

The Role of Spectroscopy in Organic Synthesis



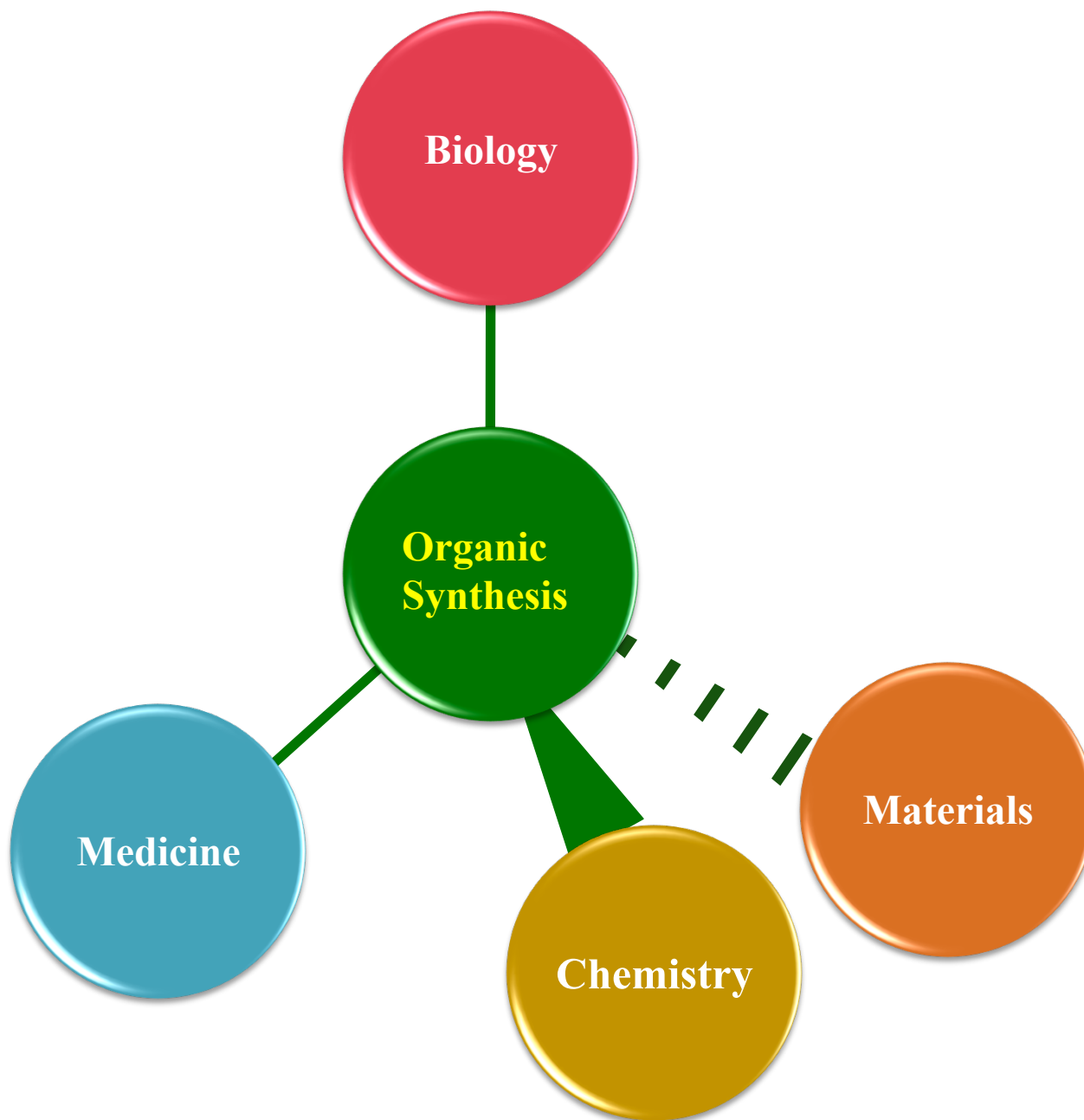
Krishna P. Kaliappan
Department of Chemistry
Indian Institute of Technology-Bombay
Mumbai 400 076 INDIA

<http://www.chem.iitb.ac.in/~kpk>

kpk@chem.iitb.ac.in

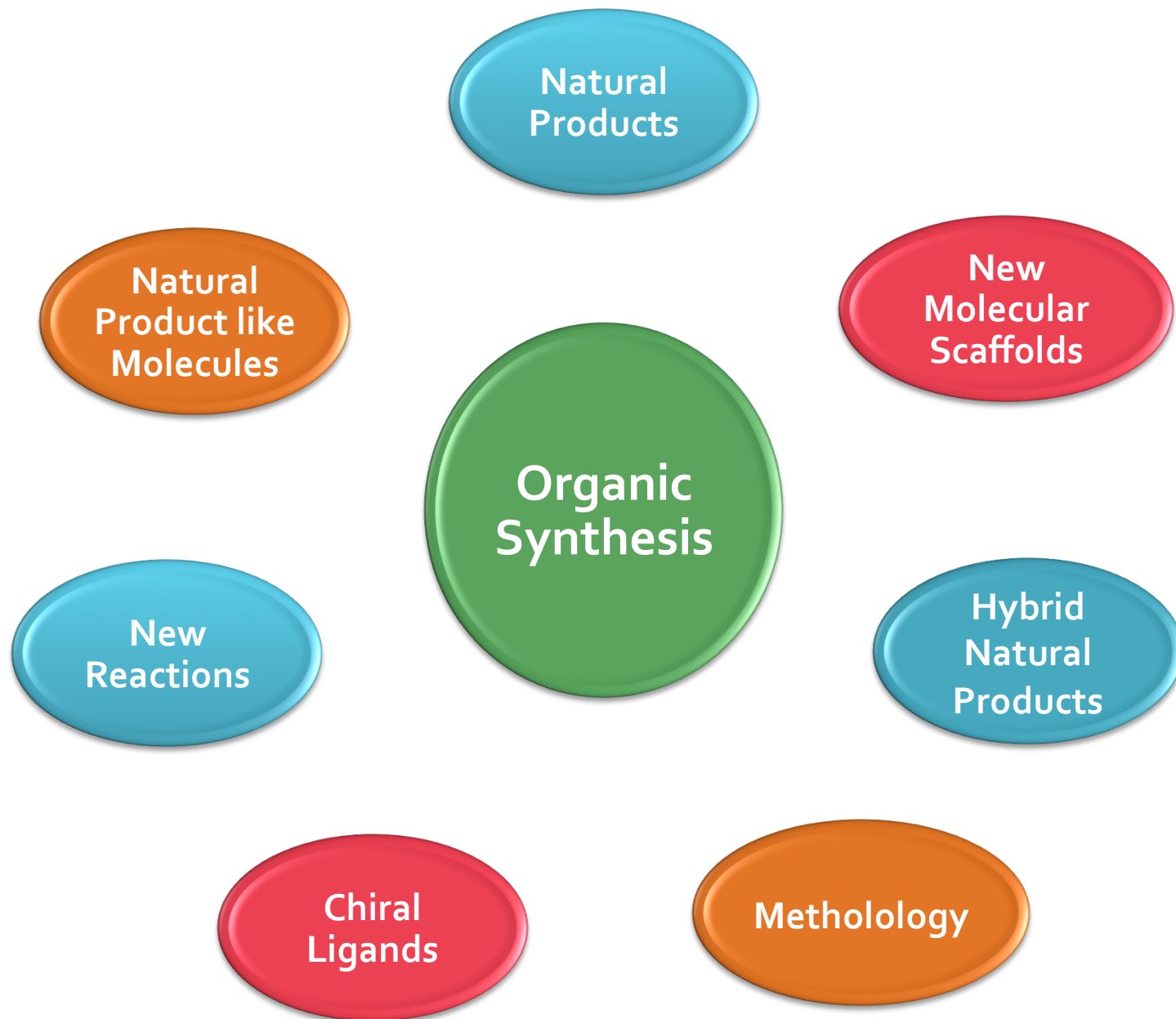


Role of Organic Synthesis





Organic Synthesis





Need for Synthesis

Structure
Confirmation

Dual
Nature,
Science &
Art

New
Reagents,
Catalyst,
Reactions

New
Reactions

Organic
Synthesis

New
Chemistry

Medicine,
Biology,
Materials
Science

Application
in everyday's
life

Structural
Activity
Relationship

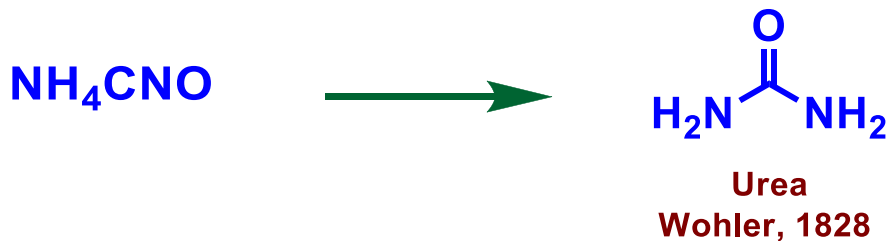


History of Organic Synthesis



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**”

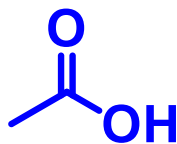


Atom Economy



Introduction of “Synthesis”

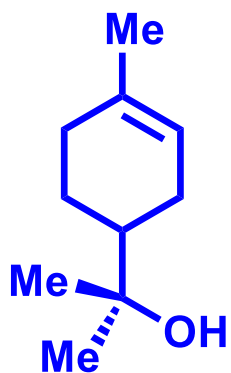
- As the second major achievement, acetic acid was synthesized from elemental carbon by **Kolbe** in 1845
- For the first time he coined the word “**synthesis**” to describe the process of assembling a chemical compound from other substances



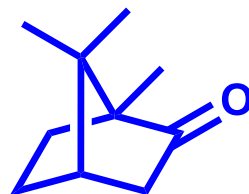
Acetic acid
Kolbe, 1845



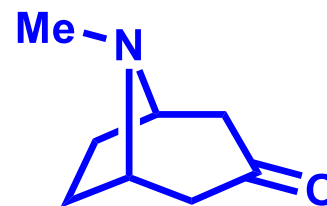
Organic Synthesis (1900-1910)



alpha-terpineol
[Perkin, 1904]



camphor
[Komppa, 1903]
[Perkin, 1904]



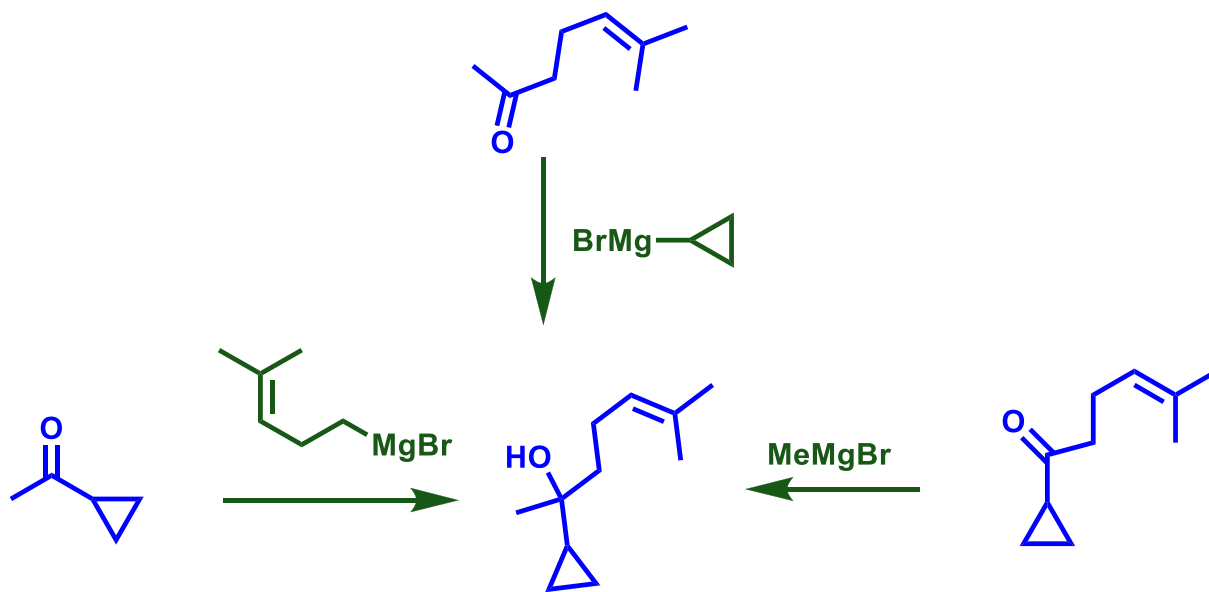
tropinone
Willstatter, 1901



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

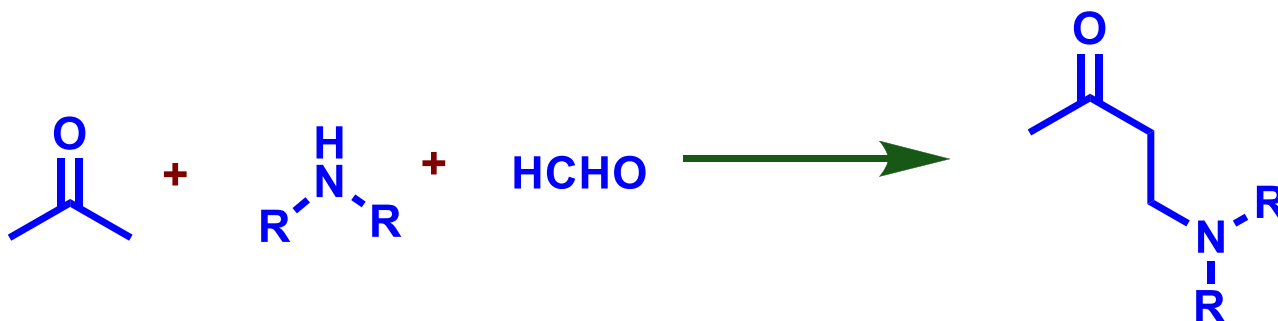




Development of Mannich Reaction

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

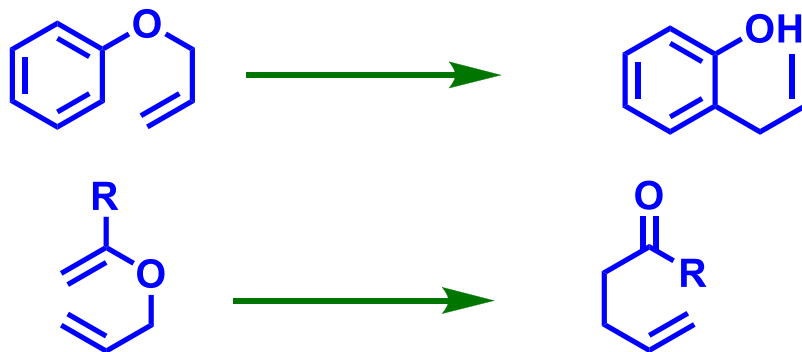
Multi-Component Reaction



Claisen Rearrangement

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.



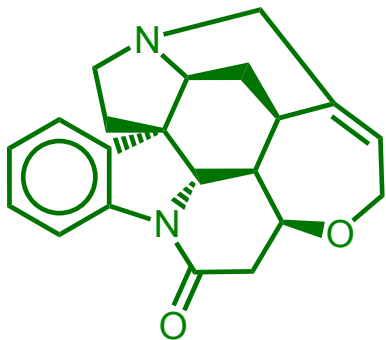
Ber. 1912, 45, 3157

First Pericyclic Reaction

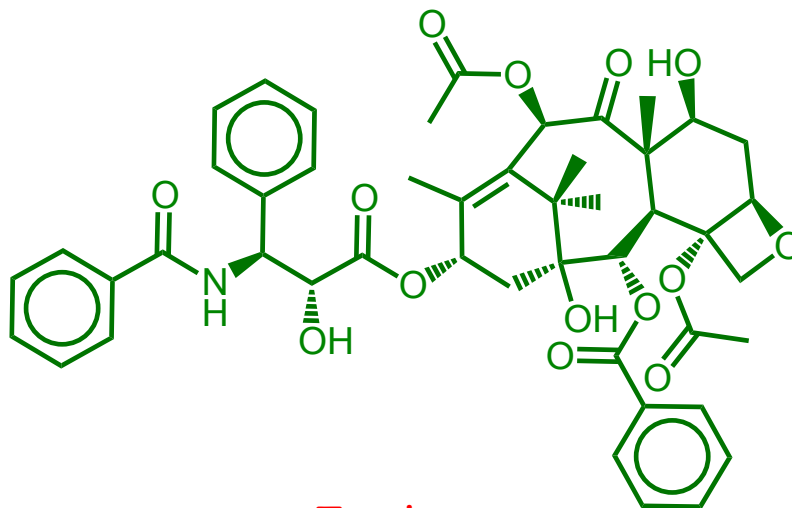


Organic Synthesis Through Time

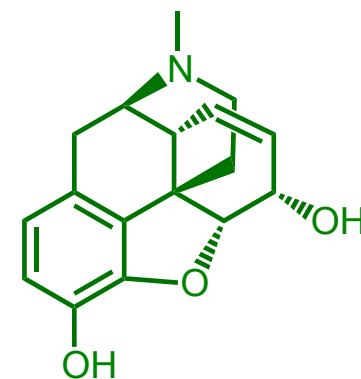
- **Organic synthesis** has always been one of the celebrated fields of research activities through the development of science.
- With time the **size and complexity** of molecular scaffolds have increased manifolds.
- With the evolution of natural products synthesis as a major field of research, **highly complex organic molecules** are regularly isolated or synthesized.



Strychnine

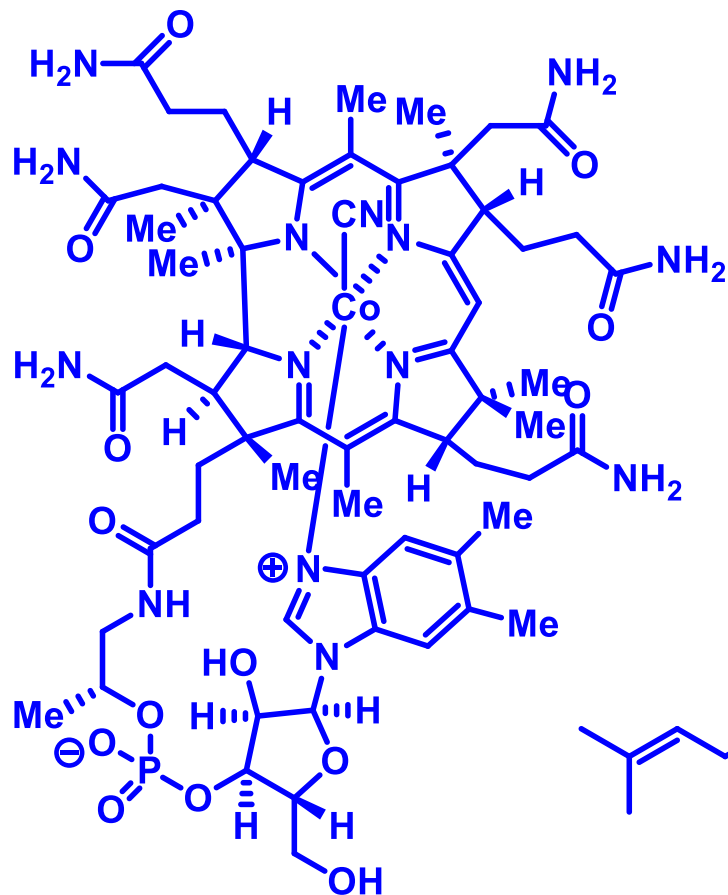


Taxol

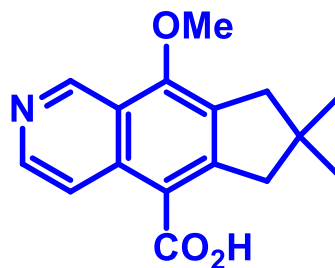


Morphine

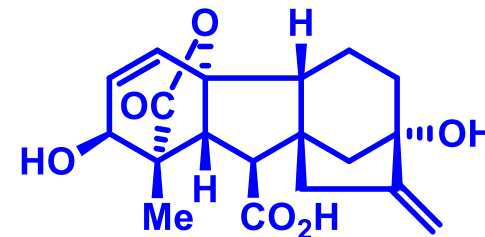
Complex Molecules



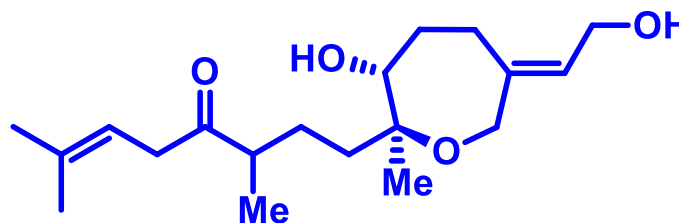
vitamin B
[Woodward-Eschenmoser, 1973]



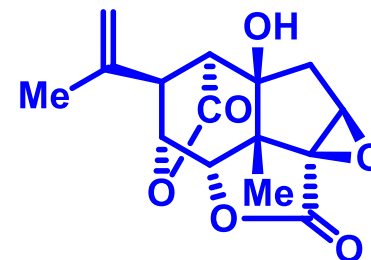
illudinine
[Woodward, 1977]



gibberellic acid
[Corey, 1978]



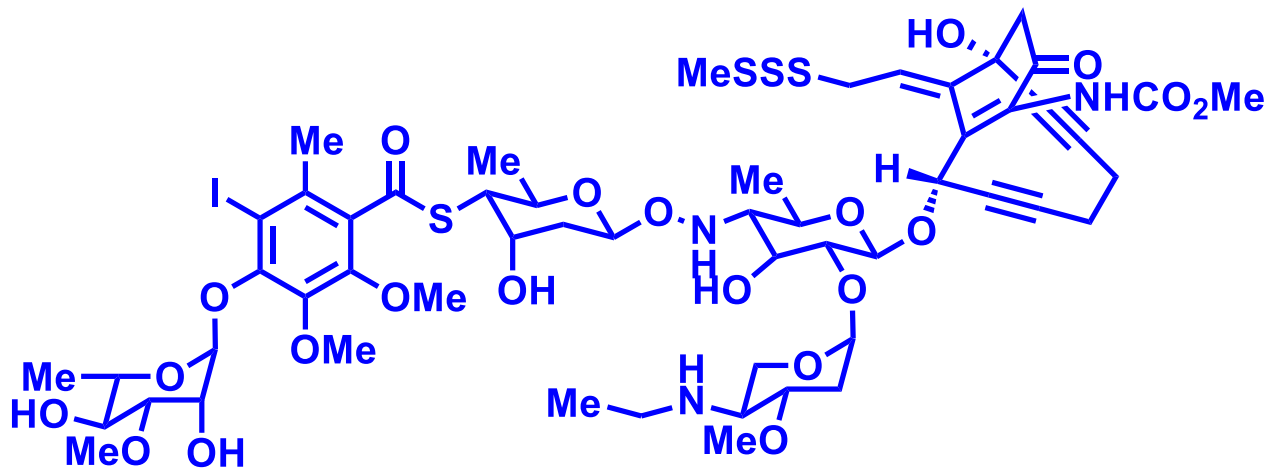
zoapatanol
[Nicolaou, 1980]



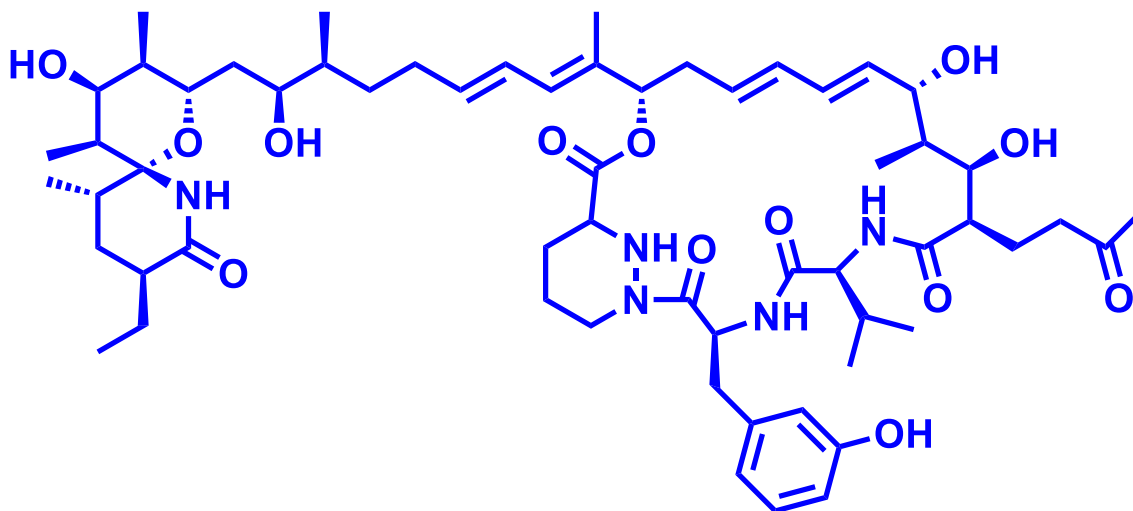
picrotoxinin
[Corey, 1979]



Complex Molecules

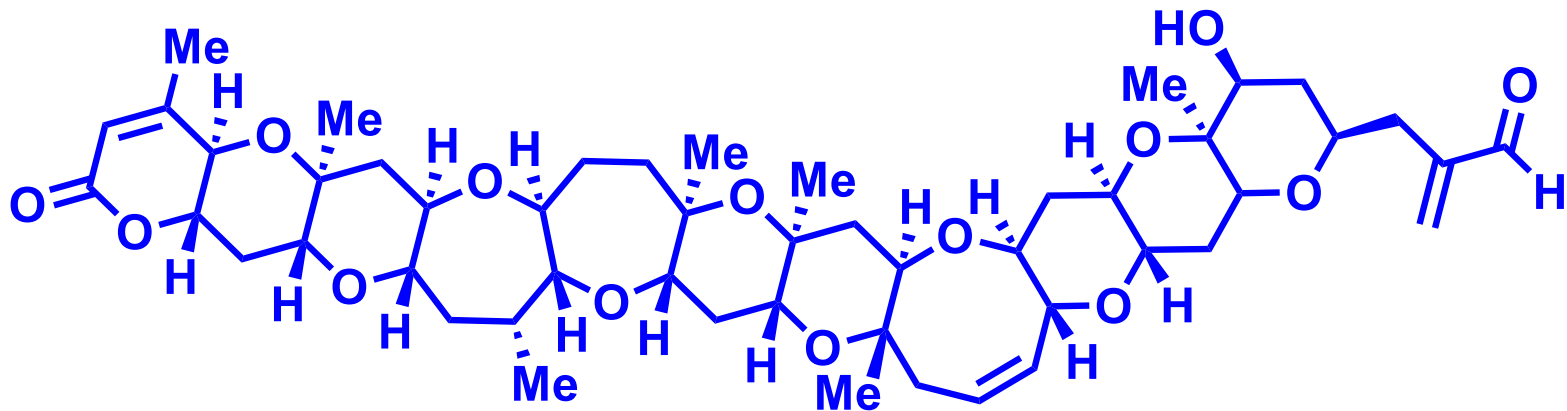


calicheamicin
[Nicolaou, 1992]

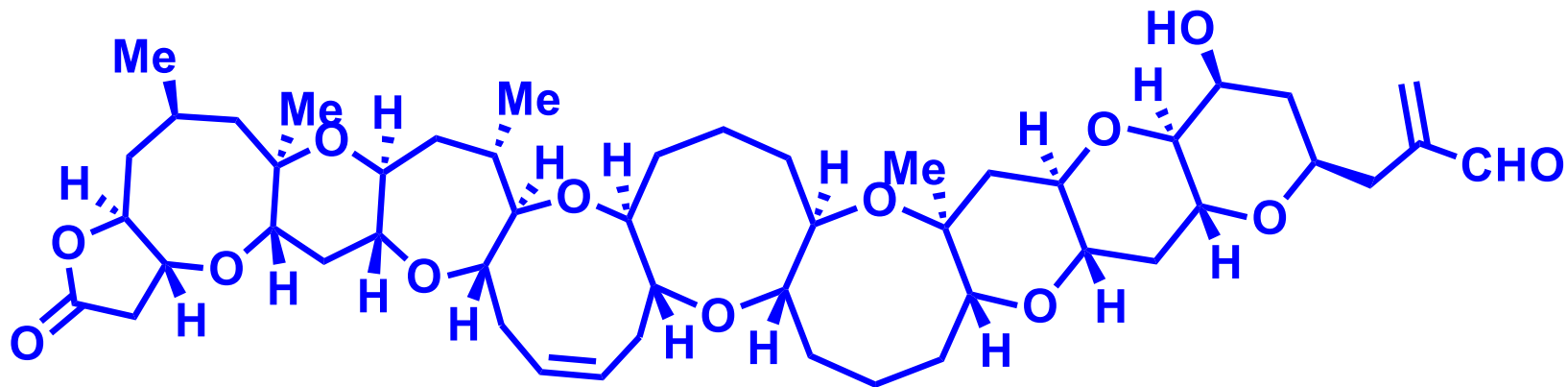


sanglifehrin A
[Nicolaou, 1999]

Complex Molecules



brevetoxin B
[Nicolaou, 1995]



brevetoxin A
[Nicolaou, 1998]



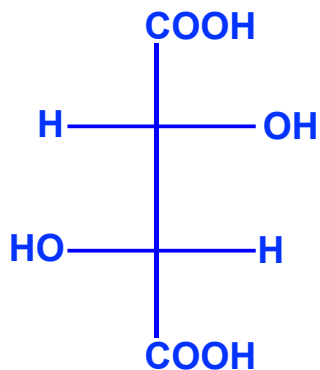
Molecular Characterization

- 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.

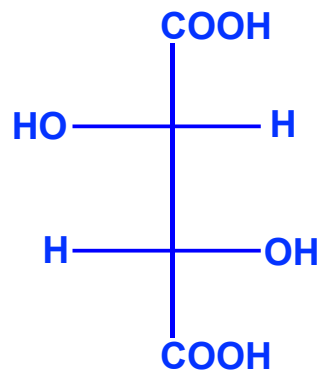


The Story of Enantiomers

- 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!



L(+) tartaric acid



D(-) tartaric acid

- But still there remained the unsolved question of identifying the bond connectivity and absolute stereochemistries...



Stereochemical Configuration

- 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

Electronic
Theory, Chemical
Bonding

Organo
metallic

Stereochemistry
& Conformational
Analysis

Mechanism,
Physical Organic
Chemistry

Cascade,
Tandem
reactions

Advances in
20th Century

Resolution
Methods

Asymmetric
Synthesis

New
Reagents

New
Reactions



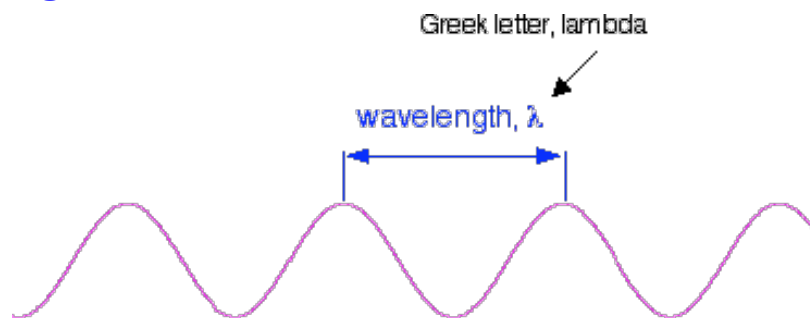
Role of Spectroscopy

- 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.



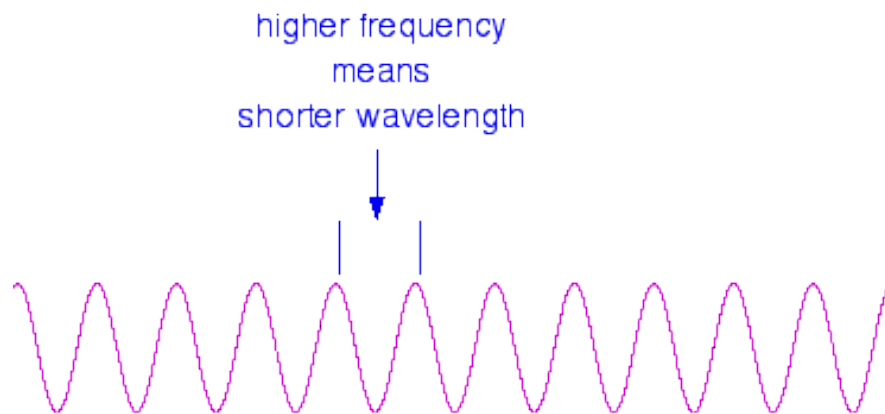
Wave

- 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



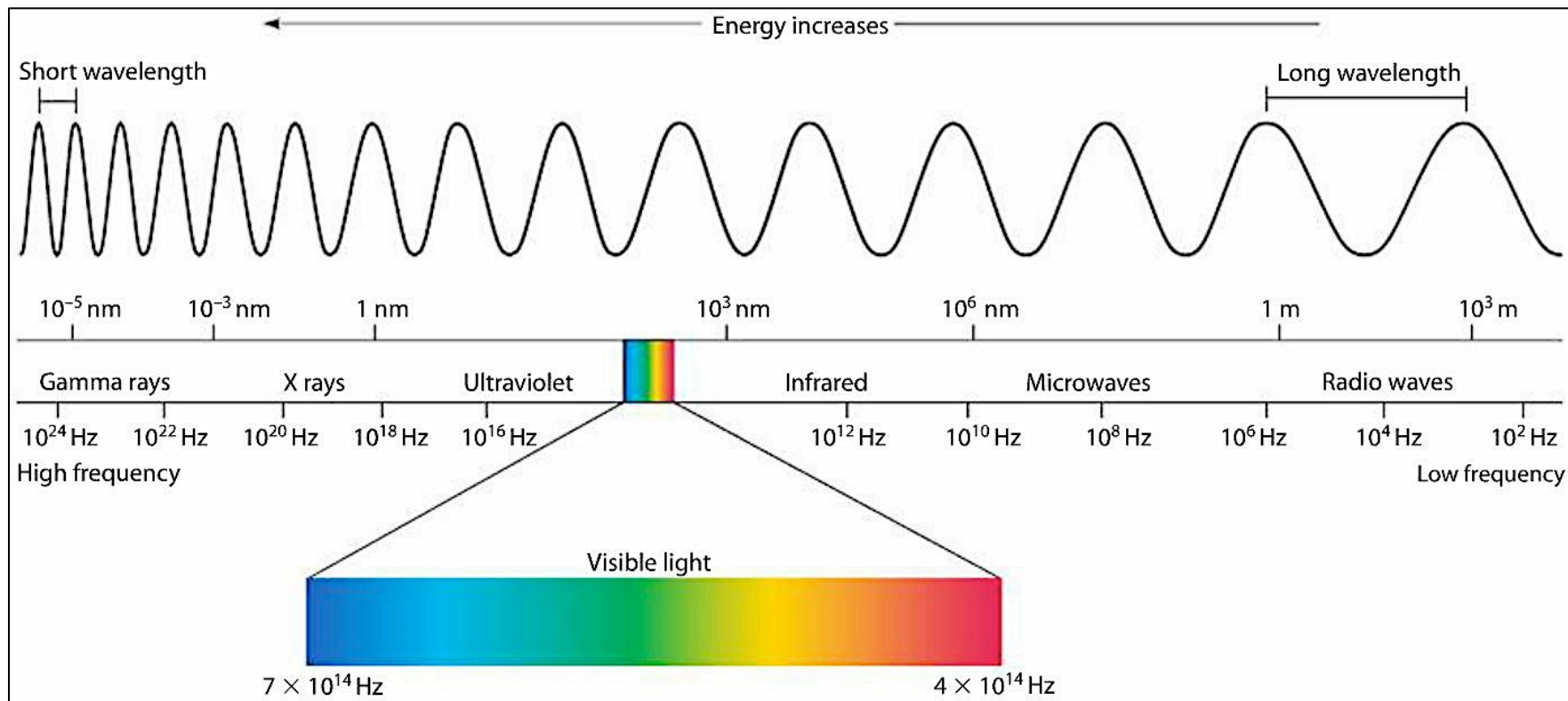
Red 625 nm
Green 520 nm

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





Electromagnetic Spectrum





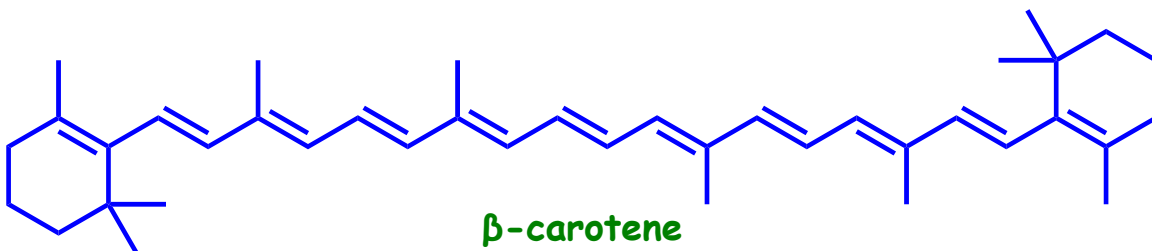
Organic Spectroscopy

- 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



Ultraviolet Spectroscopy

- 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 π -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.



β -carotene
 $\lambda_{\max} = 452 \text{ nm}$

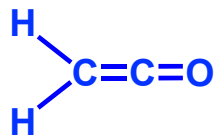


1,3-butadiene
 $\lambda_{\max} = 217 \text{ nm}$

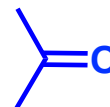


Infrared Spectroscopy

- 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.



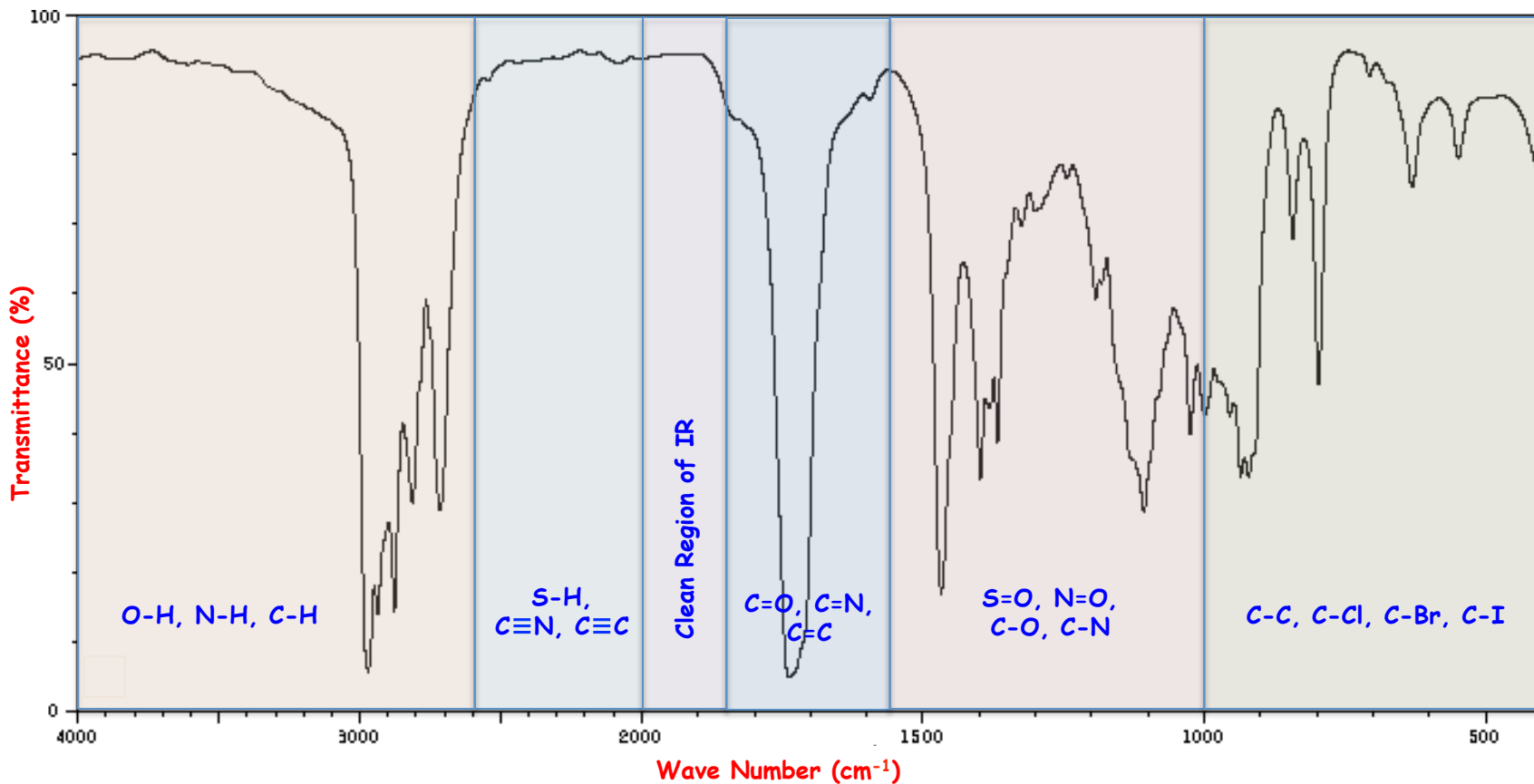
$$\nu_{\text{C=O(stretch)}} = 2140 \text{ cm}^{-1}$$



$$\nu_{\text{C=O(stretch)}} = 1715 \text{ cm}^{-1}$$



Overview of Functional Groups in IR





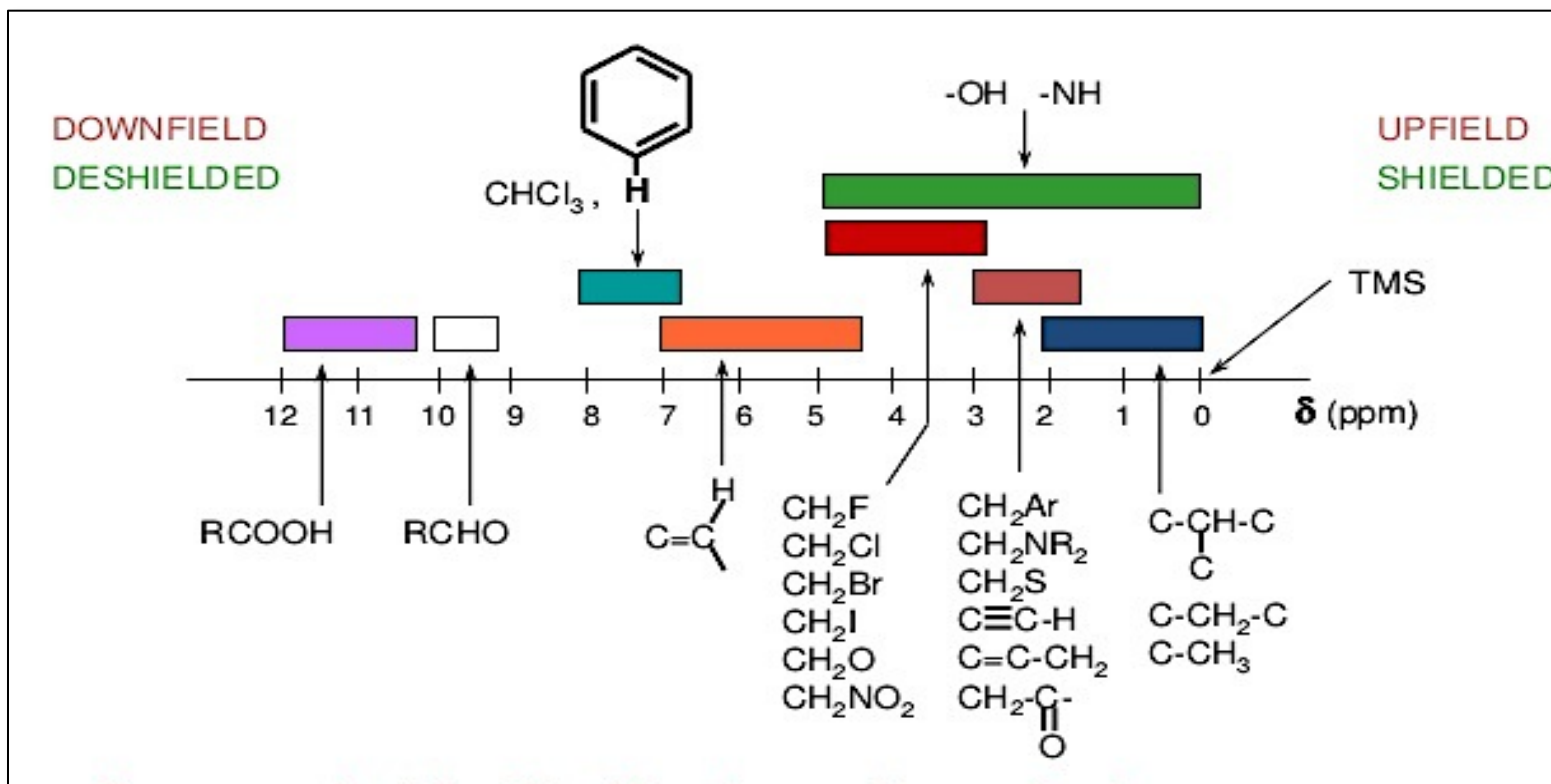
NMR Spectroscopy

- 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: ^1H , ^2D , ^{13}C , ^{19}F , ^{31}P , ^{11}B , ^{77}Se , ^{125}Te to name a few.
- ^1H 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

^1H NMR Correlation Chart:





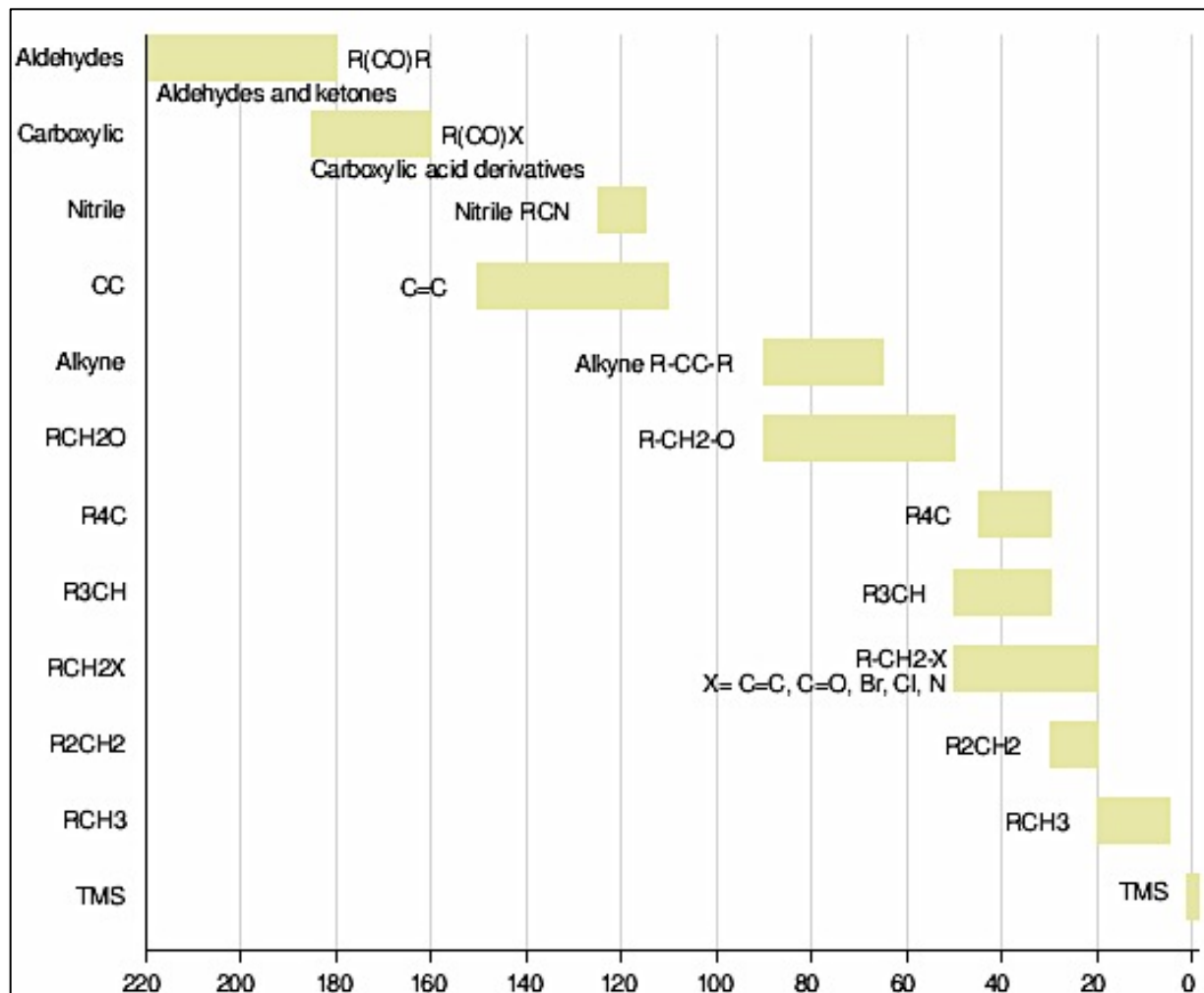
NMR Spectroscopy

- ^{13}C 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):

	^{13}C NMR	^1H NMR	IR	MS	UV/VIS
Identification of functional group	**	**	***	**	*
Measurement of molecular complexity	**	**	*	***	*
Sensitivity (sample size needed)	*	*	***	***	***
Quantitative information	*	**	**	*	***
Interpretable of all of the data	***	***	**	*	*
Theory needed to interpret spectra	***	***	**	**	*
Ease of instrument operation	**	**	***	*	***
Instrument cost	***	***	**	***	*



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.
- Organic Spectroscopy by Jagmohan.