CEE 772: Instrumental Methods in Environmental Analysis

Lecture #20
Rosa Yu & Dave Reckhow

Mass Spectrometry and Instrumentation
Content

• A brief introduction to mass spectrometry

• Mass spectrometry instrumentation
  – Important MS instrument performance factors
  – Types of mass spectrometers:
    • (Triple) Quadrupole Mass Spectrometer
    • Quadrupole Ion Traps (QIT)
    • Time-of-flight (TOF) Mass Analyzers

Ion source ➔ Mass filtration/separation ➔ Detection
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Mass Spectrometry Introduction

**Ion Formation**

**Mass Analysis**

**Detection**

- **Ionization:**
  - Electrospray Ionization
  - Electron Impact/Chemical Ionization
  - MALDI (matrix assisted laser desorption ionization)

- **Mass Analysis/Separation:**
  - Use electric and magnetic fields to apply a force on charged particles to control the trajectories of ions

- **Detection:**
  - Electron multiplier
The effect of electromagnetic fields on ions

• The relationship between force, mass, and the applied fields can be summarized in Newton's second law and the Lorentz force law.

1. **Newton's second law:**
   \[ F = ma \]
   the force causes an acceleration that is ** MASS** dependent

2. **Lorentz force law:**
   \[ F = e(E + vB) \]
   the applied force is also dependent on the **IONIC CHARGE**
   - \( F \) = the force applied to the ion
   - \( m \) = the mass of ion
   - \( a \) = acceleration
   - \( e \) = ionic charge
   - \( E \) = the electric field
   - \( vB \) = the vector cross product of the ion velocity and the applied magnetic field

• **Mass spectrometers separate ions according to their mass-to-charge ratio (m/z) rather than by their mass alone**
Tandem Mass Spectrometry

- *Tandem mass spectrometry*, also known as MS/MS or MS$^2$ (MS$^n$ only by ion traps), involves multiple steps of mass spectrometry selection, with some form of fragmentation occurring in between the stages.

- Select and fragment ions of interest to provide structural information (e.g. large molecules, such as proteins, polypeptides with a great number of residues, etc.)
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Important MS Instrument Performance Factors

- **Mass Accuracy**: How accurate is the mass measurement?

- **Resolution**: How well separated are the peaks from each other?

- **Sensitivity**: How small an amount can be analyzed? (More about sample preparation and which type of instrumentation applied.)
Mass Accuracy

• **How is mass defined?**

Assigning numerical value to the intrinsic property of “mass” is based on using carbon-12, $^{12}\text{C}$, as a reference point.

On unit of mass is defined as a Dalton (Da); thus **one Dalton is defined as 1/12 the mass of a single $^{12}\text{C}$ atom**.

By definition, one $^{12}\text{C}$ atom has a mass of 12.0000 Da.
Mass Accuracy

• Isotopes

Most elements have more than one stable isotope.

For example, most carbon atoms have a mass of 12 Da, but in nature, 1.1% of carbon atoms have an extra neutron, making their mass 13 Da.

Why do we care?

Mass spectrometers “see” the isotope peaks provided the resolution is high enough.

If an MS instrument has resolution high enough to resolve these isotopes, better mass accuracy is achieved.
### Stable Isotopes of Some Common Elements

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The decimal component is referred to as the mass defect.
The **monoisotopic mass** of a molecule is the sum of the accurate masses for the most abundant isotope of each element present. As the number of atoms of any given element increases, the percentage of the population of molecules having one or more atoms of a heavier isotope of this element also increases.
Mass Spectrometers measure mass-to-charge, not molecular mass.
Mass Resolution

Schematic representation of the two common definitions of resolution used in mass spectrometry:

• 10% valley
• Full width, half-maximum (FWHM)

The peak width definition considers a single peak in a mass spectrum made up of singly charged ions at mass m. The resolution R is expressed as m/Δm, where m is the width of the peak at a half-height (50%).

R is usually a function of m, m/Δm should be given for a
Mass Resolution

Monoisotopic mass

Average mass

A

R = 500
R = 1000
R = 5000

$C_{60}H_{86}N_{16}O_{15}$

B

Mono.

Average mass

R = 500
R = 1000
R = 5000

$C_{115}H_{161}N_{31}O_{35}$
WARNING: Insufficient Mass Accuracy Can Be Hazardous To Your Health
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Ion source ➔ Mass filtration/separation ➔ Detection
High Performance Mass Spectrometer, Circa 1976
Laboratory of Professor Klaus Beimann, MIT
(Bldg.56)
Types of Spectrometers

1. Triple Quadrupole Mass Spectrometer

- Ion Source
- Quadrupole Filters
- Electron Multiplier
Ion Formation: Electrospray Ionization (ESI)

- **Liquid-phase** dissolved analytes eluting from a chromatographic separation system (LC column) must be converted into **GAS-PHASE** under high vacuum.

- **Conversion Process**

<table>
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<tr>
<th>State-of-matter:</th>
<th>Liquid-phase</th>
<th>Evaporation</th>
<th>Gas Phase</th>
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<td>Pressure:</td>
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<td>High Vacuum</td>
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<tr>
<td>Charge State:</td>
<td>Neutral(Ionic)</td>
<td>Ionization</td>
<td>Ionic</td>
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</table>
• Either the needle or the interface has the high voltage
• Charge difference between the tip and the entrance plate
• Formation of a plume of fine droplets
• Desolvation of the droplets results in ion formation
Electrospray Ionization

ESI Types:
1. Positive – Use volatile proton donor (e.g. 0.1% formic acid)
2. Negative – Use volatile proton acceptor (e.g. 0.3% CEE 772 #20

Harris, 1999
Quadrupole Mass Filter

- The quadrupole mass analyzer is a “mass filter”.

- Quadrupole is made up of four parallel rods. The rods are electrodes, with electric fields around them.

- Combined DC and RF potentials on the quadrupole rods can be set to pass only a selected mass-to-charge ratio. All other ions do not have a stable trajectory through the quadrupole will collide with the quadrupole rods, never reaching the detector.
Quadrupole Mass Filter

Configuration of Voltages

- Each pair of rods is connected; rods have exactly the same voltage as the one directly opposite.

- One pair of rods have voltage:
  \(+V_{DC} + V_{RF} \cos(\omega t)\)
  The other pair have voltage:
  \(-V_{DC} - V_{RF} \cos(\omega t)\)

- Ions either make it through

Only ions of a specific mass-to-charge ratio make it through quadrupole based on magnitudes of \(V_{DC}\) and \(V_{RF}\).
Voltage Relationships During a Mass Scan

- Amplitude of the DC and alternating fields both increase in time.
- Amplitude of the alternating fields is \(~6\times\) strength of the DC fields.
- RF/DC ratio is constant.
How Do RF Fields Affect Ion Trajectories?

Whether an ion would make it through depends on:

- Ion charge (more charges, more forces, faster acceleration)
- Ion mass (smaller mass, easier to crash on the quadrupole rods)
- Strength of field and frequency of oscillation
How Do Combined DC & RF Fields Affect Ion Trajectories?

- If DC field is **positive**, high mass ions will have stable trajectories.
- Ions of m/z lower than some critical value will crash.
How Do Combined DC & RF Fields Affect Ion Trajectories?

- If DC field is negative, low mass ions will have stable trajectories (respond quickly)
- Ions of m/z greater than some critical value will crash
Quadrupole Is A Double Mass Filter

- In Y dimension (+DC voltage), ions make it through unless their mass is too low – low mass filter
- In X dimension (-DC voltage), ions make it through unless their mass is too high – high mass filter

At certain values of voltage, only a narrow range of m/z will make it through the quadrupole.
Tandem MS – Collision-induced Dissociation (CID)

Collision Cell

Precursor Ion aka Parent Ion → Activated Ion → Fragmenting Ion → Activated Fragment Ion Continuing to Fragment → Fragment Ions aka Product Ions

Collision Cell

Fragment Ion

Neutral loss (e.g., \(-\text{H}_2\text{O}\))

Collision Gas
Structural Information from Tandem Mass Spectrometry

**MS vs. MS/MS**

- **MS**
  - Scan m/z 350-1200
  - MS 1: Collision Cell (off)
  - MS 2: Collision Cell (on)
  - Pass m/z 834-838
  - Fragment all ions
  - Pass all ions

- **MS/MS**
  - MS or mass spectrum
  - intact peptide parent ions

**Example of MS/MS Spectrum**

- (R)FIIVGYVDDTQFVR(F)
- MS/MS spectrum of doubly charge ion at m/z 836.5
  - y7, y8, y9, y10
  - b2, b3, b4, b5, b6, b7, b8, b9, b10, b11, b12, b13
  - 261.30, 421.33, 473.16, 499.46, 650.44, 706.62, 765.40, 818.64, 907.26, 1142.53, 1251.46, 1399.48
Detector – Electron Multiplier
Detector – Electron Multiplier
Detector – Electron Multiplier

dynodes
Detector – Electron Multiplier

dynodes
Detector – Electron Multiplier
Detector – Electron Multiplier
Detector – Electron Multiplier
Detector – Electron Multiplier

One Impact → ~10^6 electrons
Benefits and Limitations of Quadrupole Mass Filter

• **Benefits**
  - Classical mass spectrometer
  - Good reproducibility
  - Relatively small and low-cost system
  - Low-energy collision-induced dissociation (CID) has efficient conversion of parent to daughter ions

• **Limitations**
  - Limited resolution
  - Not well suited for pulsed ionization methods
  - CID depends strongly on energy, collision gas, pressure and other factors
Types of Spectrometers

2. Quadrupole Ion Traps

*Ions are created inside the trapping volume

Ion Formation: Electron Impact

1. Production of Molecular Ions

In electron impact ionization (EI), electrons from filament ionizes a compound, in a certain case, by only knocking out one electron without breaking up the molecule.

M + e⁻ → M⁺ + e⁺ + e⁻

2. Production of Fragment Ions
Ion Formation: Chemical Ionization
Quadrupole Ion Trap (QIT) Configuration

All ions created over a given time period were **trapped** and then **sequentially ejected** from the ion trap into a conventional electron multiplier detector. Thus, all ions were stored while mass analysis was performed.
Ion Trap Theory

• How are ions trapped?

Quadrupole ion traps are dynamic mass analyzers that use an oscillating electric potential applied to the ring electrode, called the “fundamental RF”, to focus ions toward the center of the trap. This is accomplished by creating a parabolic potential, shaped like a “saddle”, inside the trapping volume. The strength of the restoring force linearly increases as the ion trajectory deviates from the central axis, focusing the ion back to the center of the trapping volume.
Ion Trap Theory

- How are ions SELECTIVELY AND SEQUENTIALLY ejected?

Ions are ejected through holes in the endcap electrode and are typically detected using an electron multiplier.

Trapped ions of a given m/z oscillate at a frequency known as the secular frequency. Resonance conditions are induced by matching the frequency of a supplementary potential applied to the endcap electrodes to the secular frequency of the ion. The ion will absorb energy from the applied field and the trajectory will linearly increase toward the endcap electrodes until the ion becomes unstable and is ejected.
Ionized $\rightarrow$ Focused into the trap $\rightarrow$ Trapped $\rightarrow$ Ejected $\rightarrow$ Detected

Accumulation

Ejection

Detection

Ring Electrode
Main or primary RF

He Gas

End Cap
Auxiliary RF (1/3 of main RF)

Int
m/z
Tandem MS in QIT

• **Tandem mass spectrometry (up to 12 stages, MS^{12})**

Structural information is obtained by collision-induced dissociation (CID) with a helium damping gas a mass spectrum is generated by sequentially ejected fragment ions from low m/z to high m/z.
The Damping Gas

The ion trap is typically filled with helium to a pressure of ~1 mtorr. Collisions with helium reduce the kinetic energy of the ions and serve to quickly contract trajectories toward the center of the ion trap, enabling trapping of injected ions. This is called “cooling effect”, where the ion population forms a “packet” near the center of the trap.

Benefits and Limitations of QIT

• **Benefits**
  Compact mass analyzer (roughly the size of a tennis ball)
  Up to 12 stages of tandem mass spectrometry have been performed
  (multi-stage is unique with QIT)
  Exquisitely sensitive.

• **Limitations**
  Poor dynamic range
  Subject to “space-charge” effect and ion reaction
  Collision energy not well-defined in CID MS/MS
Types of Spectrometers

1. Time-of-flight (TOF)

Ion Source → TQ → TOF → Electron Multiplier

Typical Q-TOF System
Ion Source: MALDI

- A time of flight mass spectrometer measures the mass-dependent time it takes ions of different masses to move from the ion source to the detector. This requires that the starting time (the time at which the ions leave the ion source) is well-defined. Therefore, ions are preferably formed by a pulsed ionization method, usually matrix-assisted laser desorption ionization, or MALDI.
MALDI: Matrix Assisted Laser Desorption Ionization

1. Sample is mixed with matrix (X) and dried on plate.
2. Laser flash ionizes matrix molecules.
3. Sample molecules (M) are ionized by proton transfer: $XH^+ + M \rightarrow MH^+ + X$.

Inside high vacuum manifold of instrument
MALDI: Matrix Assisted Laser Desorption Ionization

Liquid matrices used for MALDI analysis of biomolecules

- CHCA: \(\alpha\)-Cyano-4-hydroxy-cinnamic acid
  - MW 189.17
- Sinapinic acid (SA)
  - (E)-3-(4-hydroxy-3,5-dimethoxyphenyllacrylic
  - MW 224.21
- DHB: 2,5-dihydrobenzoic acid
  - MW 124.14

MALDI TOF spectrum of IgG

- MH\(^+\)
- (M+2H)\(^2+\)
- (M+3H)\(^3+\)
How does TOF separate ions?

The flight time for each mass is unique. The flight time \( t \) is determined by the energy \( E \) to which an ion is accelerated, the distance \( d \) it has to travel, and its mass (strictly speaking, its mass-to-charge ratio).

\[
E = \frac{1}{2}mv^2 \quad \Rightarrow \quad v = \sqrt{\frac{2E}{m}}
\]

This equation says that for a given kinetic energy, \( E \), smaller masses will have larger velocities, and larger masses will have smaller velocities. Therefore, ions with lower masses arrive at the detector earlier, and higher masses later.
Time-of-flight (TOF) Mass Analyzer

• How does TOF separate ions?

Because: \( v = \frac{d}{t} \), there is:

\[ m = \frac{2E}{d^2}t^2 \]

For a given energy \((E)\) and distance \((d)\), the mass is proportional to the square of the flight time of the ion. In design of an TOF mass spectrometer, much effort is devoted to holding the values of energy \((E)\) applied to the ions and the distance \((d)\) the ion travels constant, so that an accurate measurement of flight time will give an accurate mass value.
At higher masses, resolution is difficult because flight time is much longer. Also at high masses, not all of the ions of the same m/z values reach their ideal TOF velocities. To fix this problem, often a reflectron is added to the analyzer. The reflectron consists of a series of ring electrodes of very high voltage placed at the end of the flight tube. When an ion travels into the reflectron, it is reflected in the opposite direction due to the high voltage.
**Reflectron**

- A linear-field reflectron allows ions with **greater kinetic energies** to **penetrate deeper** into the reflectron than ions with smaller kinetic energies. The ions that penetrate deeper will take longer time to return to the detector. If a packet of ions of a **given m/z** contains ions with **varying kinetic energies**, then the reflectron will decrease the spread in the ion flight times, and therefore improves the resolution.
Benefits and Limitations

• **Benefits**
  - Faster MS analyzer
  - Well suited for pulse ionization methods (MALDI)
  - High ion transmission
  - Highest practical mass range of all MS analyzers

• **Limitations**
  - Requires pulsed ionization or ion beam switching
  - Limited parent-ion selectivity for tandem mass spectrometry
• To next lecture