Lecture V: Methods for Structure Determination

01-24-2020

How do we determine the four levels of structure that we discussed last time? Composition, constitution, configuration and conformation can be determined through separate of integrated methods that simultaneously give information about multiple pieces.

Composition

- Elemental (combustion) analysis
  - destructive, requires ~10mg of material
  - easy to do
    - $Mg(ClO_4)_2$ captures all water
    - today thermal conductivity measurements are used
- High-resolution mass spectrometry
  - matches isotopic composition to the calculated pattern (4 decimal places)

Constitution (connectivity)

- Typically obtained through a combination of several spectroscopic methods or by crystallography
- IR and mass spectroscopy will give you information about functional groups and certain fragments of a molecule
- NMR, especially proton, gives you critical information on how these fragments fit together - you can look at next-door neighbors through coupling analysis

- More complex spatial relationships can be established by through-bond (COSY) and through-space (NOESY) correlation spectroscopy
- X-ray diffraction can determine the whole structure

Requirements: - crystalline samples 0.1–1 mm
- X-ray source

Result: - precise positions of all atoms
- since atoms vibrate a little, their shapes look like footballs or thermal ellipsoids
- simultaneously determines all aspects of the structure

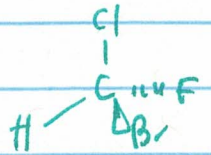
Problems: - does not show hydrogens, as they diffract little (most of the time, they're just calculated)
- just bc you can crystallize something doesn't mean it's the most stable or relevant form of the molecule
- crystal packing effects often influence molecular shape

- Neutron diffraction is much better for light atoms (^1H or ^2D)
- However, it requires a neutron source (nuclear reactor) and a significantly larger crystal
- Provides more detailed information and better bond lengths to hydrogens - relevant in the studies of hydrogen bonding

- How about in gas phase: microwave spectroscopy can determine bond lengths based on their moments of inertia

Configuration

How do we distinguish



from its enantiomer?

X-ray diffraction patterns of the two are the same.

Bijvoet method: Anomalous scattering uses X-rays close to the absorption edge of one of the atoms (typically a heavy atom) and that results in different intensities depending on the enantiomer.

Relative configuration can be determined by X-ray, and if one chiral center's absolute configuration is known, all others can follow from there. Alternatively, we can chemically modify the chiral center through a reaction of "known" stereoselectivity or through a reaction that does not affect the stereocenter. Also, making derivatives with compounds of known stereochemistry can prove the absolute configurations. These could be salts with naturally occurring chiral acids or bases, or esters with compounds of known configuration.

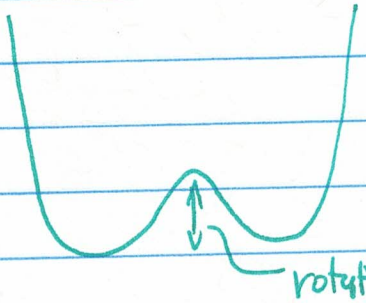
If we know the properties of a chiral compound, their polarimetry can be used, but this will not tell you about the structure—just correlates to a known piece of information

Conformation

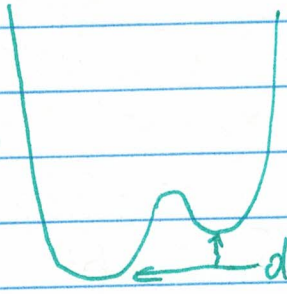
This is easy in the solid state and much harder in

solution or the gas phase. IR and NMR spectroscopy can identify different conformers, but the tricky issue is that they are dynamic. Problem especially in ^{1}H NMR, as it is a slow technique—NMR time scale is on the order of seconds, which is slower than rotation around most C-C bonds. In those cases, we see averaged chemical shifts and coupling constants:

$$\delta = \sum_i n_i \delta_i \qquad J = \sum_i n_i J_i$$



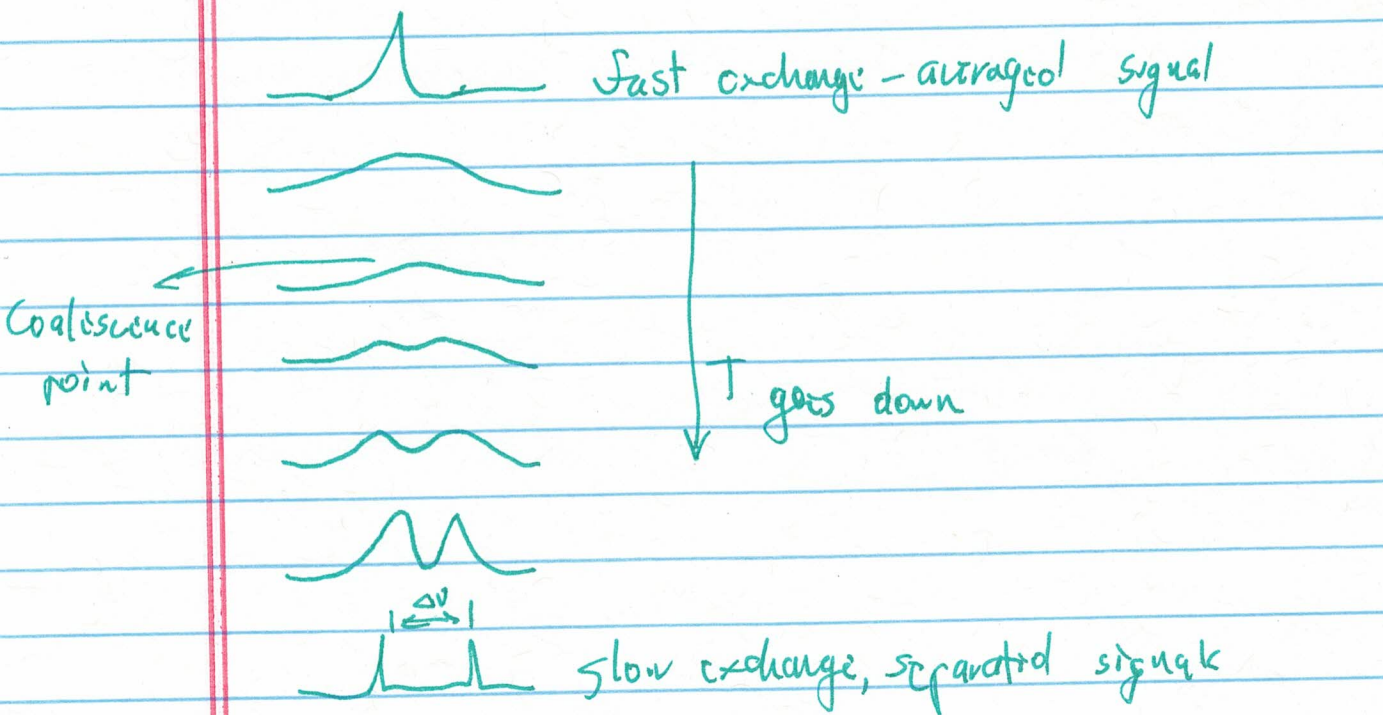
In some molecules, barriers can be quite high: $CBr_2ClCHBrF$, and their conformers can be analyzed @ room temperature



different stabilities mean different populations, and you need at least 1% of minor one for NMR analysis.

Variable-temperature (VT) NMR

-Slow down the exchange by cooling everything down



exchange rate $k = \frac{1}{2}\pi \Delta\nu \sqrt{2} = 2{,}221\,\Delta\nu$
if non-coupled

$k = (k_B T/h)\, e^{-\Delta G/RT}$

k_B Boltzmann constant
h Planck constant