



INTERNATIONAL COLLEGE
OF PHARMACEUTICAL
INNOVATION
国际创新药学院

Fundamentals of Medicinal and Pharmaceutical Chemistry

FUNCHEM.26 Analytics: Infrared Spectroscopy II

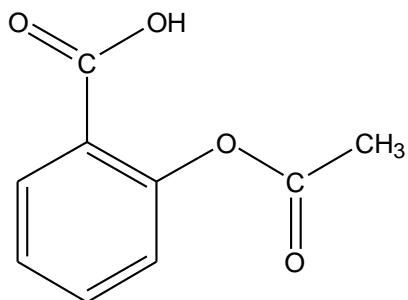
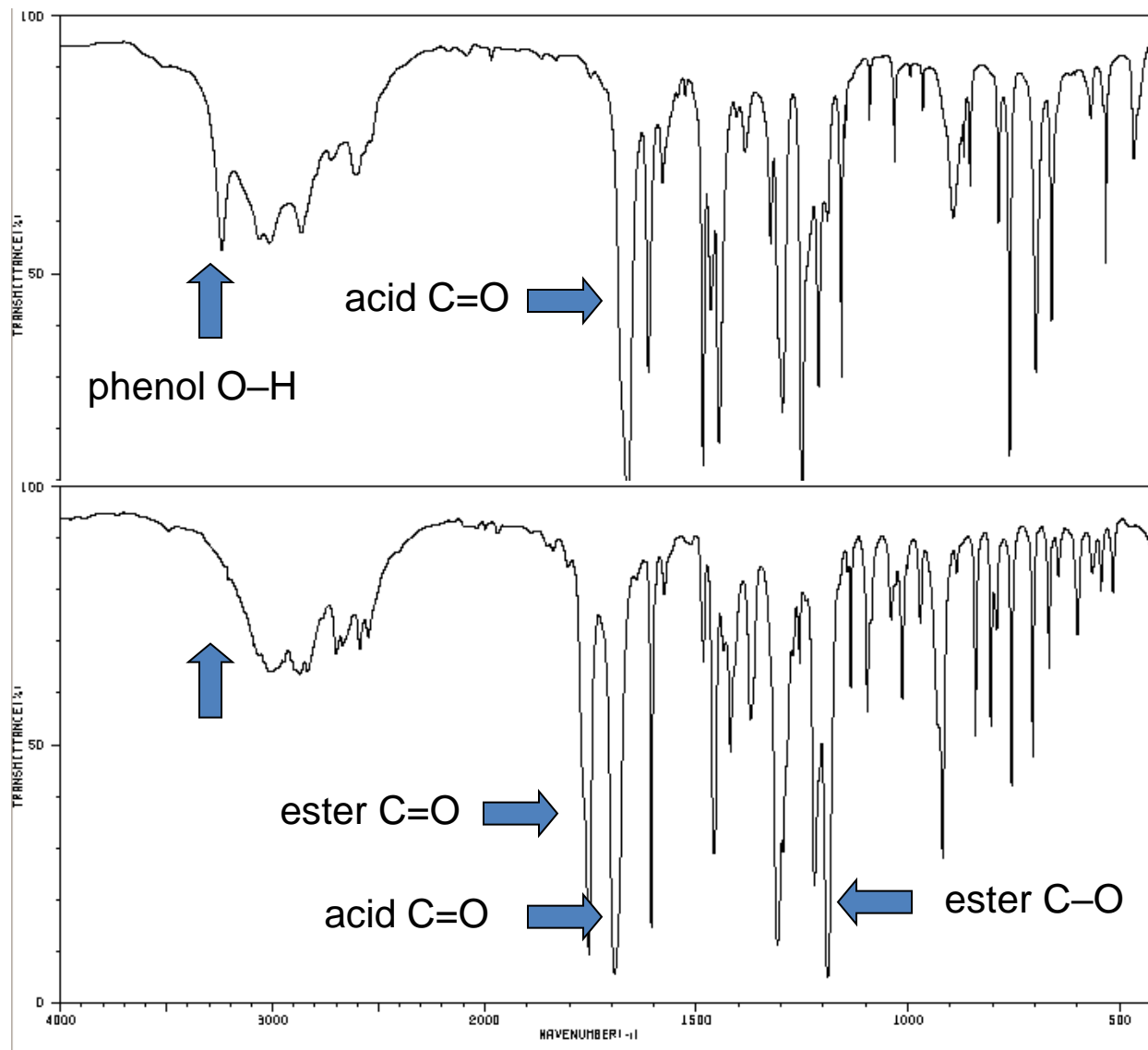
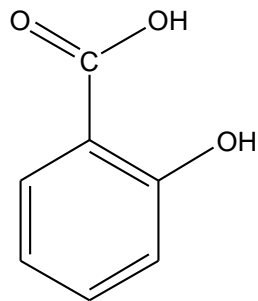
Professor Dan Wu

DATE: 13rd December 2024

LEARNING OBJECTIVES: I, II

- • Demonstrate on What is infrared spectroscopy
- • How IR spectrometry works
- • What information IR spectrometry gives
- • Know the IR used in pharmaceutical application

IR Spectroscopy: Salicylic Acid Vs. Aspirin



Vibrational Modes

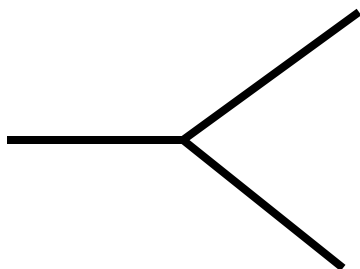
Skeletal vibrations

1300 - 600 cm^{-1}

called the 'fingerprint region'.

In this portion of the spectrum the energy of the absorption bands varies depending on the structure of a molecule.

Modes
of
vibration



Characteristic group vibrations

4000-1300 cm^{-1} .

In this region the bands are characteristic of specific functional groups in a molecule.

No two molecules will give exactly the same IR spectrum
(except enantiomers).

The exact frequency at which a given vibration occurs is determined by the strengths of the bonds involved and the mass of the component atoms.

To help understand IR, it is useful to compare a vibrating bond to the physical model of a vibrating spring system (described by Hooke's Law)

$$\bar{\nu} = \frac{1}{2\pi C} \sqrt{\frac{k}{\mu}}$$

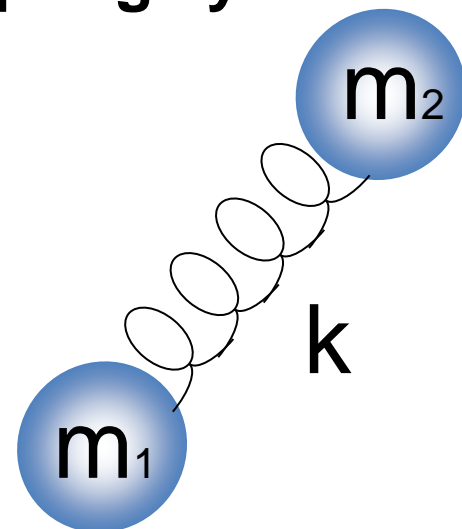
$\bar{\nu}$ = vibrational frequency of the bond,
in wavenumbers (cm^{-1})

k = force constant, indicating the strength of the bond (N/m)

μ = reduced mass, which is given by

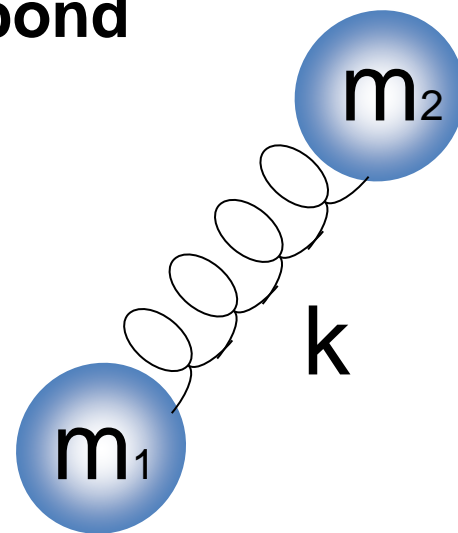
$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

where m_1 and m_2 are the masses of the two atoms
(in kilograms per molecule)



How does the strength of the bond influence the vibration?

$$\overline{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$



For a stronger bond (larger k value), $\overline{\nu}$ increases.

Examples

CC bonds:

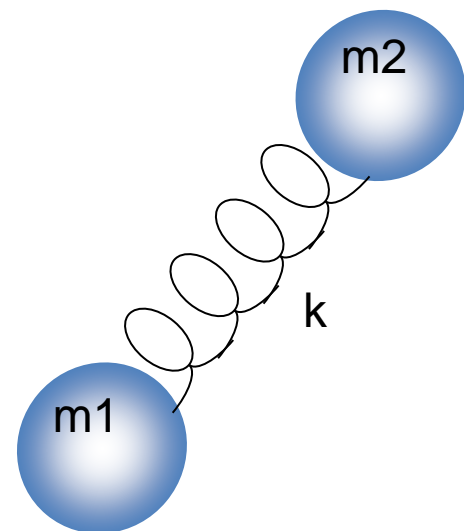
$\overline{\nu}_{\text{obs}}$ $\text{C} \equiv \text{C}$ (2200 cm^{-1}) > $\text{C}=\text{C}$ (1600 cm^{-1}) > $\text{C}-\text{C}$ (1000 cm^{-1})

CH bonds:

$\text{C} \equiv \text{C}-\text{H}$ (3300 cm^{-1}) > $\text{C}=\text{C}-\text{H}$ (3100 cm^{-1}) > $\text{C}-\text{C}-\text{H}$ (2900 cm^{-1})

How does the mass influence the vibration?

$$\bar{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$



For heavier atoms attached (larger μ value), $\bar{\nu}$ decreases.

Examples

C-H (3000 cm⁻¹)

C-C (1000 cm⁻¹)

C-Cl (800 cm⁻¹)

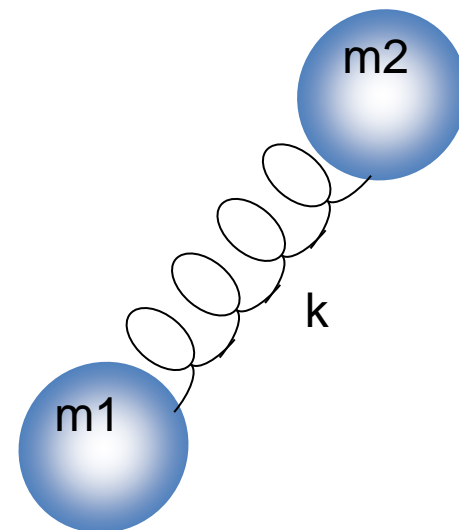
C-Br (550 cm⁻¹)

C-I (about 500 cm⁻¹)

Rules of Thumb!

The fundamental wavenumber of a bond-stretching vibration is given by:

$$\bar{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

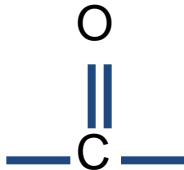


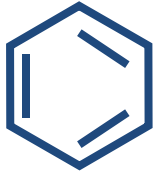


- Frequency bond stretch \propto strength of bond
 \propto 1/mass of atoms
- Bending frequencies are generally lower than stretching frequencies. ($k_{\text{bend}} < k_{\text{stretch}}$).
- Symmetric stretching frequencies are generally lower than asymmetric stretching frequencies.

Due to the complexity of an IR spectrum, it is unusual to assign every single peak on the spectra.

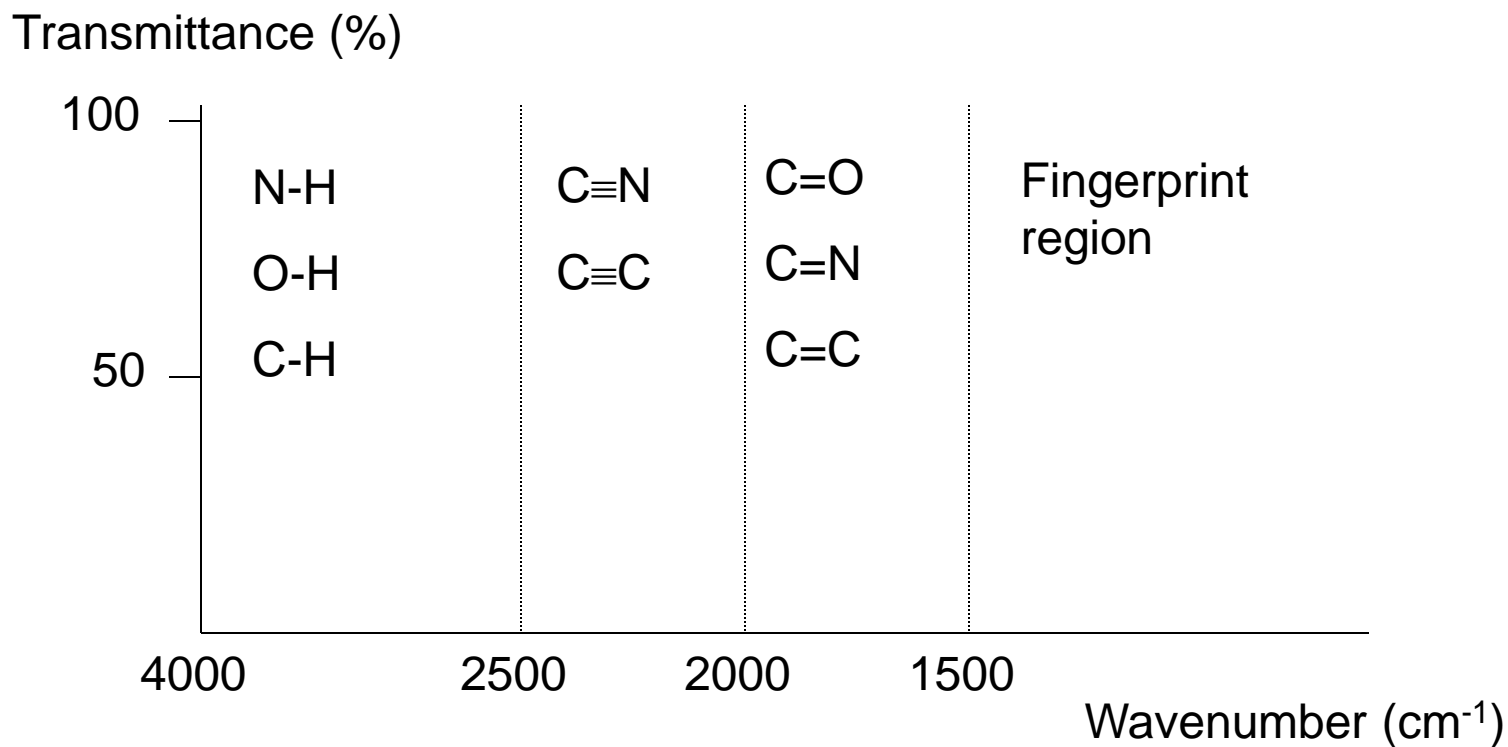
Fortunately we don't need to!

Most **functional groups** give rise to **characteristic IR absorptions** that change little in going from one compound to another

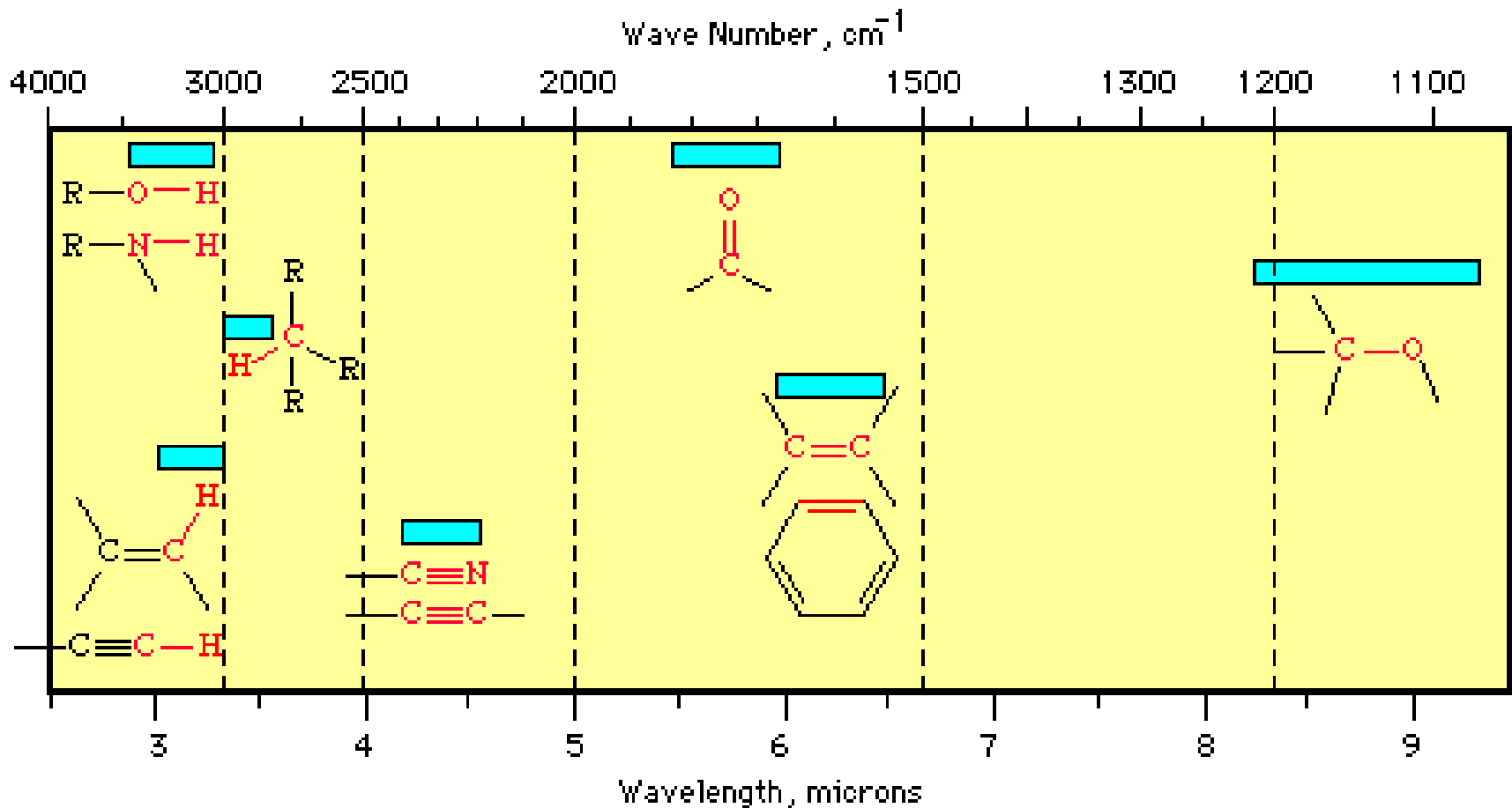
Functional group	absorption frequency
	$\sim 1690 - 1750 \text{ cm}^{-1}$
	$\sim 3200 - 3600 \text{ cm}^{-1}$
	$\sim 1650 - 1670 \text{ cm}^{-1}$
	$\sim 1600 \text{ cm}^{-1}$

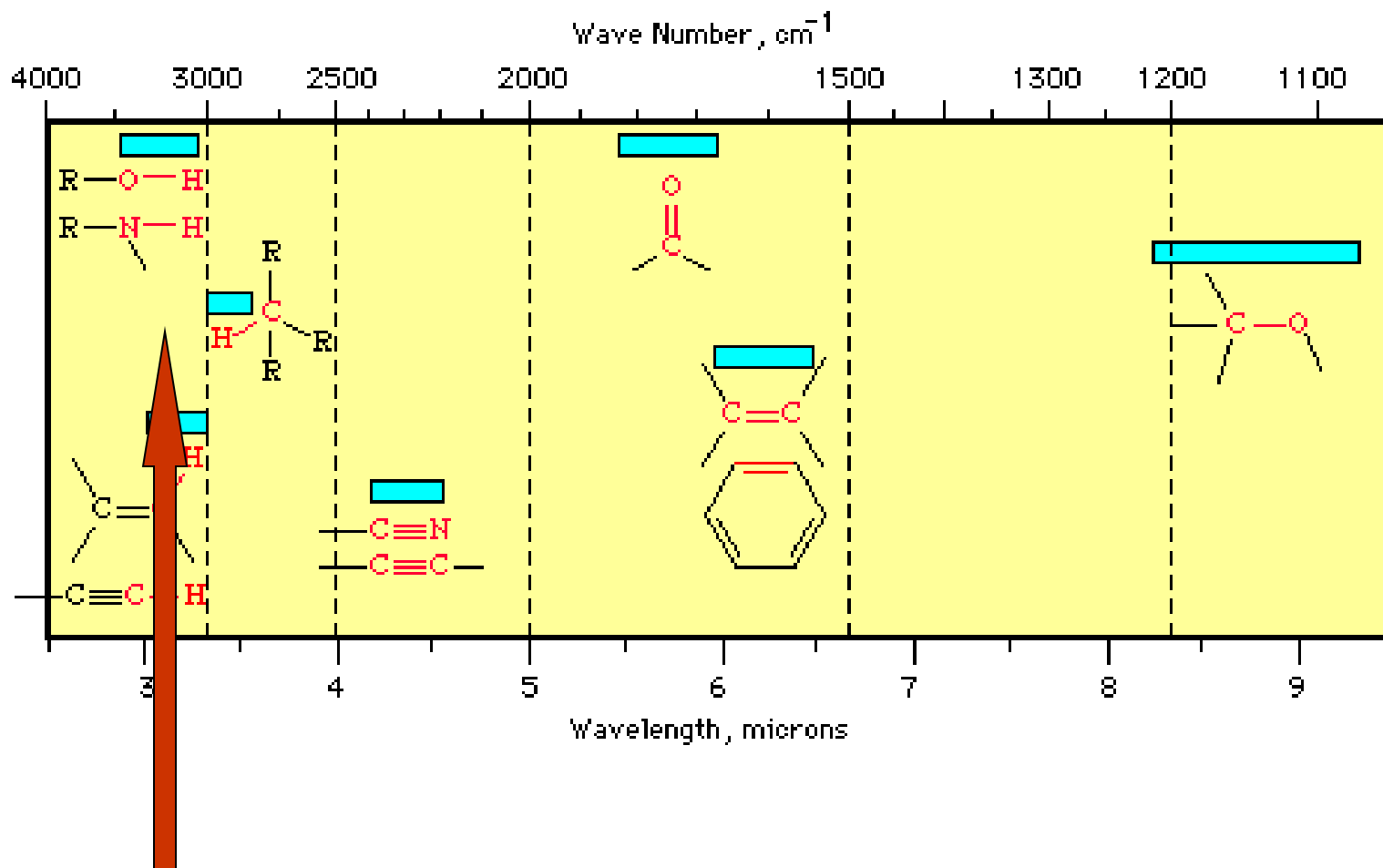
**As a rough guide, the spectrum can be split
into four sections**

$$\bar{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$



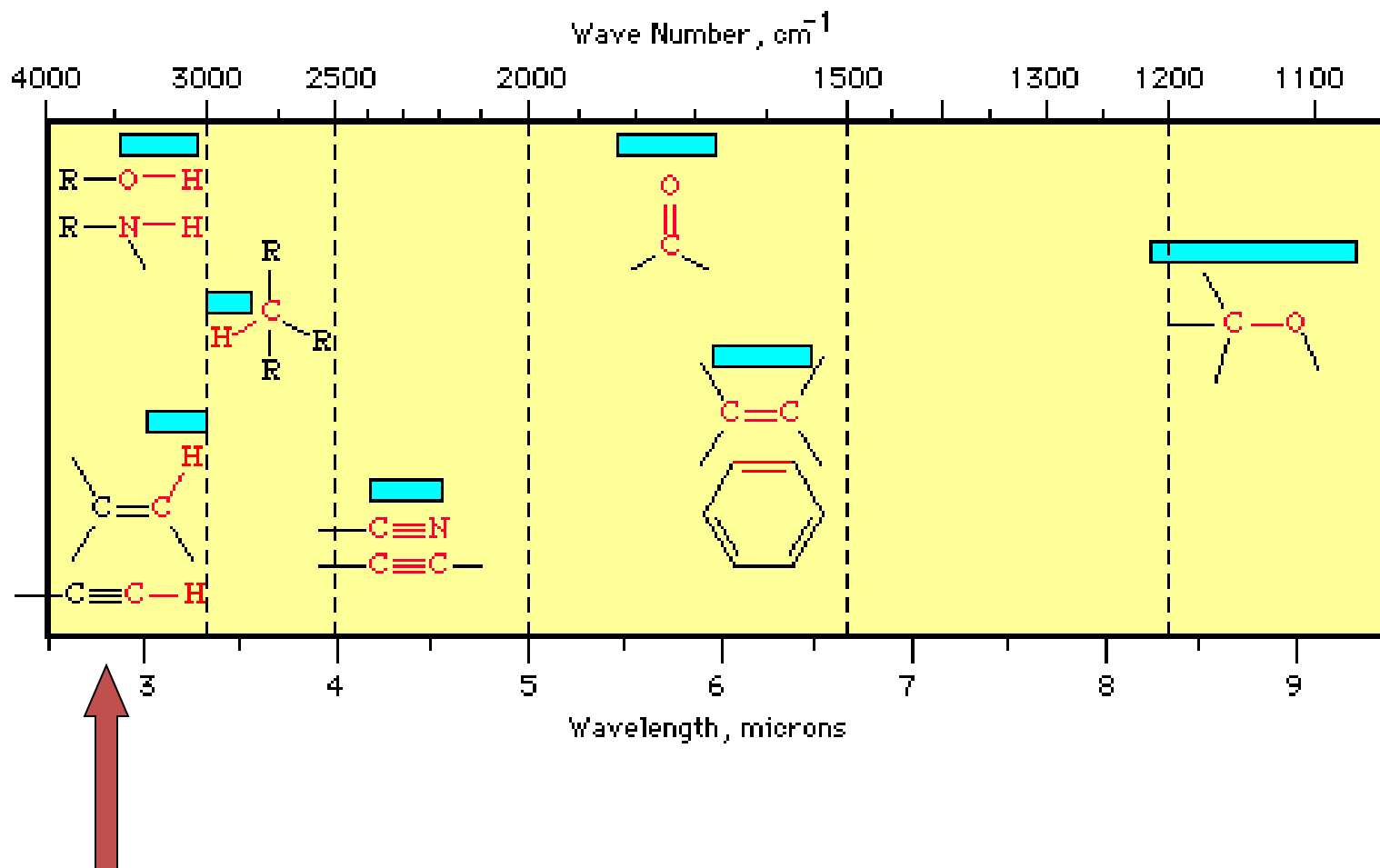
IR Characteristic Vibrations





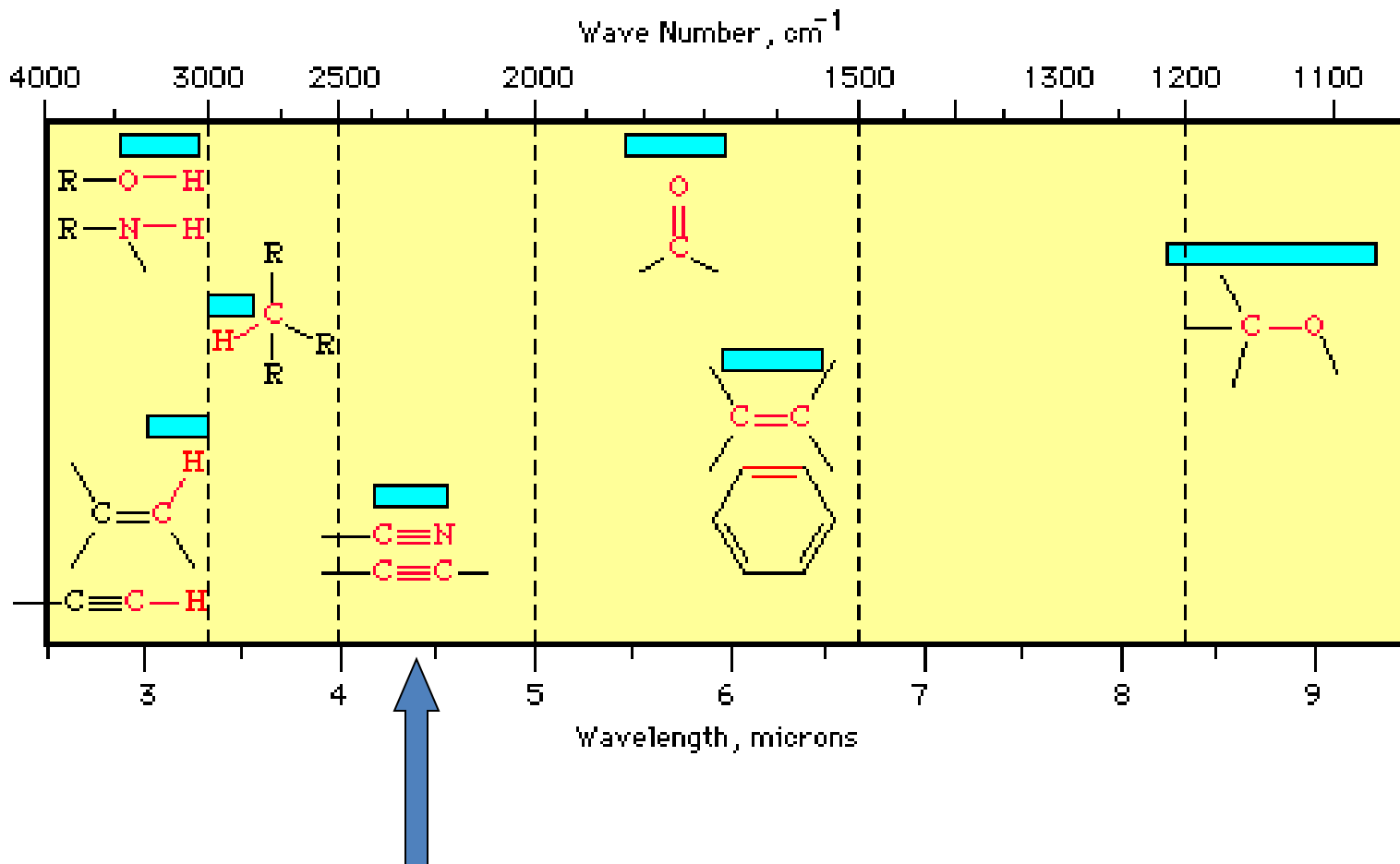
Alcohols and **amines** display strong broad O-H and N-H stretching bands in the region 3400 - 3100 cm^{-1} .

The bands are broadened due to hydrogen bonding and a sharp 'non-bonded' peak can often be seen at around 3400 cm^{-1} .

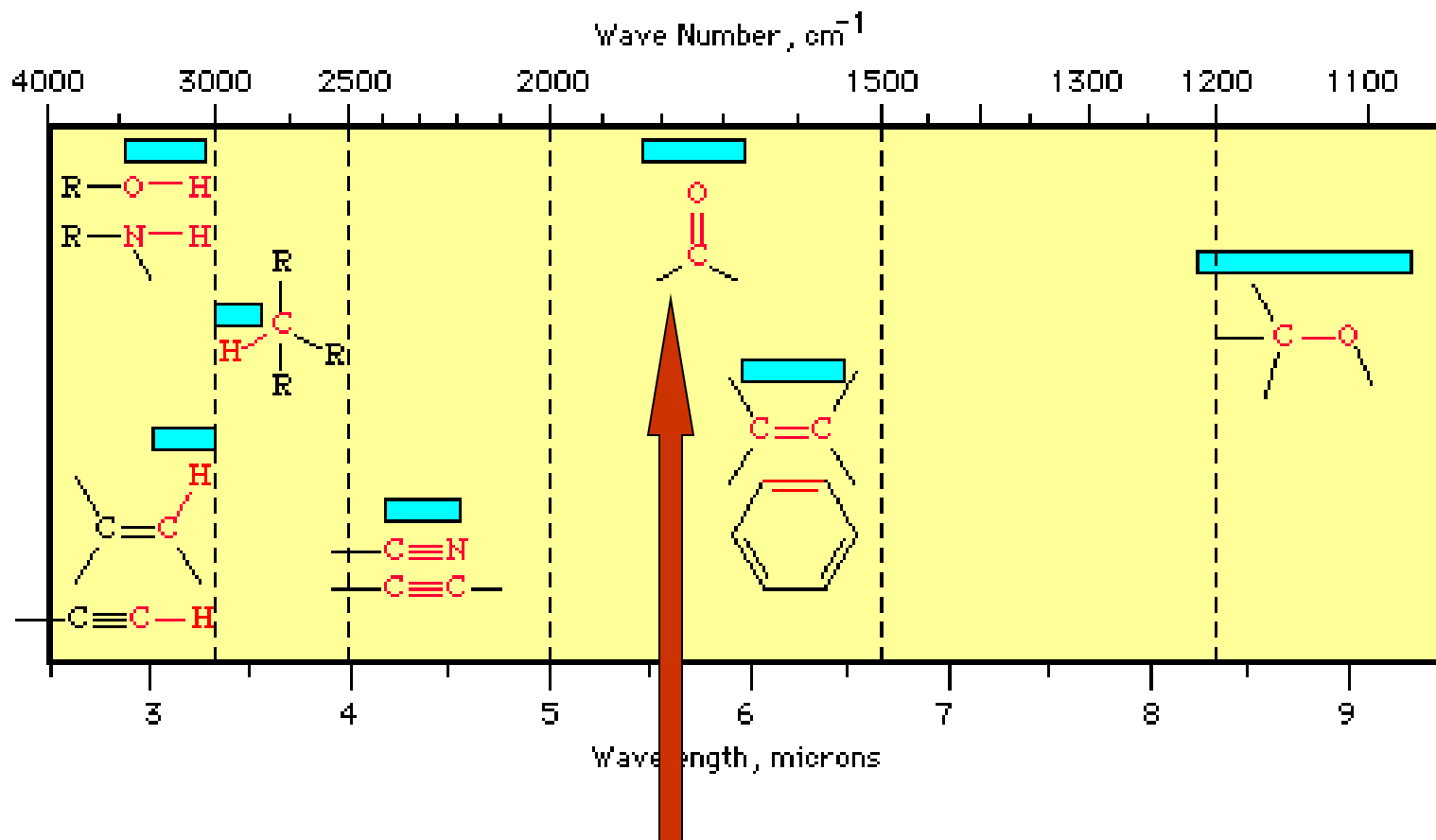


Alkene and alkyne C-H bonds display sharp stretching absorptions in the region 3100 - 3000 cm^{-1} .

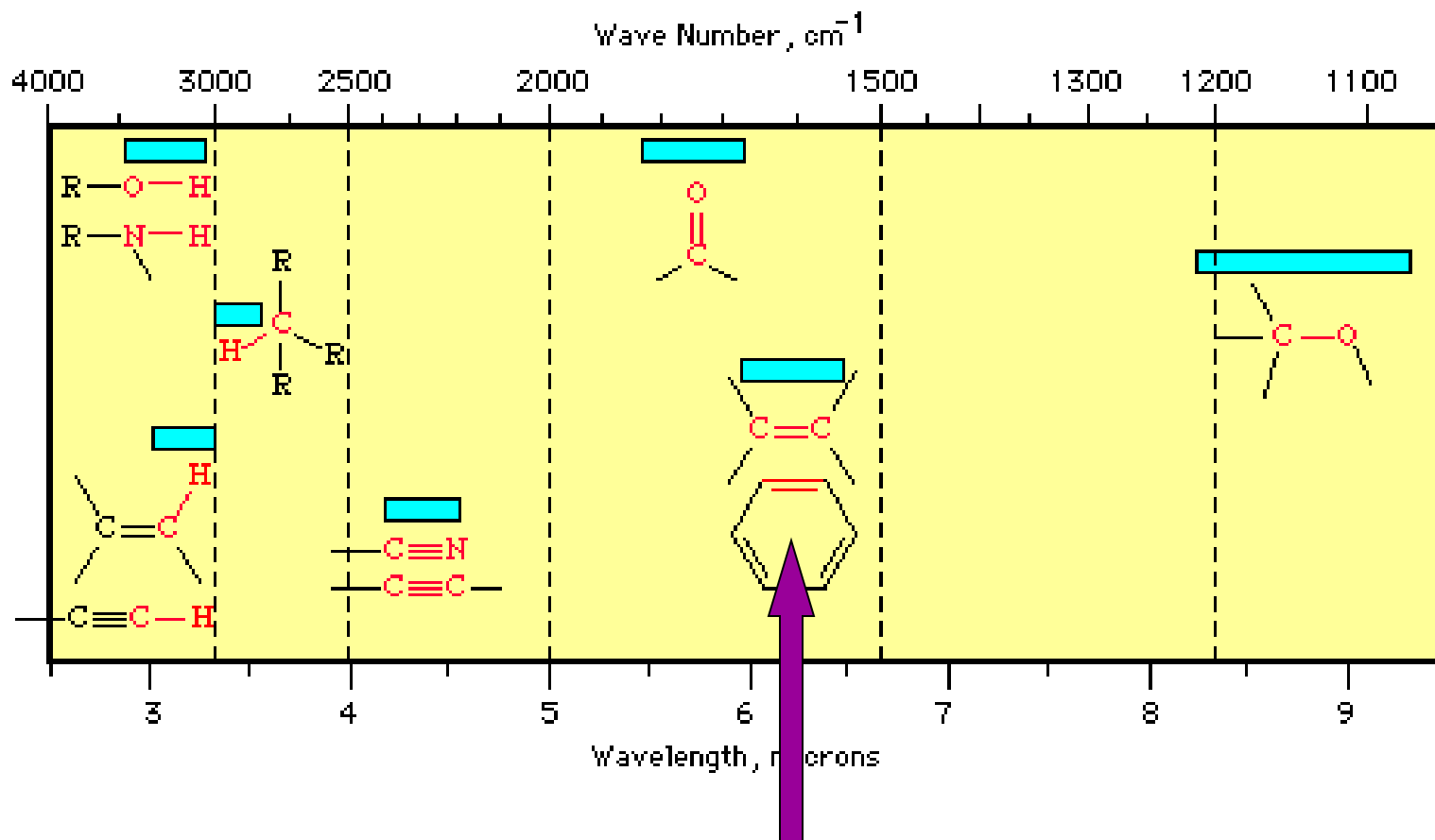
The bands are of medium intensity and are often obscured by other absorbances in the region (i.e. OH).



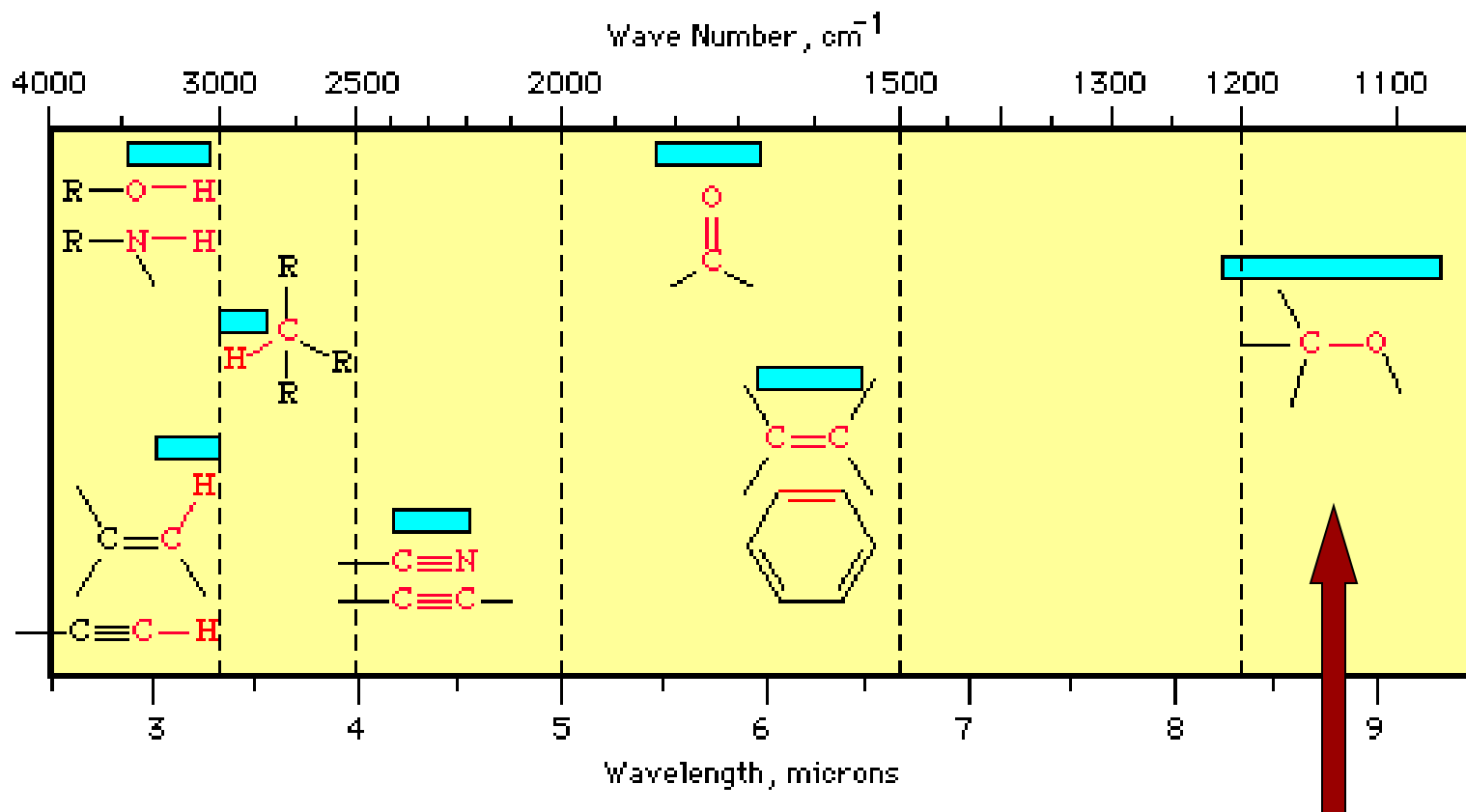
Triple bond stretching absorptions occur in the region 2400 - 2200 cm^{-1} . Absorptions from nitriles are generally of medium intensity and are clearly defined. Alkynes absorb weakly in this region unless they are highly asymmetric; symmetrical alkynes do not show absorption bands.



Carbonyl stretching bands occur in the region **1800 - 1700 cm^{-1}** . The bands are generally very strong and broad. Carbonyl compounds which are more reactive in nucleophilic addition reactions (acyl halides, esters) are generally at higher wave number than simple ketones and aldehydes, and amides are the lowest, absorbing in the region 1700 - 1650 cm^{-1} .

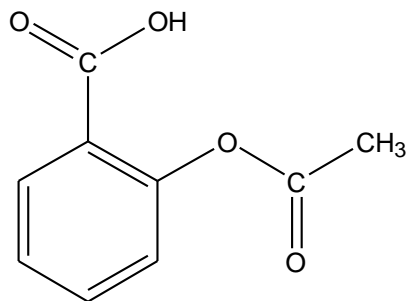


Carbon-carbon double bond stretching occurs in the region around 1650 - 1600 cm^{-1} . The bands are generally sharp and of medium intensity. Aromatic compounds will typically display a series of sharp bands in this region.

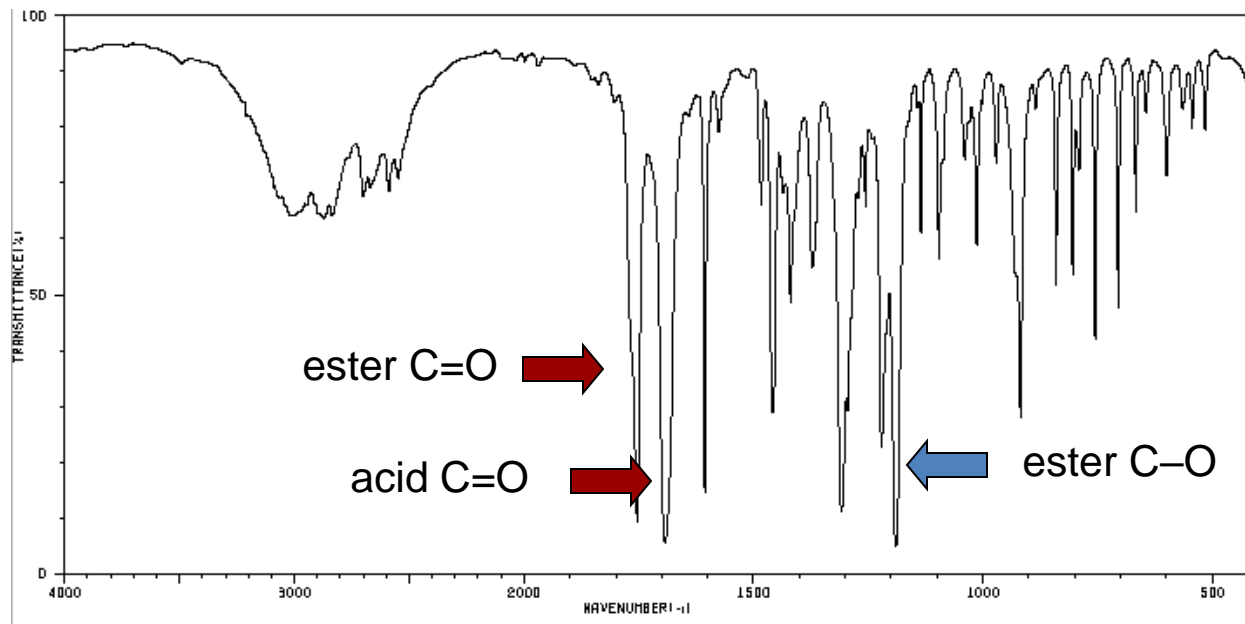


Carbon-oxygen single bonds display stretching bands in the region 1200 - 1100 cm^{-1} . The bands are generally strong and broad. You should note that many other functional groups have bands in this region which appear similar.

IR Spectroscopy: Where do you begin?!



Aspirin



Characteristic group vibrations

4000-1300 cm⁻¹

Fingerprint region

1300 - 600 cm⁻¹

Analysing IR Spectra

- Look for C=O peak (1820-1660 cm^{-1})
- If C=O check for OH (3400-2400 cm^{-1})
 - indicates carboxylic acid
- If C=O check for NH (3500 cm^{-1})
 - indicates amide
- If C=O check for C-O (1300-1000 cm^{-1})
 - indicates ester
- If no OH, NH or C-O then ketone or aldehyde

Analysing IR Spectra

- If no C=O check for OH ($3600\text{-}3300\text{ cm}^{-1}$)
 - indicates alcohol
- If no C=O check for NH (3500 cm^{-1})
 - indicates amine
- If no C=O & no OH check C-O (1300 cm^{-1})
 - indicates ether
- Look for C=C ($1650\text{-}1450\text{ cm}^{-1}$) then aromatic

Carbon-Carbon Bond Stretching

- Stronger bonds absorb at higher frequencies:
 - C-C 1200 cm^{-1}
 - C=C 1660 cm^{-1}
 - C \equiv C 2200 cm^{-1} (weak or absent if internal)
- Conjugation lowers the frequency:
 - isolated C=C 1640-1680 cm^{-1}
 - conjugated C=C 1620-1640 cm^{-1}
 - aromatic C=C approx. 1600 cm^{-1}

Carbon-Hydrogen Stretching

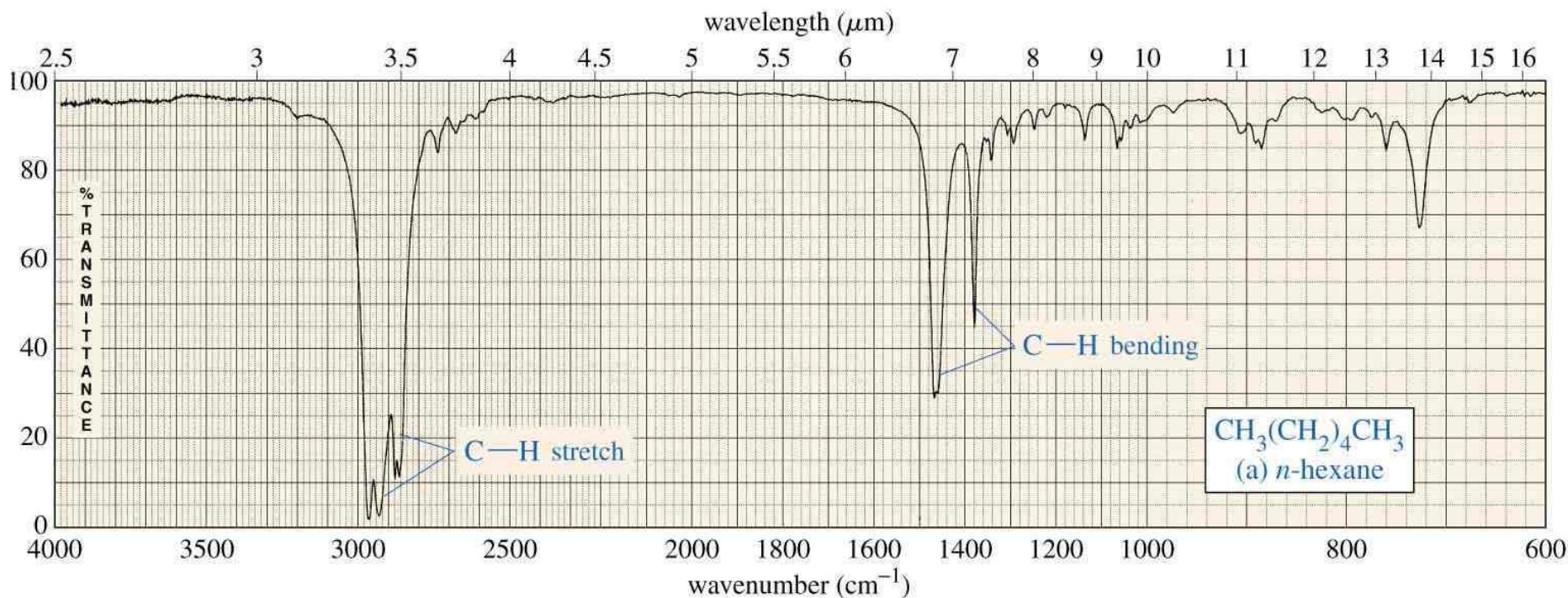
Bonds with more s character absorb at a higher frequency.

- sp^3 C-H, just below 3000 cm^{-1} (to the right)
- sp^2 C-H, just above 3000 cm^{-1} (to the left)
- sp C-H, at 3300 cm^{-1}

Recall IR equation

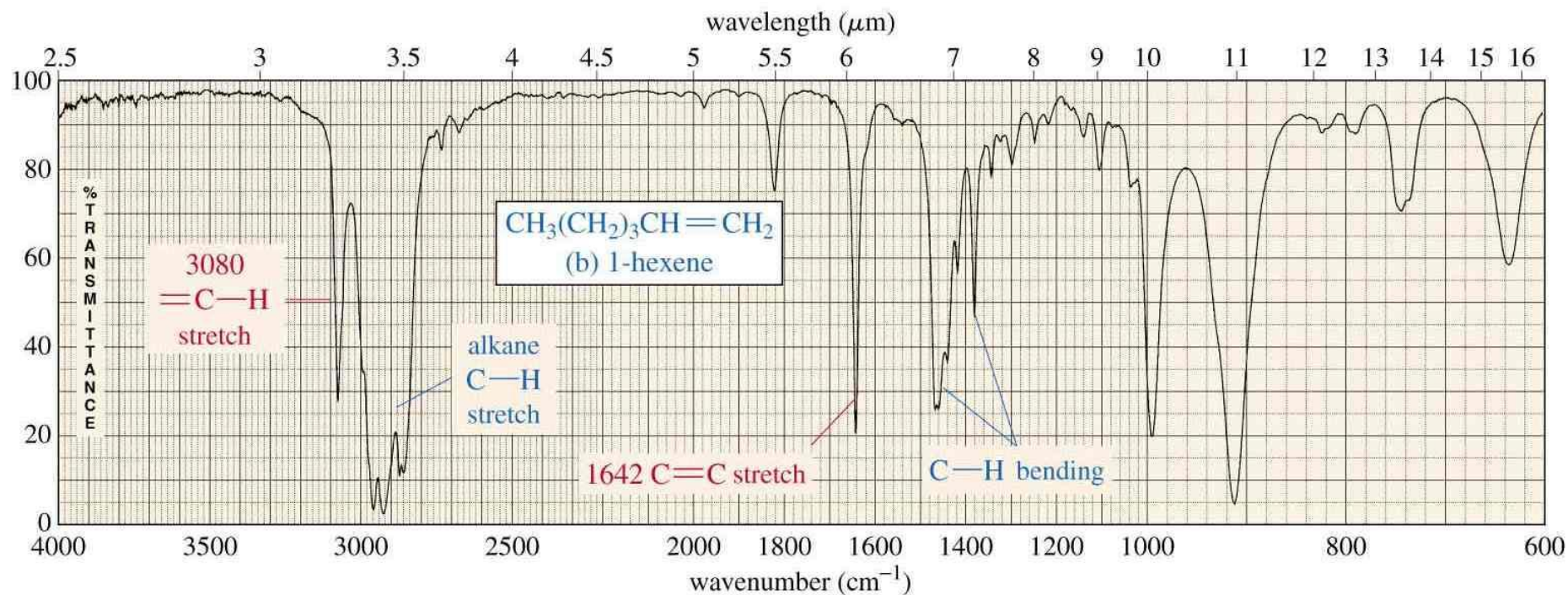
$$\bar{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

An Alkane IR Spectrum

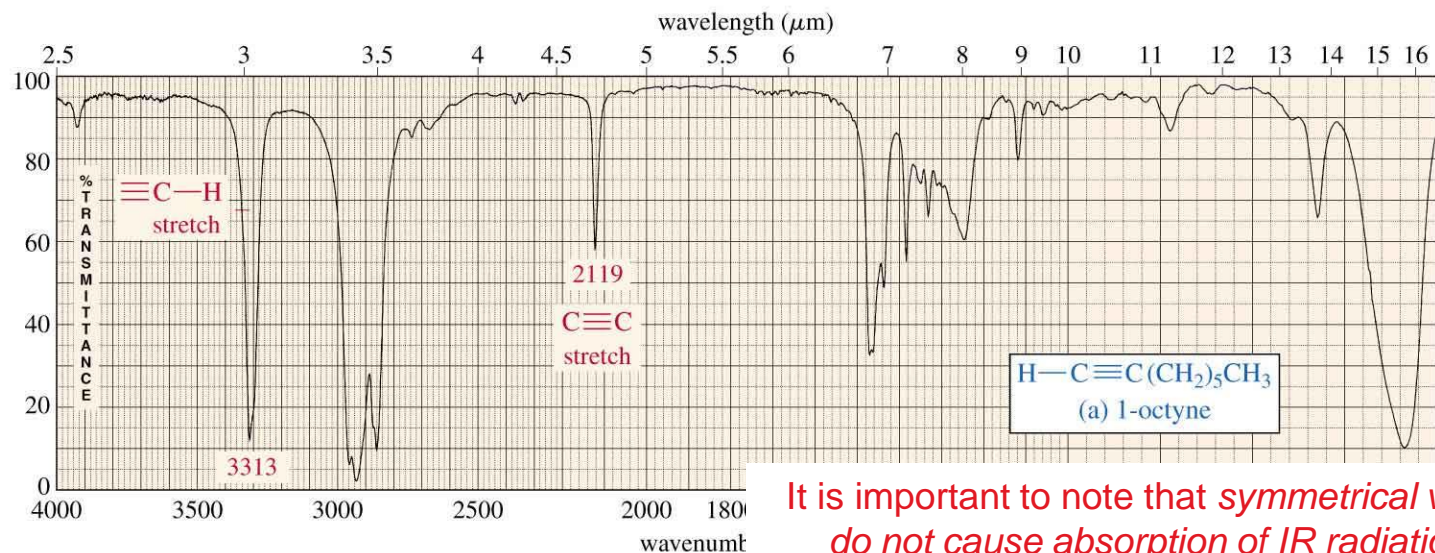


- Bending frequencies are generally lower than stretching frequencies.
- Symmetric stretching frequencies are generally lower than asymmetric stretching frequencies.

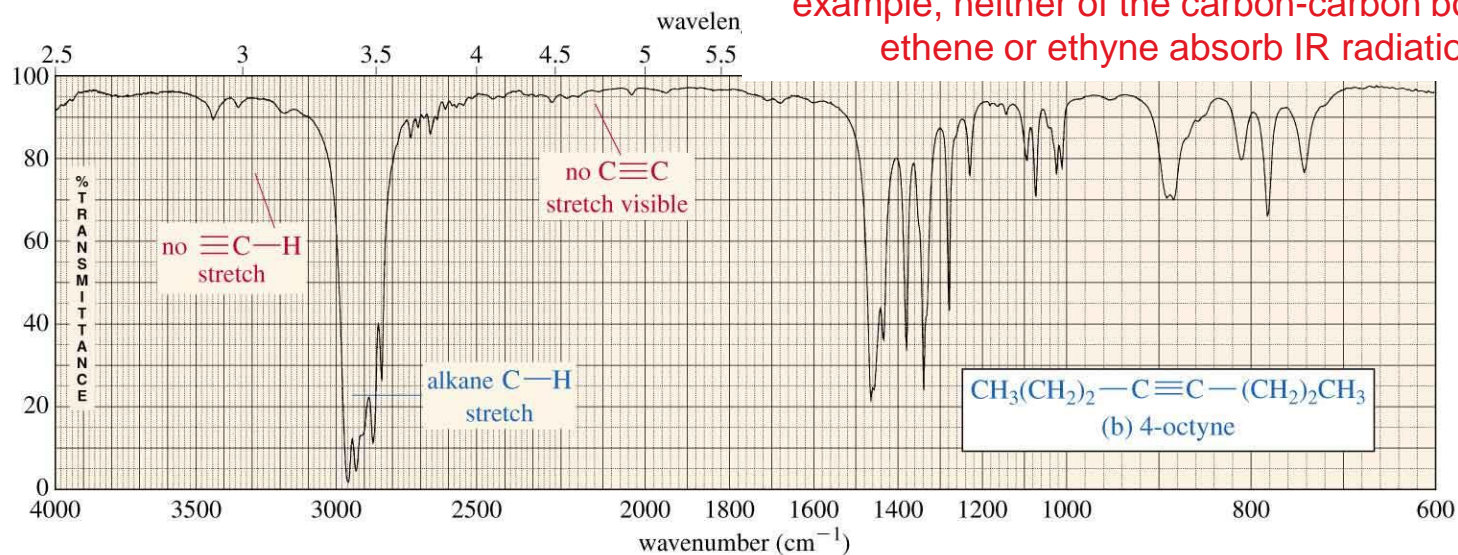
An Alkene IR Spectrum



An Alkyne IR Spectrum



It is important to note that *symmetrical vibrations do not cause absorption of IR radiation*. For example, neither of the carbon-carbon bonds in ethene or ethyne absorb IR radiation

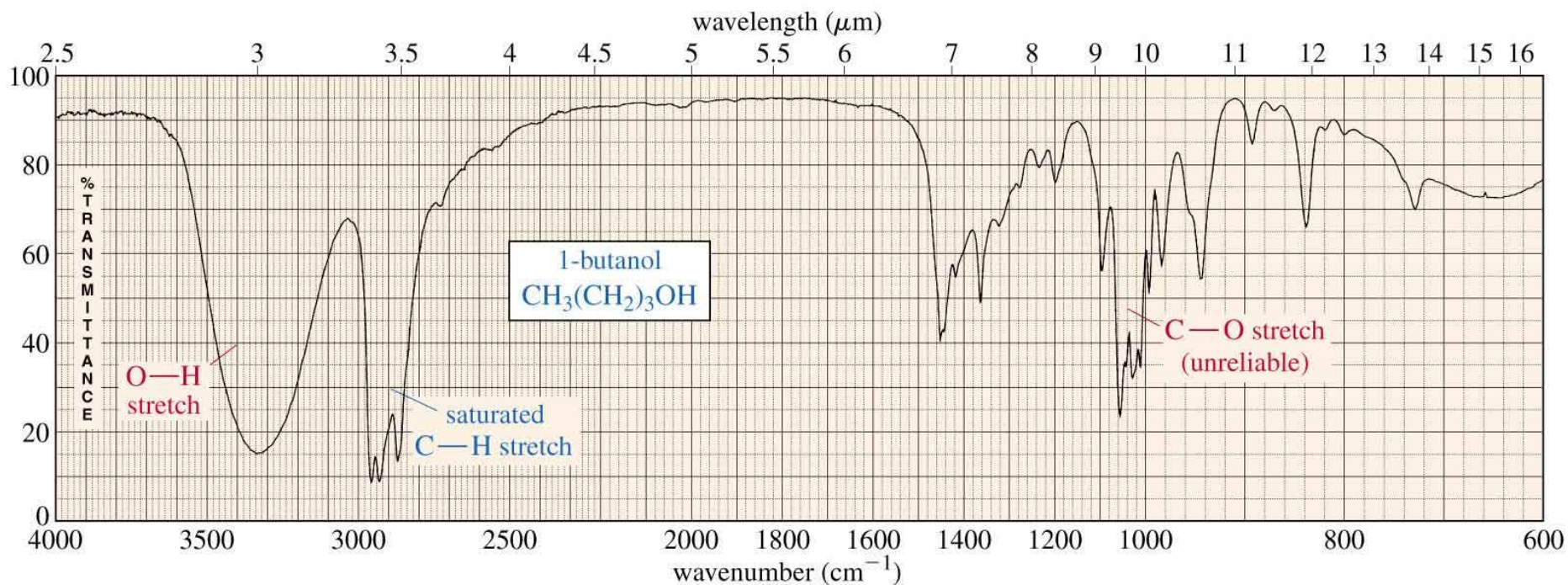


O-H and N-H Stretching

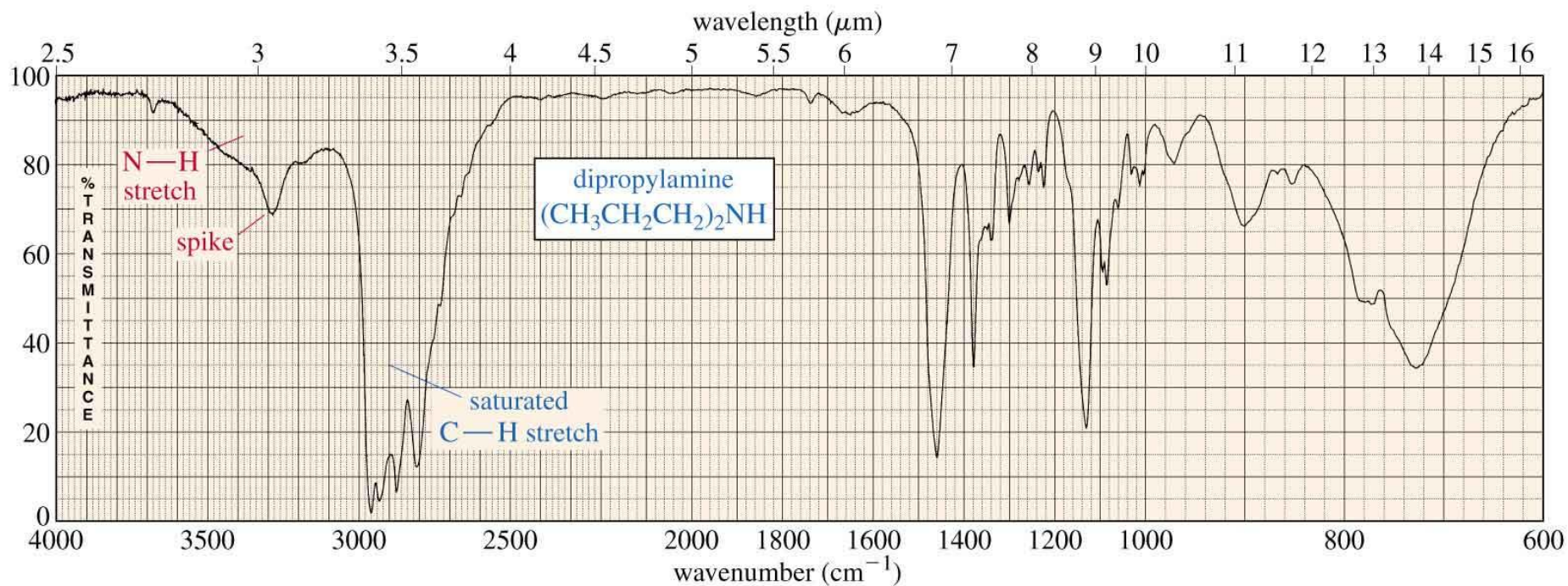
Both of these occur around 3300 cm^{-1} , but they look different.

- Alcohol O-H, broad with rounded tip.
- Secondary amine (R_2NH), broad with one sharp spike.
- Primary amine (RNH_2), broad with two sharp spikes.
- No signal for a tertiary amine (R_3N)

An Alcohol IR Spectrum



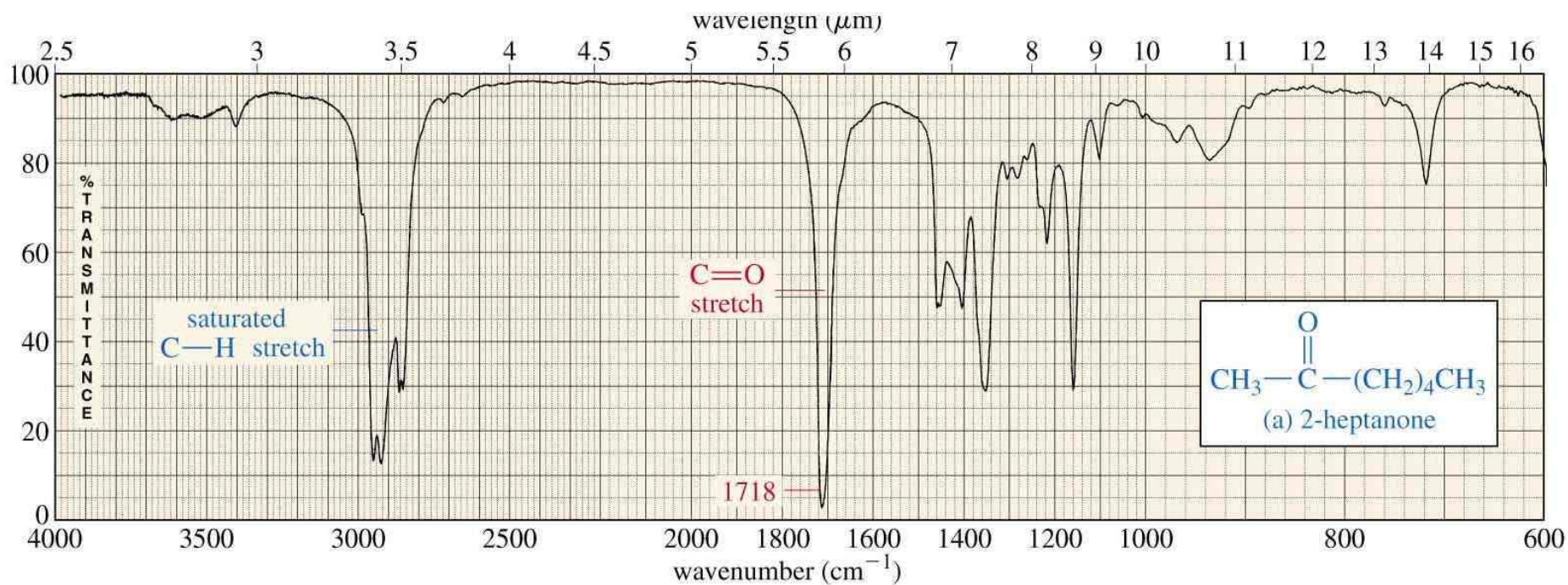
An Amine IR Spectrum



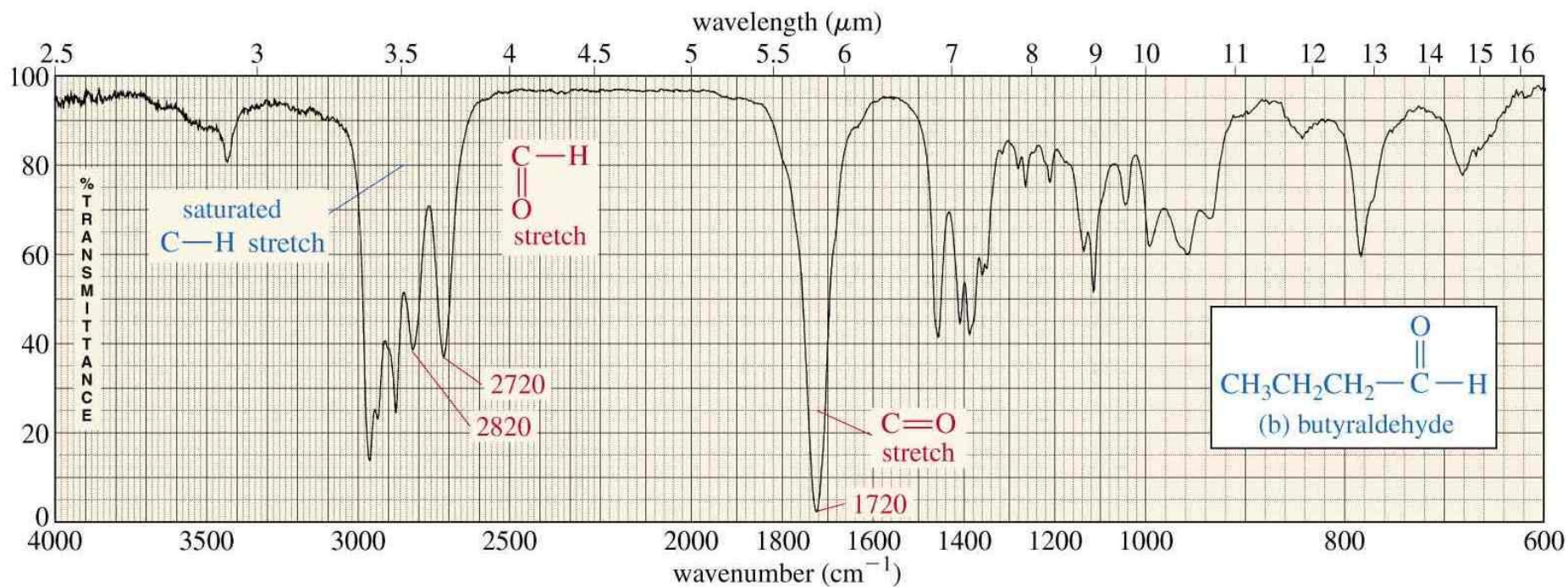
Carbonyl Stretching

- The C=O bond of simple ketones, aldehydes, and carboxylic acids absorb around 1710 cm^{-1} .
- Usually, it is the strongest IR signal.
- Carboxylic acids will have O-H also.
- Aldehydes have two C-H signals around 2700 and 2800 cm^{-1} .

A Ketone IR Spectrum

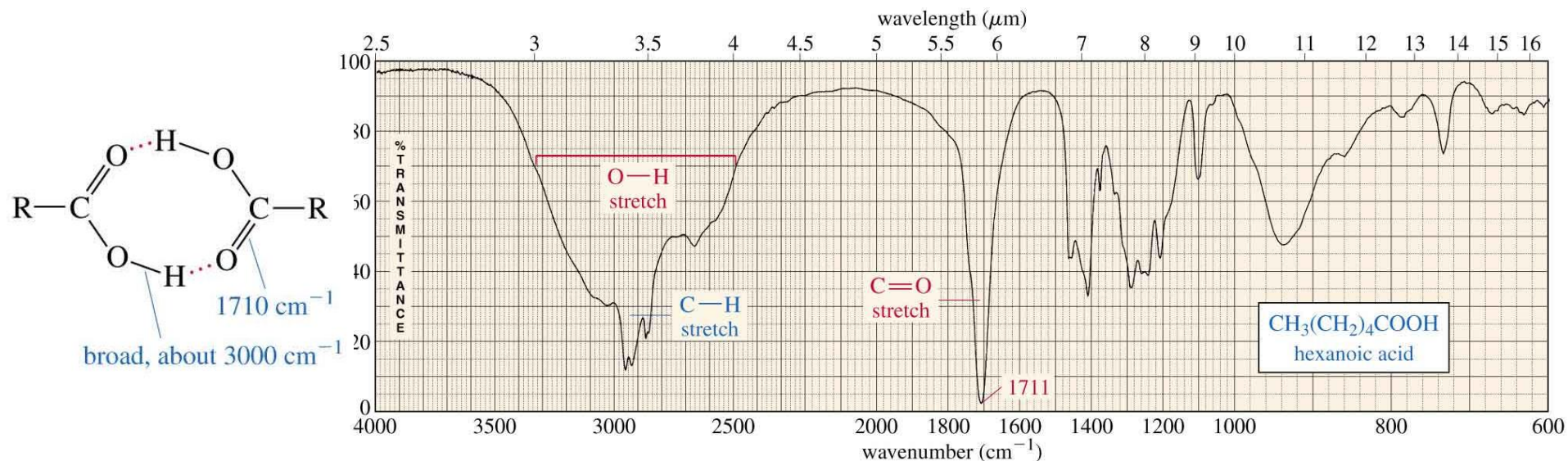


An Aldehyde IR Spectrum



O-H Stretch of a Carboxylic Acid

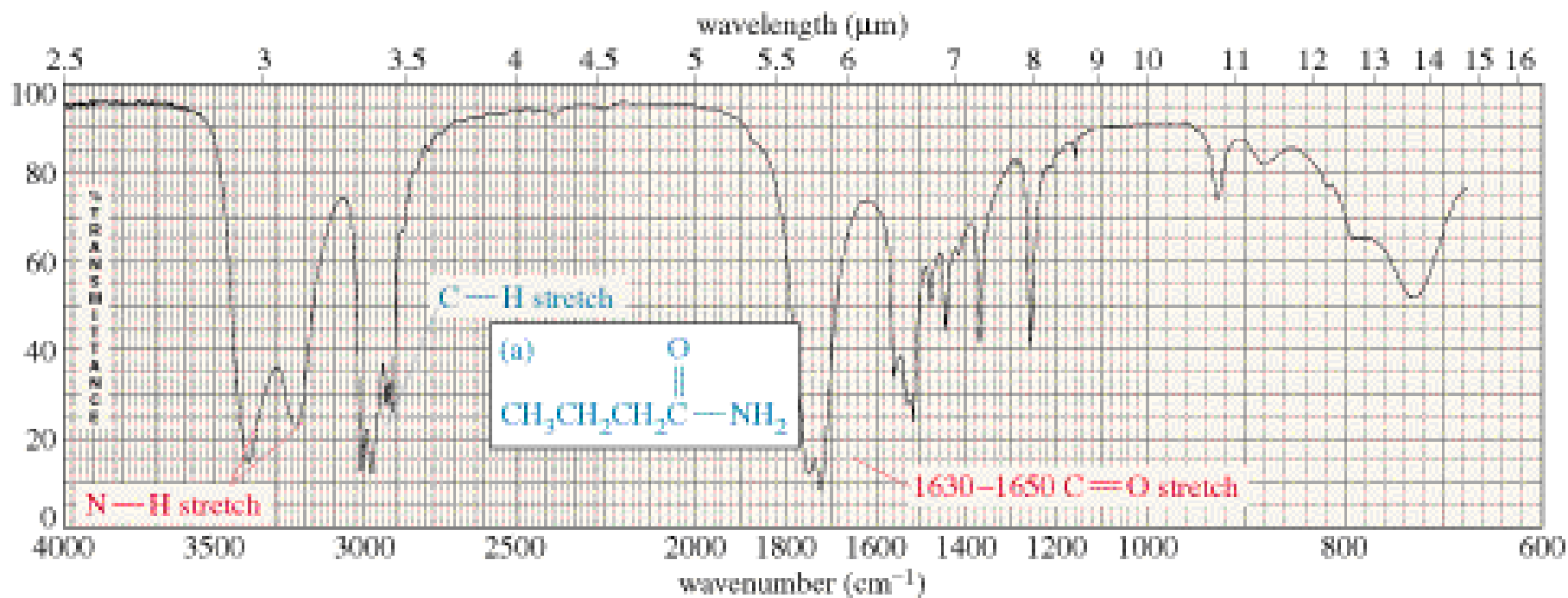
This O-H absorbs broadly, 2500-3500 cm^{-1} , due to strong hydrogen bonding.



Variations in C=O Absorption

- Conjugation of C=O with C=C lowers the stretching frequency to $\sim 1680\text{ cm}^{-1}$.
- The C=O group of an amide absorbs at an even lower frequency, $1640\text{-}1680\text{ cm}^{-1}$.
- The C=O of an ester absorbs at a higher frequency, $\sim 1730\text{-}1740\text{ cm}^{-1}$.

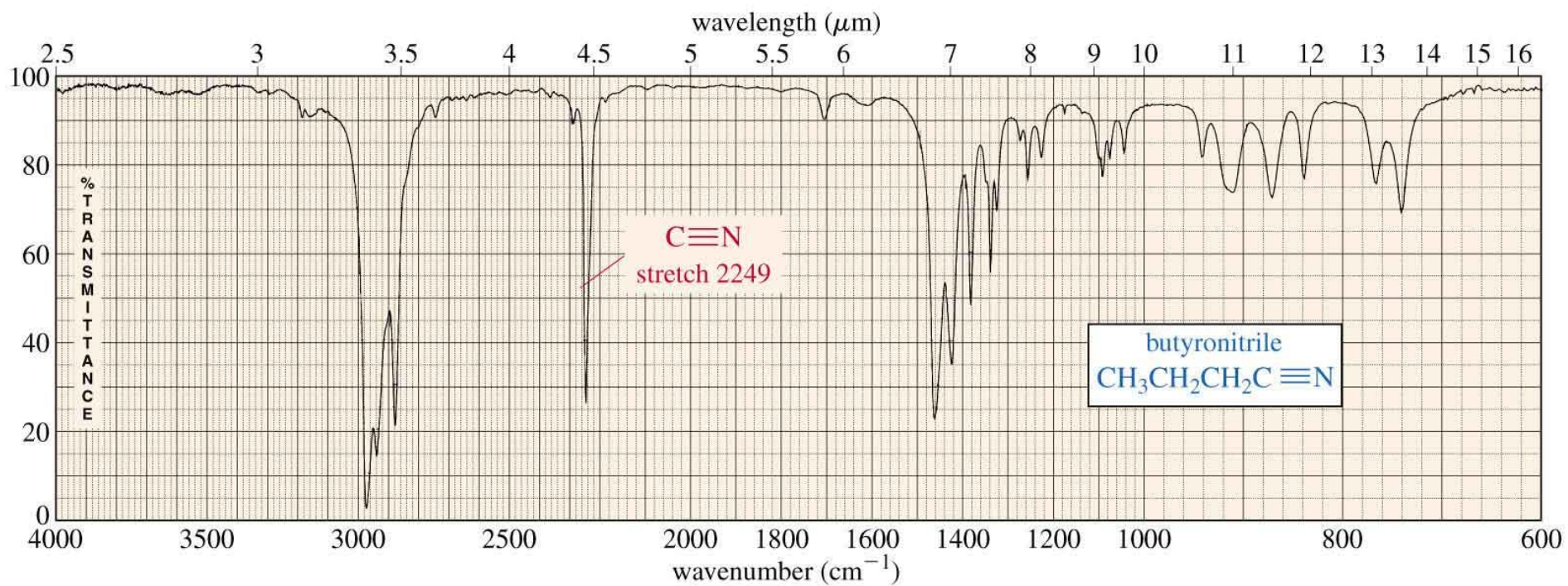
An Amide IR Spectrum



Carbon – Nitrogen Stretching

- C - N absorbs around 1200 cm⁻¹.
- C = N absorbs around 1660 cm⁻¹ and is much stronger than the C = C absorption in the same region.
- C ≡ N absorbs strongly just above 2200 cm⁻¹.
The alkyne C ≡ C signal is much weaker and is just *below* 2200 cm⁻¹.

A Nitrile IR Spectrum



The **secret to IR spectroscopy** is to memorise where on a spectrum a particular functional group will show up

Further point –

we can also devise information from the spectra about what functional groups are **NOT** present.

Example

no absorption near 3400cm^{-1} , compound **NOT** an alcohol

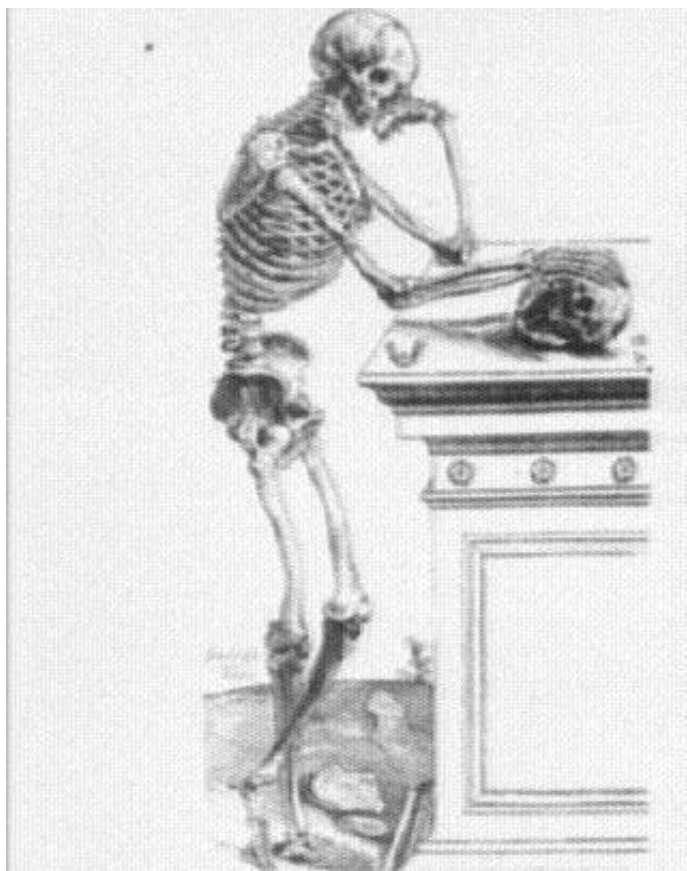
no absorption near 1700cm^{-1} , compound **NOT** a ketone



Strengths and Limitations

- IR alone cannot determine a structure.
- Some signals may be ambiguous.
- The functional group is usually indicated.
- The *absence* of a signal is definite proof that the functional group is absent.
- Correspondence with a known sample's IR spectrum confirms the identity of the compound.

So remember to look for peaks to positively identify functional groups, but also remember to look for evidence to discount others.



This is just the 'bare bones' of IR spectroscopy.

It can be a very powerful technique - the exact vibrational frequencies can shift very slightly depending on what other atoms are attached to the functional groups. So, e.g., monitoring C=O stretches can give valuable information on the nature of peptide (CONH) bond conformations.

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