Chapter 3

Infrared Spectrophotometry
The units used on IR spectrum

**WAVENUMBERS (\( \bar{\nu} \))**

\[
\bar{\nu} = \text{wavenumbers (cm}^{-1})
\]

\[
\bar{\nu} = \frac{1}{\lambda \text{(cm)}}
\]

\( \lambda = \text{wavelength (cm)} \)

\( c = 3 \times 10^{10} \text{ cm/sec} \)

\( \bar{\nu} = \text{frequency} = \bar{\nu} c \)

or

\[
\nu \left( = \frac{1}{\lambda} \right) c = \frac{c}{\lambda}
\]

\[
\frac{\text{cm/sec}}{\text{cm}} = \frac{1}{\text{sec}}
\]

wavenumbers are directly proportional to frequency
### The Infrared Region

<table>
<thead>
<tr>
<th></th>
<th>Near IR</th>
<th>Mid-IR</th>
<th>Far IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength</td>
<td>0.8 - 2.5 µm</td>
<td>2.5 - 50 µm</td>
<td>50 - 1000 µm</td>
</tr>
<tr>
<td>Units</td>
<td>12500 - 4000 cm(^{-1})</td>
<td>4000 - 200 cm(^{-1})</td>
<td>200 - 10 cm(^{-1})</td>
</tr>
</tbody>
</table>

**Near IR** are the most commonly studied region. They are used to control products like flour and animal feed. **Mid-IR** are used for structural confirmation. **Far IR** are used for various scientific applications, including material analysis and remote sensing.

---

[Table of Optical Properties](#)

<table>
<thead>
<tr>
<th>Near IR</th>
<th>Control products like flour and animal feed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-IR</td>
<td>Used for structural confirmation</td>
</tr>
<tr>
<td>Far IR</td>
<td></td>
</tr>
</tbody>
</table>
various regions in the Infrared spectrum

- Wavelengths that are longer than those for the visible region are referred to as the **near infrared**.
- The **overtone region** begins at about 12,500 cm\(^{-1}\) (0.8 \(\mu\)m).
- The **fundamental region**, which is the area generally used, extends from 4000 cm\(^{-1}\) (2.5 \(\mu\)m) to 200 cm\(^{-1}\) (50 \(\mu\)m).
- The fundamental region is further divided into
  - the **group frequency region** to [4000 cm\(^{-1}\) (2.5 \(\mu\)m) to 1300 cm\(^{-1}\) (8 \(\mu\)m)]
  - and the **fingerprint region** [1300 cm\(^{-1}\) (8 \(\mu\)m) to 200 cm\(^{-1}\) (50 \(\mu\)m)].
- In the group- frequency region the position of the absorption peaks is more or less dependent only on the **functional group** that absorbs and not on the complete molecular structure.
- The positions of the peaks in the fingerprint region, however, are dependent on the **complete molecular structure** and are thus more difficult to identify and correlate.
- The **far infrared** extends from the fundamental region [200 cm\(^{-1}\) (50\(\mu\)m)] to 10 cm\(^{-1}\) (1000\(\mu\)m), and beyond this lies the microwave region.
**n-pentane**

$n$-pentane

C\textsubscript{5}H\textsubscript{12}

- **2850-2960 cm$^{-1}$**
- **3000 cm$^{-1}$**
- **1470 & 1375 cm$^{-1}$** (sat'd C-H)

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\]
Requirements for the absorption in the IR region by matter

1. The radiation must have precisely the correct energy to satisfy the energy of the material
2. There must be a coupling (interaction) between the radiation and the matter.
   – Radiation in IR region has the proper energy to cause vibrational transitions in molecules
• To satisfy the first requirement for absorption
   – A given frequency if IR corresponds exactly to a fundamental vibration frequency of a given molecule.
To satisfy the second requirement for absorption:

- the molecule must undergo a change in dipole moment when the fundamental vibration occurs.
- If no change in dipole moment occurs, when the molecule vibrates, there will be no interaction between the EMR and the molecule and no absorption will take place regardless of energy compatibility.
- Such a vibration is said to be IR-inactive.
Separation of charge in a water molecule

All possible modes of vibration of water molecule involve a change in dipole moment.
• The figure shows that its dipole moment is zero.
• More important is that the change in dipole moment is zero when the molecule is symmetrically stretches (b).
• Thus, the symmetrical stretch of CO₂ is infrared-inactive.
• On the other hand, as shown in (c), an antisymmetrical (or asymmetrical stretch involves a change in dipole moment, and thus this mode of vibration infrared-active.
Dipole moment

• The dipole moment of two equal and opposite charges is

The product of the charge and the distance

\[ \mu = q \cdot r \]

r is the distance between the centers of the two charges.
The IR Spectroscopic Process

- As a covalent bond oscillates – due to the oscillation of the dipole of the molecule – a varying electromagnetic field is produced.
- The greater the dipole moment change through the vibration, the more intense the EM field that is generated.

Vibration of a Diatomic Molecule Approximates an Oscillating Spring
When a wave of infrared light encounters this oscillating EM field generated by the oscillating dipole of the same frequency, the two waves couple, and IR light is absorbed.

The coupled wave now vibrates with twice the amplitude.

![Diagram showing the interaction between an IR beam from a spectrometer and an oscillating wave from bond vibration, resulting in a "coupled" wave.](image-url)
Types of molecular Vibrations

The fundamental vibrations of a molecule are

• *Stretching vibration*. The stretching vibration in which the distance between two atoms around a bond varies with time are of two types, symmetrical and unsymmetrical.

• In the **symmetrical** stretching vibration, the side atoms move away from the central atom along the molecular axis and, after reaching maximum displacement, move back toward the central atom.

• In the **asymmetrical** stretching vibration, one side atom approaches the central atom while moving back from the other.
METHYLENE GROUP STRETCHING VIBRATIONS

Two C-H bonds share a central carbon (hydrogens attached to the same carbon)

in-phase

Symmetric Stretch
~2853 cm\(^{-1}\)

out-of-phase

Asymmetric Stretch
~2926 cm\(^{-1}\)
METHYL GROUP STRETCHING VIBRATIONS

Three C-H bonds share a central carbon (hydrogens attached to the same carbon)

**in-phase**

[Diagram of in-phase C-H bonds]

**Symmetric Stretch**

\[ \sim 2872 \text{ cm}^{-1} \]

**out-of-phase**

[Diagram of out-of-phase C-H bonds]

**Asymmetric Stretch**

\[ \sim 2962 \text{ cm}^{-1} \]
2. *Bending vibrations*. In the bending (deformation) vibration, the angle between two atoms varies with time.
Scissoring

\[ \sim 1465 \text{ cm}^{-1} \]

Wagging

\[ \sim 1250 \text{ cm}^{-1} \]

Rocking

\[ \sim 720 \text{ cm}^{-1} \]

Twisting

\[ \sim 1250 \text{ cm}^{-1} \]

METHYLENE GROUP BENDING VIBRATIONS

- **Bending Vibrations**
  - **in-plane**
  - **out-of-plane**

\[ ~1465 \text{ cm}^{-1} \]
\[ ~720 \text{ cm}^{-1} \]
\[ ~1250 \text{ cm}^{-1} \]
The bending vibrations can be further classified as

- **Wagging**, where the structural unit swings back and forth in the plane of the molecule
- **Rocking**, where the structural unit swings back and forth out of the plane of the molecule
- **Twisting**, where the structural unit rotates about the bond which joins it to the rest of the molecule
- **Scissoring**, where, for example, the two hydrogens of a methylene group move toward each other
When stretching and bending vibrations are IR active?

- Molecular dipole moment must change during a vibration to be IR active.
- This oscillating dipole interacts with the oscillating E-M field of the photon, leading to absorption.

**Stretching Vibrations**
- Symmetric
- Asymmetric

**Bending Vibrations**
- Rocking
- Scissoring
- Twisting
- Wagging

**Changes in bond length**
- In-Plane
- Out-of-Plane

**Changes in bond angle**
The theoretical number of fundamental modes of vibration

- It is useful and fairly accurate to visualize a molecule as an assembly of balls and springs in constant motion, the balls representing nuclei and the springs representing chemical bonds.
- The theoretical number of fundamental modes of vibration of a molecule containing N atoms is
  - $3N-6$ modes a nonlinear molecule
  - or $3N-5$ modes for a linear molecule
- Each normal vibration is associated with a characteristic frequency.
- Toluene, for example, with 15 atoms has 39 normal vibrations, thus, 39 fundamental frequencies can be found spectroscopically
• For a molecule with N atoms, a total of $3N$ coordinates is required, and the molecule is said to have $3N$ degrees of freedom of motion.

• Of these, **three degrees must** be subtracted for *translational* motion, since the molecule as a whole can drift off in a straight-line (transitional) motion in any of three directions in space.

• For a **nonlinear molecule**, **three additional degrees must** be subtracted out for *rotational motion* about the three Cartesian coordinates, *leaving* $3N - 6$ fundamental modes of vibration for a nonlinear molecule.

• For a **linear molecule** only two degrees of rotational motion need be subtracted out, since a linear molecule can be placed along one Cartesian coordinate and rotation about this axis cannot be recognized as a spatial movement. Hence, a linear molecule will have $3N - 5$ fundamental modes of vibration.
Observed number of modes of vibration

• The correlation between the expected and observed number of absorption bands does not hold in every case.
• Occasionally more absorption bands than would be predicted are found, and more often fewer absorption bands are identified.
• First, why more absorption bands may be found?
  – The number of observed absorption bands may be increased by the presence of bands which are not fundamentals but combination tones, overtones, or difference tones.
  – A combination tone is the sum of two or more frequencies, such as $\nu_1 + \nu_2$. An overtone is a multiple of a given frequency, as $2\nu$ (first overtone), $3\nu$ (second overtone), etc.
  – A difference tone is the difference between two frequencies, such as $\nu_1 - \nu_2$. 
The number of observed bands may be diminished by the following effects:

• If the molecule is highly symmetrical some of the frequencies in the infrared spectrum may not appear. High symmetry also often results in certain pairs or triads of the fundamental frequencies being exactly identical. They are then said to be **degenerate** and are observed as only one band.

• It may happen to have Frequencies of some vibrations so nearly alike that they are not separated by the spectrometer.

• Some fundamental bands may be so weak that they are not observed or are overlooked.

• Some of the fundamentals may occur at such low wave numbers that they fall outside the range of the usual infrared spectrophotometers.
Example

How many fundamental vibrational frequencies would you expect to observe in the absorption spectrum of HCl and give the names of these fundamental modes of vibration?

• With only two atoms, HCl is obviously linear and has $3N - 5 = 1$ fundamental mode of vibration, which is the *symmetrical stretch*. This vibration is observed to occur at 2886 cm$^{-1}$, or 3.46 Am.
Example

How many fundamental vibrational frequencies would you expect to observe in the absorption spectrum of H$_2$O?

• The bent H$_2$O molecule will have $3N - 6 = 3$ fundamental modes of vibration.
Equation of a simple Harmonic oscillator

\[ \nu = \frac{1}{2\pi c} \sqrt{\frac{K}{\mu}} \]

where

\[ \mu = \frac{m_1 m_2}{m_1 + m_2} \]

This equation describes the vibrations of a bond.

\( \nu \) = Wave number in cm\(^{-1} \)

\( c \) = velocity of light \( (3 \times 10^{10} \text{ cm/sec}) \)

\( K \) = force constant in dynes/cm

\( \mu \) = reduced mass

Theoretical Group frequencies

The equation which determines the energy level of a bond

\[ \nu = \frac{1}{2\pi c} \sqrt{\frac{K}{\mu}} \]

multiple bonds have higher K’s

\( m \) = atomic masses

\( \mu \) = reduced mass

\( C≡C > C═C > C―C \)
\[
\bar{v} = \frac{1}{2\pi c} \sqrt{\frac{K}{\mu}}
\]

- Larger \( K \), higher frequency
- Larger atom masses, lower frequency

<table>
<thead>
<tr>
<th>bond type</th>
<th>increasing ( K )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}≡\text{C} )</td>
<td>( \text{C}=\text{C} )</td>
</tr>
<tr>
<td>2150</td>
<td>1650</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>bond type</th>
<th>increasing ( \mu )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}-\text{H} )</td>
<td>( \text{C}-\text{C} )</td>
</tr>
<tr>
<td>3000</td>
<td>1200</td>
</tr>
</tbody>
</table>
Example

Estimate the frequency of absorption of the C-H stretching vibration

\[ \mu = \frac{(1)(12)}{(1+12)} = 0.92 \]

\[ K_{(C-H)} = 5 \times 10^5 \text{ dyne/cm} \]

\[ \bar{\nu} = 1307 \sqrt{\frac{5.0}{0.92}} = 3000 \text{cm}^{-1} \]

In agreement with this estimate, approximately observed C-H stretching vibrations are in this frequency region. CHCl\(_3\) is 2915 cm\(^{-1}\)
Example

• Estimate the frequency of absorption of the C-D stretching vibration where D is deuterium.

\[ \mu = \frac{(2)(12)}{(2+12)} = 1.71 \]

\[ K_{(C-D)} = 5 \times 10^5 \text{ dyne/cm} \]

\[ \overline{V} = 1307 \sqrt{\frac{5.0}{1.71}} = 2200 \text{ cm}^{-1} \]

Substituting deuterium for hydrogen lowers the absorption frequency
IR Instrumentation

• Mid infrared spectroscopy began commercially in the 1940s with single beam spectrometers allowing the point-by-point recording of the transmission spectrum.

• Today, instruments fall into two categories: dispersive spectrometers that function in a sequential mode and Fourier transform spectrometers that are capable of simultaneous analysis of the full spectral range using interferometry.

• The first category uses a monochromator with a motorised grating that can scan the range of frequencies studied.

• The second is based on the use of a Michelson interferometer or similar device coupled to a specialized computer that can calculate the spectrum from the interferogram obtained from the optical bench.

• However, the light sources and optical materials are identical for all instruments.
Contrary to UV/VIS spectrometers, the sample is placed immediately after the light source. Since photon energy in this range is insufficient to break chemical bonds and degrade the sample, it can be permanently exposed to the full radiation of the source.
Single beam dispersive spectrophotometer

• The filament used is made of metal oxides, e.g. zirconium, yttrium and thorium oxides, and is heated to incandescence in air.
• The sample is contained in various ways within discs or cells made of alkali metal halides.
• Once the light has passed through the sample, it is dispersed so that an individual wavenumber or small number of wavenumbers can be monitored in turn by the detector across the range of the spectrum.
Single beam dispersive spectrophotometer

IR radiation source

Sample between KCl discs

Monochromator

Slit

Thermocouple

Readout
Dispersive Double beam IR Spectrophotometer

- *double beam* spectrometers is a more complex arrangement that can directly yield the spectrum corrected for background absorption.

- The use of two distinct but similar optical paths, one as a reference and the other for the sample, allows the alternate measurement of the transmitted intensity ratios at each wavelength.
Dispersive Double beam IR Spectrophotometer

- The radiation coming from the light source is split in two by a set of mirrors.
- For small intervals in wavelength defined by the monochromator, light that has alternately travelled both paths (reference and sample) arrives at the detector.
- A mirror (chopper) rotating at a frequency of approximately 10 Hz orients the beam towards each of the optical paths.
- The comparison of both signals, obtained in a very short time period, can be directly converted into transmittance.
- Depending on the spectral range and on various constraints (rotation of the monochromator grating, response time of the detector) the spectrum can be recorded within minutes.
- The detector in this type of instrument is only exposed to a weak amount of energy in a given period of time because the monochromator only transmits a narrow band of wavelengths.
Double beam IR spectrophotometer
Fourier transform infrared spectrometer (FTIR)

- Fourier transform infrared spectrometers first appeared in the 1970s.
- In 1997, only less than 5% of IR instruments were dispersive.
- In a FTIR spectrometer, the single beam instrument works on the same principles such as the dispersive instruments except that an interferometer of the Michelson type is placed between the source and the sample, replacing the monochromator.
- Irradiation from the source impacts on the beam splitter which is made of a germanium film on an alkali halide support (KBr).
- This device allows the generation of two beams, one of which falls on a fixed mirror and the other on a mobile mirror whose distance from the beam splitter varies.
Fourier transform IR instrument

• In a Fourier transform IR instrument, the principles are the same except that the monochromator is replaced by an interferometer.

• An interferometer uses a moving mirror to displace part of the radiation produced by a source, thus producing an interferogram, which can be transformed using an equation called the 'Fourier transform' in order to extract the spectrum from a series of overlapping frequencies.

• The advantage of this technique is that a full spectral scan can be acquired in about 1s, compared with the 2-3 min required for a dispersive instrument to acquire a spectrum.

• Also, because the instrument is attached to a computer, several spectral scans can be taken and averaged in order to improve the signal to noise ratio for the spectrum.
Optical arrangement of a Fourier transform IR spectrometer

a) A 90° Michelson interferometer
b) Optical diagram of a single beam spectrometer (based on a Nicolet model).
FTIR is a simultaneous method in that signal processing is global. Each spectral point is calculated from all the given data.
Advantages of FTIR method

- There is no stray light, and replacement of the entrance slit by an iris yields a brighter signal so that the detector receives *more energy*.
- The signal-to-noise ratio is *much higher* than with the sequential method because it can be increased by accumulating several scans.
- Wavelengths are calculated with a *high precision* which facilitates the comparison of spectra.
- The resolution is constant throughout the domain studied.
Instrument calibration

• In order to ensure that instruments conform with BP specifications, the wavelength scale of the instrument is checked by obtaining an IR spectrum of polystyrene film.

• The permitted tolerance for variation in wavelength of absorption is ± 0.3
1. Transmission analysis

- The sample is run as a film sandwiched between two NaCl or potassium chloride (KCl) discs. For this method the sample must be a liquid, or must be ground to a paste in a liquid matrix, usually liquid paraffin (Nujol)
  - Nujol contributes some peaks to the spectrum at about $3000 \text{ cm}^{-1}$ and $1400-1500 \text{ cm}^{-1}$
- The sample is ground to a powder with KBr or KCl. KBr is usually used unless a hydrochloride salt is being analysed. On a weight-for-weight basis, the weight of the sample used is about 1% of the weight of KBr used. About 200 mg of the finely ground powder are transferred to a die block and the sample is then compressed into a disc under vacuum by subjecting it to a pressure of 800 kPa
  - This is the procedure used in pharmacopoeia methods to prepare a drug for analysis by IR.
• IR spectra of liquids or solutions in an organic solvent, commonly chloroform, may be obtained by putting the liquid into a short path length cell with a width of about 1 mm. Cells are constructed from sodium or potassium chlorides and obviously aqueous samples cannot be used.

• Solid samples may be dissolved in appropriate solvents and run same as solvents.
2. Reflection analysis for solid samples

• Diffuse reflectance is a readily observed phenomenon. When light is reflected off a matt surface, the light observed is of the same intensity no matter what the angle of observation. Samples for diffuse

• When the incident beam reaches the interface of a second medium with a greater refractive index, the beam, depending on the incident angle, will be totally reflected as on a mirror or partially reflected after penetrating the medium by approximately one half wavelength. The sample absorbs part of this radiation.

• The spectrum obtained from reflected light is not identical to that obtained by transmittance.

• The spectral composition of the reflected beam depends on the variation of the refractive index of the compound with wavelength.

• This can lead to *specular reflection*, *diffuse reflection* or *attenuated total reflection*. Each device is designed to favor only one of the above. The recorded spectrum must be corrected using computer software.
• **Specular reflection** is mostly used for transparent samples which have a reflective surface (such as polymer films, enamel, certain coatings).

• **Diffuse reflection.** Samples for diffuse reflection are treated in the same way as those prepared for KBr disc formation except that, instead of being compressed, the fine powder is loaded into a small metal cup, which is placed in the path of the sample beam. The incident radiation is reflected from the base of the cup and, during its passage through the powdered sample and back, absorption of radiation takes place, yielding an infrared spectrum which is very similar to that obtained from the KBr disc method.
• **Attenuated total reflection.** The sample may be run in a gel or cream, and this method may be used to characterise both formulation matrices and their interactions with the drugs present in them.

  – If the active ingredient is relatively concentrated and if a blank of the matrix is run using the same technique it may be subtracted from the sample to yield a spectrum of the active ingredient.
  – ATR also provides another technique which can be used for the characterization of polymorphs.
## Applications of IR spectrophotometry

The four primary regions of the IR spectrum

<table>
<thead>
<tr>
<th>Bonds to H</th>
<th>Triple bonds</th>
<th>Double bonds</th>
<th>Single Bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-H single bond</td>
<td>C≡C</td>
<td>C=O</td>
<td>C-C</td>
</tr>
<tr>
<td>N-H single bond</td>
<td>C≡N</td>
<td>C=N</td>
<td>C-N</td>
</tr>
<tr>
<td>C-H single bond</td>
<td></td>
<td>C=C</td>
<td>C-O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fingerprint Region</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>4000 cm⁻¹</th>
<th>2700 cm⁻¹</th>
<th>2000 cm⁻¹</th>
<th>1600 cm⁻¹</th>
<th>400 cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fingerprint Region**
Simple correlations of group vibrations in the fundamental infrared region
Factors Influencing Group Frequencies

1. Resonance

- The effect of resonance is to decrease the bond order of the double bonds and their vibrational frequencies by about 30 cm\(^{-1}\) (bathochromic shift) and simultaneously to increase the bond order and frequency of the interspersed single bonds (hypsochromic shift).
2. Hydrogen Bonding

- The spectra of alcohols are characterized by an absorption band at 3300 cm$^{-1}$ (3μm), which corresponds to the O-H stretching vibration.

- The exact position of this band depends to a large extent upon the degree of hydrogen bonding or association to which the hydroxyl group is subject.

- Upon association, the energy and force constant of the O-H bond decreases, and the absorption band is therefore shifted to a lower frequency by about 200 cm$^{-1}$.
The IR Spectrum

1. Each stretching and bending vibration occurs with a characteristic frequency as the atoms and charges involved are different for different bonds.

The y-axis on an IR spectrum is in units of % transmittance.

In regions where the EM field of an oscillating bond interacts with IR light of the same frequency, transmittance is low (light is absorbed).

In regions where no oscillating bond is interacting with IR light, transmittance nears 100%.
The IR Spectrum

2. The x-axis of the IR spectrum is in units of wavenumbers, $\nu$, which is the number of waves per centimeter — in units of cm$^{-1}$ (Remember $E = h\nu$ or $E = hc/\lambda$)
The IR Spectrum

This wavenumber unit is used rather than wavelength (microns) because wavenumbers are directly proportional to the energy of transition being observed –

*High frequencies and high wavenumbers equate higher energy*

*is quicker to understand than*

*Short wavelengths equate higher energy*

This unit is used rather than frequency as the numbers are more “real” than the exponential units of frequency
The IR Spectrum

In general:
Lighter atoms will allow the oscillation to be faster – *higher energy*

This is especially true of bonds to hydrogen – C-H, N-H and O-H

Stronger bonds will have higher energy oscillations

Triple bonds > double bonds > single bonds in energy
**Peak intensities**

It is important to make note of peak intensities to show the effect of these factors:

- **Strong (s)** – peak is tall, transmittance is low (0-35 %)
- **Medium (m)** – peak is mid-height (75-35%)
- **Weak (w)** – peak is short, transmittance is high (90-75%)
- *** Broad (br)** – if the Gaussian distribution is abnormally broad
  (*this is more for describing a bond that spans many energies*)

*Exact transmittance values are rarely recorded*
Infrared detection of functional groups

The primary use of the IR spectrometer is to detect functional groups

• Because the IR looks at the interaction of the EM spectrum with actual bonds, it provides a unique qualitative analysis of the functionality of a molecule, as functional groups are different configurations of different types of bonds

• Since most “types” of bonds in covalent molecules have roughly the same energy, i.e., C=C and C=O bonds, C-H and N-H bonds they show up in similar regions of the IR spectrum

• Remember all organic functional groups are made of multiple bonds and therefore show up as multiple IR bands (peaks)
The four primary regions of the IR spectrum

<table>
<thead>
<tr>
<th>Bonds to H</th>
<th>Triple bonds</th>
<th>Double bonds</th>
<th>Single Bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-H single bond</td>
<td>C≡C</td>
<td>C=O</td>
<td>C-C</td>
</tr>
<tr>
<td>N-H single bond</td>
<td>C≡N</td>
<td>C=N</td>
<td>C-N</td>
</tr>
<tr>
<td>C-H single bond</td>
<td></td>
<td>C=C</td>
<td>C-O</td>
</tr>
</tbody>
</table>

Fingerprint Region

Table:

<table>
<thead>
<tr>
<th>Wavenumber (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4000 cm⁻¹</td>
</tr>
<tr>
<td>2700 cm⁻¹</td>
</tr>
<tr>
<td>2000 cm⁻¹</td>
</tr>
<tr>
<td>1600 cm⁻¹</td>
</tr>
<tr>
<td>400 cm⁻¹</td>
</tr>
</tbody>
</table>
Typical Infrared Absorption Regions

<table>
<thead>
<tr>
<th>FREQUENCY (cm⁻¹)</th>
<th>WAVELENGTH (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4000</td>
<td>15.4</td>
</tr>
<tr>
<td>2500</td>
<td>6.5</td>
</tr>
<tr>
<td>2000</td>
<td>6.1</td>
</tr>
<tr>
<td>1800</td>
<td>5.5</td>
</tr>
<tr>
<td>1650</td>
<td>5.1</td>
</tr>
<tr>
<td>1550</td>
<td>4</td>
</tr>
<tr>
<td>650</td>
<td>2.5</td>
</tr>
</tbody>
</table>

- O-H
- C-H
- N-H
- C≡N
- C≡C
- X=C=Y
- (C,O,N,S)
- Very few bands
- C=O
- C=N
- C=C
- N=O
- N=O*
- C-Cl
- C-O
- C-N
- C-C

We will look at this area first
**BASE VALUES**  
(+/- 10 cm⁻¹)

These are the minimum number of values to memorize.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-H</td>
<td>3600</td>
</tr>
<tr>
<td>N-H</td>
<td>3400</td>
</tr>
<tr>
<td>C-H</td>
<td>3000</td>
</tr>
<tr>
<td>C≡N</td>
<td>2250</td>
</tr>
<tr>
<td>C≡C</td>
<td>2150</td>
</tr>
<tr>
<td>C=O</td>
<td>1715</td>
</tr>
<tr>
<td>C=C</td>
<td>1650</td>
</tr>
<tr>
<td>C-O</td>
<td>~1100</td>
</tr>
</tbody>
</table>
The C-H stretching region

BASE VALUE = 3000 cm\(^{-1}\)

- C-H sp\(^3\) stretch \(\sim 3300\) cm\(^{-1}\) (UNSATURATED)
- C-H sp\(^2\) stretch > 3000 cm\(^{-1}\) (3000 divides)
- C-H sp\(^3\) stretch < 3000 cm\(^{-1}\) (SATURATED)

- C-H aldehyde, two peaks (both weak) \(\sim 2850\) and 2750 cm\(^{-1}\)
STRONGER BONDS HAVE LARGER FORCE CONSTANTS AND ABSORB AT HIGHER FREQUENCIES

increasing frequency (cm$^{-1}$)

<table>
<thead>
<tr>
<th>3300</th>
<th>3100</th>
<th>3000</th>
<th>2900</th>
</tr>
</thead>
<tbody>
<tr>
<td>≡C-H</td>
<td>=C-H</td>
<td>-C-H</td>
<td></td>
</tr>
<tr>
<td>sp-1s</td>
<td>sp$^2$-1s</td>
<td>sp$^3$-1s</td>
<td></td>
</tr>
</tbody>
</table>

-CH=O (weak)

increasing s character in bond

increasing CH Bond Strength

increasing force constant K

CH BASE VALUE = 3000 cm$^{-1}$
METHYLENE GROUP STRETCHING VIBRATIONS

Two C-H bonds share a central carbon (hydrogens attached to the same carbon)

**Symmetric Stretch**

\[ \sim 2853 \text{ cm}^{-1} \]

**Asymmetric Stretch**

\[ \sim 2926 \text{ cm}^{-1} \]

Any time you have two or more of the same kind of bond sharing a central atom you will have symmetric and asymmetric modes.
METHYL GROUP STRETCHING VIBRATIONS

Three C-H bonds share a central carbon (hydrogens attached to the same carbon)

in-phase

Symmetric Stretch

\[ \sim 2872 \text{ cm}^{-1} \]

out-of-phase

Asymmetric Stretch

\[ \sim 2962 \text{ cm}^{-1} \]
Hexane

CH\_3 - CH\_2 - CH\_2 - CH\_2 - CH\_2 - CH\_2 - CH\_3

CH\_2\_stretching vibrations

includes CH\_3 sym and asym
CH\_2 sym and asym

CH bending vibrations discussed shortly
C-H BENDING
THE C-H BENDING REGION

• CH$_2$ bending $\sim 1465$ cm$^{-1}$

• CH$_3$ bending (asym) appears near the CH$_2$ value $\sim 1460$ cm$^{-1}$

• CH$_3$ bending (sym) $\sim 1375$ cm$^{-1}$
METHYLENE GROUP BENDING VIBRATIONS

Scissoring

Wagging

~1465 cm\(^{-1}\)

~720 cm\(^{-1}\)

Rocking

Twisting

in-plane

out-of-plane

Bending Vibrations
METHYLENE AND METHYL BENDING VIBRATIONS

CH$_2$  CH$_3$

1465  1460  1375

C-H Bending, look near 1465 and 1375 cm$^{-1}$

these two peaks frequently overlap and are not resolved
METHYLENE AND METHYL BENDING VIBRATIONS

ADDITIONAL DETAILS FOR SYM CH₃

The *sym* methyl peak splits when you have more than one CH₃ attached to a carbon.

CH₂    CH₃

asym  sym

1465  1460  1375

geminal dimethyl (isopropyl) → 1380  1370

t-butyl → 1390  1370

---

One peak

Two peaks

Two peaks
Hexane

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \]

CH\_2\text{ stretch}

CH\_2 bend

CH\_3 bend

\text{CH\_2 rocking > 4C}

Wavenumbers

% Transmittance

4000 3500 3000 2500 2000 1500 1000 500
Specific functional groups

1. **Alkanes** – combination of C-C and C-H bonds
   - Show various C-C stretches and bends between 1360-1470 cm\(^{-1}\) (m)
   - C-C bond between methylene carbons (CH\(_2\)'s) 1450-1470 cm\(^{-1}\) (m)
   - C-C bond between methylene carbons (CH\(_2\)'s) and methyl (CH\(_3\)) 1360-1390 cm\(^{-1}\) (m)
   - Show sp\(^3\) C-H between 2800-3000 cm\(^{-1}\) (s) cm\(^{-1}\)

![Octane spectrum](image)
2. Alkenes – addition of the C=C and vinyl C-H bonds
   • C=C stretch occurs at 1620-1680 cm\(^{-1}\) and becomes weaker as substitution increases
   • vinyl C-H stretch occurs at 3000-3100 cm\(^{-1}\)
   • Note that the bonds of alkane are still present!
   • The difference between alkane and alkene or alkynyl C-H is important! If the band is slightly above 3000 it is vinyl sp\(^2\) C-H or alkynyl sp C-H if it is below it is alkyl sp\(^3\) C-H
3. Alkynes – addition of the C≡C and vinyl C-H bonds

- C≡C stretch occurs between 2100-2260 cm\(^{-1}\); the strength of this band depends on asymmetry of bond, strongest for terminal alkynes, weakest for symmetrical internal alkynes (w-m)
- C-H for terminal alkynes occurs at 3200-3300 cm\(^{-1}\) (s)
- Remember internal alkynes (R-C≡C-R) would not have this band!

![1-Octyne](image)
4. Aromatics

- Due to the delocalization of electrons in the ring, where the bond order between carbons is 1½, the stretching frequency for these bonds is slightly lower in energy than normal C=C.
- These bonds show up as a *pair* of sharp bands, 1500 (s) & 1600 cm⁻¹ (m), where the lower frequency band is stronger.
- C-H bonds off the ring show up similar to vinyl C-H at 3000-3100 cm⁻¹ (m).
4. Aromatics

- If the region between 1667-2000 cm\(^{-1}\) (w) is free of interference (C=O stretching frequency is in this region) a weak grouping of peaks is observed for aromatic systems.
- Analysis of this region, called the overtone of bending region, can lead to a determination of the substitution pattern on the aromatic ring.

![Graph showing different substitution patterns of aromatics](image)

- Monosubstituted
- 1,2 disubstituted (ortho or o-)
- 1,2 disubstituted (meta or m-)
- 1,4 disubstituted (para or p-)
5. **Unsaturated Systems – substitution patterns**

- The substitution of aromatics and alkenes can also be discerned through the out-of-plane bending vibration region.
- However, other peaks often are apparent in this region. *These peaks should only be used for reinforcement of what is known or for hypothesizing as to the functional pattern.*

<table>
<thead>
<tr>
<th>Substitution Pattern</th>
<th>cm(^{-1})</th>
<th>cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R}C=\text{CH}_2$</td>
<td>985-997</td>
<td>730-770</td>
</tr>
<tr>
<td></td>
<td>905-915</td>
<td>690-710</td>
</tr>
<tr>
<td>$\text{R}C=\text{C}$</td>
<td>960-980</td>
<td>735-770</td>
</tr>
<tr>
<td>$\text{H}C=\text{C}$</td>
<td>665-730</td>
<td>860-900</td>
</tr>
<tr>
<td>$\text{H}C=\text{C}$</td>
<td>885-895</td>
<td>750-810</td>
</tr>
<tr>
<td>$\text{H}C=\text{C}$</td>
<td>790-840</td>
<td>680-725</td>
</tr>
<tr>
<td>$\text{H}C=\text{C}$</td>
<td></td>
<td>800-860</td>
</tr>
</tbody>
</table>
6. Ethers – addition of the C-O-C asymmetric band and vinyl C-H bonds
   - Show a strong band for the antisymmetric C-O-C stretch at 1050-1150 cm\(^{-1}\)
   - Otherwise, dominated by the hydrocarbon component of the rest of the molecule
7. Alcohols

- Show a strong, broad band for the O-H stretch from 3200-3400 cm\(^{-1}\) (s, br) this is *one of the most recognizable IR bands*
- Like ethers, show a band for C-O stretch between 1050-1260 cm\(^{-1}\) (s)
- This band changes position depending on the substitution of the alcohol: 1° 1075-1000; 2° 1075-1150; 3° 1100-1200; phenol 1180-1260
- The shape is due to the presence of hydrogen bonding
8. Amines - Primary

- Shows the –N-H stretch for NH₂ as a **doublet** between 3200-3500 cm⁻¹ (s-m); symmetric and anti-symmetric modes
- -NH₂ group shows a deformation band from 1590-1650 cm⁻¹ (w)
- Additionally there is a “wag” band at 780-820 cm⁻¹ that is not diagnostic
9. **Amines – Secondary**

- N-H band for R$_2$N-H occurs at 3200-3500 cm$^{-1}$ (br, m) as a single sharp peak weaker than –O-H
- Tertiary amines (R$_3$N) have no N-H bond and **will not** have a band in this region

[pic: Infrared spectrum highlighting the N-H region for pyrrolidine]
10. Aldehydes

- Show the C=O (carbonyl) stretch from 1720-1740 cm⁻¹(s)
- Band is sensitive to conjugation, as are all carbonyls (upcoming slide)
- Also displays a highly unique sp² C-H stretch as a doublet, 2720 & 2820 cm⁻¹ (w) called a “Fermi doublet”
11. Ketones

- Simplest of the carbonyl compounds as far as IR spectrum – carbonyl only
- C=O stretch occurs at 1705-1725 cm\(^{-1}\) (s)
12. Esters

1. C=O stretch occurs at 1735-1750 cm\(^{-1}\) (s)
2. Also displays a strong band for C-O at a higher frequency than ethers or alcohols at 1150-1250 cm\(^{-1}\) (s)

![Ethyl pivalate](image)
13. **Carboxylic Acids:**

- Gives the messiest of IR spectra
- C=O band occurs between 1700-1725 cm\(^{-1}\)
- The highly dissociated O-H bond has a broad band from 2400-3500 cm\(^{-1}\) (m, br) covering up to half the IR spectrum in some cases
14. Acid anhydrides

- Coupling of the anhydride though the ether oxygen splits the carbonyl band into two with a separation of 70 cm$^{-1}$.
- Bands are at 1740-1770 cm$^{-1}$ and 1810-1840 cm$^{-1}$ (s)
- Mixed mode C-O stretch at 1000-1100 cm$^{-1}$ (s)
15. **Acid halides**

- Dominant band at 1770-1820 cm\(^{-1}\) for C=O (s)
- Bonds to halogens, due to their size (see Hooke’s Law derivation) occur at low frequencies, where their presence should be used to reinforce rather than be used for diagnosis, C-Cl is at 600-800 cm\(^{-1}\) (m)
16. Amides

- Display features of amines and carbonyl compounds
- C=O stretch occurs from 1640-1680 cm\(^{-1}\)
- If the amide is primary (\(-\text{NH}_2\)) the N-H stretch occurs from 3200-3500 cm\(^{-1}\) as a doublet
- If the amide is secondary (\(-\text{NHR}\)) the N-H stretch occurs at 3200-3500 cm\(^{-1}\) as a sharp singlet

```
\text{pivalamide}
```

```
O
\text{NH}_2
```

![Graph showing IR spectrum with annotations for amide groups.](image)
17. **Nitro group (-NO$_2$)**

- Proper Lewis structure gives a bond order of 1.5 from nitrogen to each oxygen.
- Two bands are seen (symmetric and asymmetric) at 1300-1380 cm$^{-1}$ (m-s) and 1500-1570 cm$^{-1}$ (m-s).
- This group is a strong resonance withdrawing group and is itself vulnerable to resonance effects.
18. Nitriles (the cyano- or –C≡N group)

- Principle group is the carbon nitrogen triple bond at 2100-2280 cm\(^{-1}\) (s)
- This peak is usually much more intense than that of the alkyne due to the electronegativity difference between carbon and nitrogen
Examples of IR spectra of drug molecules

Paracetamol

Table 5.3 Interpretation of the IR spectrum of paracetamol

<table>
<thead>
<tr>
<th>Wavenumber</th>
<th>Assignment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 3360 cm(^{-1})</td>
<td>N–H amide stretch</td>
<td>This band can be seen quite clearly although it is on top of the broad OH stretch</td>
</tr>
<tr>
<td>B 3000–3500 cm(^{-1})</td>
<td>Phenolic OH stretch</td>
<td>Very broad due to strong hydrogen bonding and thus obscures other bands in this region</td>
</tr>
<tr>
<td>C ca 3000 cm(^{-1})</td>
<td>C–H stretching</td>
<td>Not clear due to underlying OH absorption</td>
</tr>
<tr>
<td>D 1840–1940 cm(^{-1})</td>
<td>Aromatic overtone region</td>
<td>Quite clear fingerprint but does not reflect 2 band pattern proposed for p-di-substitution.(^2)</td>
</tr>
<tr>
<td>E 1650 cm(^{-1})</td>
<td>C=O amide stretch</td>
<td>C=O stretching in amides occurs at a low wavenumber compared to other unconjugated C=O groups</td>
</tr>
<tr>
<td>F 1608 cm(^{-1})</td>
<td>Aromatic C=C stretch</td>
<td>This band is strong since the aromatic ring has polar substituents which increase the dipole moment of the C=C bonds in the ring</td>
</tr>
<tr>
<td>G 1568 cm(^{-1})</td>
<td>N–H amide bending</td>
<td>Strong absorption in this case but this is not always so</td>
</tr>
<tr>
<td>H 1510 cm(^{-1})</td>
<td>Aromatic C=C stretch</td>
<td>Evidence of a doublet due to interaction with ring substituents</td>
</tr>
<tr>
<td>I 810 cm(^{-1})</td>
<td>=C–H bending</td>
<td>Possibly aromatic C–H bending but the fingerprint region is too complex to be completely confident of the assignment</td>
</tr>
</tbody>
</table>
Aspirin

Table 5.4 Interpretation of the IR spectrum of aspirin

<table>
<thead>
<tr>
<th>Wavenumber</th>
<th>Assignment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 2400–3300 cm⁻¹</td>
<td>Carboxylic OH stretch</td>
<td>Very broad and complex due to strong hydrogen bonding. The broad band obscures other bands in this region</td>
</tr>
<tr>
<td>B ca 3000 cm⁻¹</td>
<td>C–H stretching</td>
<td>Not clear due to underlying OH absorption</td>
</tr>
<tr>
<td>C 1757 cm⁻¹</td>
<td>C=O ester stretch</td>
<td>Owing the acetyl group, which is an unconjugated aliphatic ester</td>
</tr>
<tr>
<td>D 1690 cm⁻¹</td>
<td>C=O conjugated carboxylic acid stretch</td>
<td>C=O of the acid is conjugated to the aromatic ring</td>
</tr>
<tr>
<td>E 1608 cm⁻¹</td>
<td>Aromatic C=C stretch</td>
<td>These bands are intense since the ring is substituted with polar groups</td>
</tr>
<tr>
<td>F 1460 cm⁻¹</td>
<td>Aromatic C=C stretch</td>
<td></td>
</tr>
</tbody>
</table>
The infrared spectrum of dexamethasone obtained as a KBr disc. Corticosteroids provide some of the best examples for the assignment of IR bands because of the prominence of the bands in their spectra above 1500 cm⁻¹.
IR Spectrophotometry as a fingerprint technique

Preparation of samples for fingerprint determination

• To conform with the BP standards samples are prepared as KBr or KCl discs.
• 1-2 mg of the substance should be ground with 0.3-0.4 g of KBr or KCl.
• The KBr or KCl should be free from moisture.
• The mixture should be compressed at 800 kPa and discs should be discarded if they do not appear uniform.
• Any disc having a transmittance < 75% at 2000 cm\(^{-1}\) in the absence of a specific absorption band should be discarded.
Comparison of the fingerprint regions of dexamethasone and betamethasone.

- Closely related compounds give different IR spectra in the fingerprint region.
- Dexamethasone and betamethasone only differ in their stereochemistry at the 16 position on the steroid skeleton.
- However, this small difference is great enough to result in a different fingerprint spectrum for the two compounds.
- There are even slight differences in the absorptions of the bands due to C=C stretching at 1620 cm

*Infrared spectrophotometry as a method for identifying polymorphs*
The existence of polymorphs (different crystalline forms of a substance) has an important bearing on drug bioavailability, the chemical processing of the material during manufacturing and on patent lifetime.
Near infrared analysis

- The near-infrared region range is from 0.75 μm (750 nm or 13000 cm⁻¹) to about 2.5 μm (2500 nm or 4000 cm⁻¹).
- The absorption bands in this region of the spectrum are due to overtones and combinations of fundamental mid-IR vibration bands.
- Quantum mechanical selection rules forbid transitions over more than one energy level.
- High intensity sources such as tungsten halogen lamps with strong steady radiation over the entire near ir range are used. Very sensitive detectors can be used. Quartz and silica can be used for both optical systems and the sample containers.
- Long path length cells can be used to compensate for weaker absorption.
• Such overtone bands are 1000 times weaker than the bands seen in the mid-infrared region.
• The radiation in this region is weakly absorbed by the X-H bonds (O-H or N-H or C-H) of molecules. The wavelength of radiation absorbed is characteristic of the bond absorbing it.
• Most of the useful bands in this region are overtones of X-H stretching.
• The strength of NIRA lies in the quantitative information which it can yield and its ability to identify constituents in multicomponent samples.
• The applications in quantitative analyses arrived with the ready availability of advanced computing facilities and this is the weakness of the technique, i.e. extensive software development has to take place before the spectral measurements yield useful information.
• NIRA has the potential to produce great savings in sample preparation and analysis and lends itself very well to process control. The technique is largely used
Determination of particle size in United States Pharmacopoeia (USP) grade aspirin

• It has been found that there is a linear relationship between NIR absorption and particle size.
• NIRA can provide a rapid means for determining particle size.
• The absorbance of the sample increases with decreasing particle size.
• Particle size is an important factor to be controlled in formulation and manufacture
Determination of blend uniformity

- NIRA provides an excellent method for the direct monitoring of the uniformity of blends when drugs are being formulated.

The effect of differences in blend time on the uniformity of a formulation containing lactose and hydrochlorothiazide.
• The most notable variations in absorbance intensity in the spectrum of the blend occur at 2030 nm and 2240 nm.
• Absorbance at these wavelengths can be attributed to hydrochlorothiazide and lactose, respectively.
• The more complete the blend, the less the standard deviations of the absorbances at these wavelengths obtained when several batches sampled at the same time point are compared.
• As would be expected, the standard deviations decrease with blend time, but the decrease is less marked after 10 min.
• In this study it was found that blending for more than 20 min caused a loss in uniformity due to an alteration in the flow properties of the powder, resulting from a change in the distribution of the magnesium stearate.
• NIR probes can be inserted directly into blenders to monitor mixing.
Determination of active ingredients in multicomponent dosage forms

• NIRA has been used to analyse multicomponent tablets, e.g. aspirin/caffeine/butalbarbital, and can examine such tablets in a pass/fail manner.

• The tablets fail when the ingredients fall outside the specified range as shown in the Figure, which is derived by the monitoring of two wavelengths in the NIR spectrum of the formulation.

• This might appear simple but a great deal of development work was earned out in order to determine which wavelengths to monitor in order give the best discrimination
Application of NIRA to control of the ingredients in tablets containing three components.
Quantitative Analysis

• The fundamental rule that correlates component concentration with the absorption intensity of the component is the well-known Beer's Law
  \[ P = P_0 e^{-\varepsilon bc}. \]

• Theoretically, the application of Beer's Law to the analysis of any mixture is quite straightforward, especially when a band unique to a single component can be found.

• Direct application of Beer's Law is difficult in infrared work because of instrumental limitations. The source and detector have limited output. The instrument thus uses a large slit width and a wide spectral bandwidth in comparison to the sharp peaks found in most infrared spectra.
Quantitative Analysis

• For this reason the instrument cannot measure the actual height of the peak chosen for analysis but measures an average or integrated height across the peak in the range of wavelengths passed by the instrument. Another instrumental factor that produces deviation from Beer's Law, especially in the infrared, is the large amount of stray radiation.

• A calibration curve must be prepared and checked frequently for direct quantitative work in the infrared. A base-line technique is generally used. An internal standard method is also frequently employed.
Determination of isopropanol in the unknown solution

• Consider the spectra for toluene and 2%, 4%, 6% and 8% (v/v) isopropanol solutions. Consider the absorption band at 815 cm\(^{-1}\) (12.2 \(\mu\)m) in the spectra of the isopropanol solutions. In fact, it belongs solely to isopropanol.

• Measure the minimum transmittance at the bottom of the band at 815 cm\(^{-1}\), (call that \(t\)), and compare it with the transmittance reading obtained by drawing a straight line across the top of the band, and take the reading at the same wavelength as the band minimum; let this be \(t_0\).

• Calculate the absorbance caused by the isopropanol by taking the log (\(t_0/t\)). Plot a graph of this absorbance against the volume percentage of isopropanol, ideally this should be straight line. Use this graph to find the fraction of isopropanol in the unknown.