The Role of Spectroscopy in Organic Synthesis

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Role of Organic Synthesis

- Biology
- Medicine
- Chemistry
- Materials
Organic Synthesis

Structure Confirmation

Dual Nature, Science & Art

New Reagents, Catalyst, Reactions

New Chemicals

New Reactions

New Chemistry

Medicine, Biology, Materials Science

Application in everyday's life

Structural Activity Relationship

Need for Synthesis
History of Organic Synthesis
Birth of Organic Synthesis

- First total synthesis of a natural product, urea by Wohler in 1828
- Marks the beginning of organic synthesis
- Conversion of an inorganic substance (ammonium cyanate) into an organic substance for the first time
- Until this discovery, it was believed that organic substances could only be formed under the influence of the "vital force" in the bodies of animals and plants
- Hence, this disproved the "vitalism"

\[ \text{NH}_4\text{CNO} \rightarrow \text{H}_2\text{N} &= \text{C} &= \text{NH}_2 \]

Urea
Wohler, 1828

Atom Economy
Introduction of “Synthesis”

- As the second major achievement, acetic acid was synthesized from elemental carbon by Kolbe in 1845.

- For the first time he coined the word “synthesis” to describe the process of assembling a chemical compound from other substances.

\[ \text{Acetic acid} \]

\[ \text{Kolbe, 1845} \]
Organic Synthesis (1900-1910)

a-terpineol
[Perkin, 1904]

camphor
[Komppa, 1903]
[Perkin, 1904]

tropinone
Willstatter, 1901
Development of Grignard Reagent

Grignard Reaction: Nobel prize in 1912 for the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry.

Powerful tool to synthesize new C-C bond
Provides flexibility in the synthesis

Compt. Rend. 1900, 130, 1322
Mannich Reaction:

- Amino alkylation of an acidic proton placed next to a carbonyl functional group
- The final product is a β-amino-carbonyl compound

*Archiv der Pharmazie 1912, 250, 6457*
Claisen Rearrangement:

- Carbon-carbon bond-forming chemical reaction
- The heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl.

\[ \text{Ber. 1912, 45, 3157} \]
Organic synthesis has always been one of the celebrated fields of research activities through the development of science.

With time the size and complexity of molecular scaffolds have increased manifolds.

With the evolution of natural products synthesis as a major field of research, highly complex organic molecules are regularly isolated or synthesized.
Complex Molecules

calicheamicin
[Nicolaou, 1992]

sanglifehrin A
[Nicolaou, 1999]
Complex Molecules

brevetoxin B
[Nicolaou, 1995]

brevetoxin A
[Nicolaou, 1998]
Molecular Characterization

- Once synthesized, a molecule had to be characterized.
- Old characterization techniques involved destructive methods like breaking down the molecule into smaller fragments or breaking it down completely for elemental analysis.
- Apart from being time consuming and painstaking, such methods led to loss of precious compounds during characterization.
- With molecules being more and more stereochemically diverse, methods of assigning stereochemistry had to be invented.
In 1848, Louis Pasteur discovered that tartaric acid had two types of crystals which had opposite effect on plane polarized light.

He was the first person to separate the two enantiomers manually by the help of nothing but a pair of tweezers and a microscope!

But still there remained the unsolved question of identifying the bond connectivity and absolute stereochemistries...
During the turn of the 19th to 20th century, Emil Fischer made his greatest contribution towards the synthesis of sugars and assigning the stereochemical relation between them.

For characterization, he used chemical techniques like oxidation, reduction, homologation and common osazone formation (which he used to crystalize through the help of his beard!).

Combining all these techniques together, he successfully assigned the stereochemical relationship between epimers like glucose and mannose.

More importantly, he correctly assigned the relative stereochemistries of all the stereocenters of the sugars, which in that era was a remarkable achievement!
Organic Synthesis in 20th Century

- Spectroscopy
- Stereochemistry & Conformational Analysis
- Cascade, Tandem reactions
- Asymmetric Synthesis
- Advances in 20th Century
- Electronic Theory, Chemical Bonding
- Mechanism, Physical Organic Chemistry
- Resolution Methods
- New Reagents
- New Reactions
- Organo metallic
Role of Spectroscopy

- Spectroscopy literally means the study of the interaction of matter with electromagnetic radiation.

- Spectroscopy was invented and subsequently developed as a major tool for molecular characterization as a replacement for destructive methods previously used.

- Electromagnetic spectroscopy can be broadly classified into the following categories:
  
  - **Absorption Spectroscopy:** The energy absorbed by the matter when it interacts with the radiation is measured.
  
  - **Emission Spectroscopy:** The energy released by the matter when it decays from an excited state to its ground state is measured.
  
  - **Scattering or Reflection Spectroscopy:** Studies the nature of scattering of high energy incident radiation by a matter.
Wave

- It transfers energy from one place to another.
- In case of light, the energy is transferred due to local fluctuations in electric and magnetic field.
- Wavelength = Distance between two crests

\[
\text{wavelength, } \lambda
\]

- Frequency = No. of crests passing through a particular point per second

\[
\text{higher frequency means shorter wavelength}
\]

Red 625 nm
Green 520 nm
Electromagnetic Spectrum

Energy increases

Short wavelength

Long wavelength

\[ 10^{-5} \text{ nm} \quad 10^{-3} \text{ nm} \quad 1 \text{ nm} \quad 10^3 \text{ nm} \quad 10^6 \text{ nm} \quad 1 \text{ m} \quad 10^3 \text{ m} \]

Gamma rays  X rays  Ultraviolet  Infrared  Microwaves  Radio waves

High frequency

\[ 10^{24} \text{ Hz} \quad 10^{22} \text{ Hz} \quad 10^{20} \text{ Hz} \quad 10^{18} \text{ Hz} \quad 10^{16} \text{ Hz} \quad 10^{12} \text{ Hz} \quad 10^{10} \text{ Hz} \quad 10^{8} \text{ Hz} \quad 10^{6} \text{ Hz} \quad 10^{4} \text{ Hz} \quad 10^{2} \text{ Hz} \]

Low frequency

Visible light

\[ 7 \times 10^{14} \text{ Hz} \quad 4 \times 10^{14} \text{ Hz} \]
Organic spectroscopy relates to the study and characterization of typical organic molecules.

The following techniques are most commonly used to elucidate the structure of an organic molecule:

- Ultraviolet Spectroscopy (UV)
- Infrared Spectroscopy (IR)
- Nuclear Magnetic Resonance Spectroscopy (NMR)
- Mass Spectrometry
UV light can be absorbed by molecules to excite higher energy (most loosely bound) electrons from lower energy states to higher states.

Such transitions can be studied extensively to understand the binding energy of the corresponding electrons undergoing transition.

Since \( \pi \)-electrons are most loosely bound in an organic molecule, UV spectroscopy yields a lot of information about the degree of unsaturation in a molecule.

When the wavelength of the transition exceeds the UV range, based on the same principle, even the colours of molecules can be explained on the basis of absorption of visible light.

\( \beta \)-carotene
\[ \lambda_{\text{max}} = 452 \text{ nm} \]

1,3-butadiene
\[ \lambda_{\text{max}} = 217 \text{ nm} \]
Infrared Spectroscopy

- IR light can be absorbed by the vibrational modes of molecules to get excited to higher vibrational levels.
- Molecular vibrations constitute of vibrations across bonds or certain groups as a whole.
- So IR spectroscopy gives a lot of information on the functional groups and types of bonds present in the molecule.
- Even for the same functional group, there is distinct difference between the stretching frequencies.

\[
\begin{align*}
\nu_{C=O\text{(stretch)}} &= 2140 \text{ cm}^{-1} \\
\nu_{C=O\text{(stretch)}} &= 1715 \text{ cm}^{-1}
\end{align*}
\]

CH-521 Course on Interpretative Molecular Spectroscopy; Course Instructor: Krishna P. Kaliappan
Overview of Functional Groups in IR

- O-H, N-H, C-H
- S-H, C≡N, C≡C
- C=O, C=N, C=C
- S=O, N=O, C-O, C-N
- C-C, C-Cl, C-Br, C-I

Wave Number (cm⁻¹)

Transmittance (%)
NMR Spectroscopy

- Magnetically active nuclei split into their corresponding nuclear spin states upon being exposed to magnetic field.

- When the frequency of this nuclear transition couples with that of an externally supplied radiofrequency wave, resonance is said to take place.

- A huge number of magnetically active nuclei can be probed through this technique: $^1\text{H}$, $^2\text{D}$, $^{13}\text{C}$, $^{19}\text{F}$, $^{31}\text{P}$, $^{11}\text{B}$, $^{77}\text{Se}$, $^{125}\text{Te}$ to name a few.

- $^1\text{H}$ NMR is probably the most informative and widely used technique.

- NMR spectroscopy provides information about the different types of protons present in the system, the number of each type of proton present and also the chemical environment in which the different types of protons are present.
NMR Spectroscopy

$^1$H NMR Correlation Chart:
13C NMR also can be very useful in providing information about the types of carbons present in the molecule.

Attached Proton Test (APT) and Distortionless Enhancement by Polarization Transfer (DEPT) can also give information about the number of protons attached to any carbon.

2-dimensional NMR spectroscopy correlates different nuclei with one another and gives information about how they are connected between themselves either through bond or through space.

For a standard organic molecule of average complexity, a properly recorded combination of all these NMR techniques is more than sufficient to identify the structure of the molecule completely.
NMR Spectroscopy

$^{13}$C NMR Correlation Chart:
Mass Spectrometry

- Molecules are ionized by various techniques and then filtered according to their masses.

- During this process, molecules might break down into constituent fragments, based on the stability of ions formed. Even these fragments are detected and returned according to their masses.

- Technique is fundamentally different from others described because here there is no interaction of matter with electromagnetic radiation. Hence this technique is called spectrometry (and not spectroscopy).

- A mass spectrum can give information about the molecular weight of the parent compound.

- Based on the mass of the fragments formed, or of those which are eliminated, one can deduce vital information about the possible functional groups present.
Carbon-Hydrogen Stretching

Some comparisons among the principal spectroscopic methods (Good features score three stars):

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<th>$^{13}$C NMR</th>
<th>$^{1}$H NMR</th>
<th>IR</th>
<th>MS</th>
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Text Books

- Spectrometric Identification of Organic compounds by Silverstein and Webster, 5th Ed (UV), 7th Ed (Mass, IR, NMR).

- Organic Spectroscopy by William Kemp, 3rd Ed.

- Spectroscopy by Pavia, Lampman, Kriz, Vyvyan, IE.

- Application of absorption spectroscopy of organic compounds by John Dyer.

- Spectroscopic problems in organic chemistry, Williams and Flemings.

- Solving problems with NMR spectroscopy Atta-Ur-Rahman.