions is reported as a % of abundance of the base peak.
**MS of dopamine**

- a partial mass spectrum of dopamine showing all peaks with intensity equal to or greater than 0.5% of the base peak.
• The number of peaks in the mass spectrum of dopamine is given here as a function of detector sensitivity.

<table>
<thead>
<tr>
<th>Peak Intensity Relative to Base Peak</th>
<th>Number of Peaks Recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5%</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 1%</td>
<td>31</td>
</tr>
<tr>
<td>&gt; 0.5%</td>
<td>45</td>
</tr>
<tr>
<td>&gt; 0.05%</td>
<td>120</td>
</tr>
</tbody>
</table>

HO NH₂
What we have described is called electron ionization mass spectrometry (EI-MS).

Other mass spectrometry techniques include

- fast atom bombardment (FAB).
- matrix-assisted laser desorption ionization (MALDI).
- chemical ionization (CI).
- electrospray ionization (ESI).
Resolution

- **Resolution:** A measure of how well a mass spectrometer separates ions of different mass.
  - **Low resolution:** Refers to instruments capable of separating only ions that differ in nominal mass; that is ions that differ by at least 1 or more atomic mass units (amu).
  - **High resolution:** Refers to instruments capable of separating ions that differ in mass by as little as 0.0001 amu.
Resolution

- C₃H₆O and C₃H₈O have nominal masses of 58 and 60, and can be distinguished by low-resolution MS.
- C₃H₈O and C₂H₄O₂ both have nominal masses of 60.
- distinguish between them by high-resolution MS.

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>Nominal Mass</th>
<th>Precise Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₃H₈O</td>
<td>60</td>
<td>60.05754</td>
</tr>
<tr>
<td>C₂H₄O₂</td>
<td>60</td>
<td>60.02112</td>
</tr>
</tbody>
</table>
Isotopes

- Virtually all elements common to organic compounds are mixtures of isotopes.

<table>
<thead>
<tr>
<th>Element</th>
<th>Atomic weight</th>
<th>Isotope</th>
<th>Mass (amu)</th>
<th>Relative Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrogen</td>
<td>1.0079</td>
<td>$^1$H</td>
<td>1.00783</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^2$H</td>
<td>2.01410</td>
<td>0.016</td>
</tr>
<tr>
<td>carbon</td>
<td>12.011</td>
<td>$^{12}$C</td>
<td>12.0000</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{13}$C</td>
<td>13.0034</td>
<td>1.11</td>
</tr>
<tr>
<td>nitrogen</td>
<td>14.007</td>
<td>$^{14}$N</td>
<td>14.0031</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{15}$N</td>
<td>15.0001</td>
<td>0.38</td>
</tr>
<tr>
<td>oxygen</td>
<td>15.999</td>
<td>$^{16}$O</td>
<td>15.9949</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{18}$O</td>
<td>17.9992</td>
<td>0.20</td>
</tr>
<tr>
<td>sulfur</td>
<td>32.066</td>
<td>$^{32}$S</td>
<td>31.9721</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{34}$S</td>
<td>33.9679</td>
<td>4.40</td>
</tr>
<tr>
<td>chlorine</td>
<td>35.453</td>
<td>$^{35}$Cl</td>
<td>34.9689</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{37}$Cl</td>
<td>36.9659</td>
<td>32.5</td>
</tr>
<tr>
<td>bromine</td>
<td>79.904</td>
<td>$^{79}$Br</td>
<td>78.9183</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{81}$Br</td>
<td>80.9163</td>
<td>98.0</td>
</tr>
</tbody>
</table>
Isotopes

- Carbon, for example, in nature is 98.90% $^{12}\text{C}$ and 1.10% $^{13}\text{C}$.
- There are 1.11 atoms of carbon-13 in nature for every 100 atoms of carbon-12.

$$1.10 \times \frac{100}{98.90 \times 12} \times 100 = 1.11 \text{ atoms}^{13}\text{C}\text{ per 100 atoms}^{12}\text{C}$$
M+2 and M+1 Peaks

- The most common elements giving rise to significant M + 2 peaks are chlorine and bromine.
  - Chlorine in nature is 75.77% $^{35}\text{Cl}$ and 24.23% $^{37}\text{Cl}$.
  - A ratio of $M$ to $M + 2$ of approximately 3:1 indicates the presence of a single chlorine in a compound, as seen in the MS of chloroethane.
M+2 and M+1 Peaks

- Bromine in nature is 50.7% $^{79}$Br and 49.3% $^{81}$Br.
- A ratio of $M$ to $M + 2$ of approximately 1:1 indicates the presence of a single bromine atom in a compound, as seen in the MS of 1-bromopropane.
Because M + 1 peaks are relatively low in intensity compared to the molecular ion and often difficult to measure with any precision, they are generally not useful for accurate determinations of molecular weight.
To attain high efficiency of molecular ion formation and give reproducible mass spectra, it is common to use electrons with energies of approximately 70 eV [6750 kJ (1600 kcal)/mol].

- This energy is sufficient not only to dislodge one or more electrons from a molecule, but also to cause extensive fragmentation.
- These fragments may be unstable as well and, in turn, break apart to even smaller fragments.
Fragmentation of a molecular ion, M, produces a radical and a cation.

- Only the **cation** is detected by MS.
A great deal of the chemistry of ion fragmentation can be understood in terms of the formation and relative stabilities of carbocations in solution.

- Where fragmentation occurs to form new cations, the mode that gives the most stable cation is favored.
- The probability of fragmentation to form new carbocations increases in the order:

\[
\text{CH}_3^+ < 1^\circ < 1^\circ \text{ allylic} < 2^\circ \text{ allylic} < 3^\circ \text{ allylic}
\]

\[
1^\circ \text{ benzylic} < 2^\circ \text{ benzylic} < 3^\circ \text{ benzylic}
\]
Interpreting a mass spectrum

- The only elements to give significant M + 2 peaks are Cl and Br.
  - If no large M + 2 peak is present, these elements are absent.
- Is the mass of the molecular ion odd or even?
- **Nitrogen Rule:** If a compound has
  - zero or an even number of nitrogen atoms, its molecular ion will have an even \( m/z \) value.
  - an odd number of nitrogen atoms, its molecular ion will have an odd \( m/z \) value.
Alkanes

- Fragmentation tends to occur in the middle of unbranched chains rather than at the ends.
- The difference in energy among allylic, benzylic, 3°, 2°, 1°, and methyl cations is much greater than the difference among comparable radicals.
  - Where alternative modes of fragmentation are possible, the more stable carbocation tends to form in preference to the more stable radical.
Alkanes

- Mass spectrum of octane.
Alkanes

- Mass spectrum of 2,2,4-trimethylpentane.
Alkanes

- Mass spectrum of methylcyclopentane.
Alkenes

- Alkenes characteristically
  - show a strong molecular ion peak.
  - cleave readily to form resonance-stabilized allylic cations.

\[
\text{[CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_3]^+ \rightarrow \text{CH}_2=\text{CHCH}_2^+ + \cdot \text{CH}_2\text{CH}_3
\]
Cyclohexenes

- Cyclohexenes give a 1,3-diene and an alkene, a process that is the reverse of a Diels-Alder reaction (Chapter 24).

\[
\begin{align*}
\text{Limonene} & \quad (m/z \ 136) \\
\text{A neutral diene} & \quad (m/z \ 68) \\
\text{A radical cation} & \quad (m/z \ 68)
\end{align*}
\]
Alkynes

- Alkynes typically
  - show a strong molecular ion peak.
  - cleave readily to form the resonance-stabilized propargyl cation or substituted propargyl cations.

3-Propynyl cation (Propargyl cation)
Alcohols

- One of the most common fragmentation patterns of alcohols is loss of $\text{H}_2\text{O}$ to give a peak which corresponds to $\text{M-18}$.
- Another common pattern is loss of an alkyl group from the carbon bearing the OH to give a resonance-stabilized oxonium ion and an alkyl radical.

![Chemical diagram]

- Molecular ion (a radical cation)
- A radical
- A resonance-stabilized oxonium ion
Alcohols

- Mass spectrum of 1-butanol.
Aldehydes and Ketones

- Characteristic fragmentation patterns are:
  - cleavage of a bond to the carbonyl group (α-cleavage).
  - McLafferty rearrangement.

\[
\begin{align*}
\text{Molecular ion} & \quad \text{m/z 114} \\
\text{m/z 128} & \quad \text{α-cleavage} \\
\end{align*}
\]

\[
\begin{align*}
\text{m/z 58} & \quad \text{McLafferty rearrangement} \\
\end{align*}
\]
Aldehydes and Ketones

- Mass spectrum of 2-octanone.
Carboxylic Acids

 смысл characteristic fragmentation patterns are

• α-cleavage to give the ion [CO₂H]⁺ with m/z 45.
• McLafferty rearrangement.

Molecular ion
m/z 88

Molecular ion
m/z 88

+ [O= C-O-H]⁺

m/z 45

m/z 60
Carboxylic Acids

- Mass spectrum of butanoic acid.
Esters

α-cleavage and McLafferty rearrangement

\[
\begin{align*}
\text{Molecular ion} & \quad m/z 102 \\
\text{OCH}_3 \\
\text{α-cleavage} & \\
\text{m/z 71} \\
\text{m/z 59} \\
\text{OCH}_3 \\
\text{McLafferty rearrangement} & \\
\text{m/z 74}
\end{align*}
\]
Esters

- Mass spectrum of methyl butanoate.
Aromatic Hydrocarbons

- Most show an intense molecular ion peak.
- Most alkylbenzenes show a fragment ion of \( m/z \) 91.

\[
\begin{align*}
\text{Toluene radical cation} & \quad \xrightarrow{-H^+} \quad \text{Tropylium cation (m/z 91)} \\
\end{align*}
\]
The most characteristic fragmentation pattern of 1°, 2°, and 3° aliphatic amines is $\beta$-cleavage.

$$\text{CH}_3\text{-CH-CH}_2\text{-CH}_2\text{-NH}_2 + \xrightarrow{\beta\text{-cleavage}} \text{CH}_3\text{-CH-CH}_2\cdot + \text{CH}_2=\text{NH}_2$$

$m/z$ 30
Mass Spectrometry

End Chapter 14