Week 6

Molecular Dynamics

6.1 Chemical Exchange and DOSY

3/11:

- Lecture outline.
  - Chemical exchange.
  - PFGs and DOSY.
  - PSet 4.
  - Final project.
- PSet 4: ROESY and NOESY for Aflatoxin B1.
  - Understand why there are three peaks in the ROESY.
  - What do they mean? Where do they come from? Should there be others?
  - This is a fairly simple, 400 ms ROESY.
  - NOESY does not look as nice.
    - But looks better after phase and baseline spectrum.
    - You can also adjust the density/level of contours. This makes peaks more defined.
- Make sure to properly phase and baseline 2D spectra, too!
  - How do you do this??
  - There are equivalents in MNova.
  - Capture a place in the spectrum in Interactive Phase Correction, look at the columns.
  - Zero-order phase correction at the pivot, first-order phase correction at the sides.
  - *Automatic* phase and baseline correction can be good, too.
- Chemical exchange and NMR timescales in *N*,*N*-dimethylacetamide (DMA).
  - Methyls are in two different chemical environments at room temperature, but they merge into one peaks at higher temperatures. It's like a high-temperature equivalent of cyclohexane ring flipping at low temperatures!
  - Proton peaks get closer together and broader at higher temperatures, before coalescing. You have a point at which the exchange rate (rotation around the bond) is basically equal to the chemical shift difference (in hertz).
  - The difference between the two signals in hertz tells you the exchange rate!
  - Glenn Facey (NMR tech at University of Ottawa) has some really good examples in his blog.
  - Two broad peaks may be different compounds, or **rotamers**; the typical test is heating up!

  - Coalescence happens for carbon at a higher temperature than for protons! Sometimes, your signal just goes away/disappears into the background.

- **Rotamer**: A molecule that has two forms differentiated by rotation about a chemical bond.
- If the populations are equal, the final average will be equidistant between the two; if the populations are unequal, the final average will be weighted.
- Examples of chemical exchange.
  - Often tertiary amides (restricted bond rotation).
  - Ring flipping.
  - Tautomerization (e.g., 6π electrocyclization in cyclohepta-1,3,5-trienes).
  - Center inversion (i.e., nitrogens becoming chiral at low temperatures).
  - Rearrangement reactions.
  - **Fluxionality**.
- Protonated tertiary nitrogens (with TFA vapor) may be useful for rotamers??
- **Pulsed field gradient**: Allow for the precies introduction of a linear field gradient across the sample. *Also known as* **PFG**.
  - Using molecular tumbling to figure out how big molecules are.
  - Your proton gets super spread out, e.g., over 200 ppm.
  - Instead of a Fourier transform, you apply a **Laplace transform** (or **Bayesian processing**) to figure out diffusion time and correlate that to molecular weight.
  - To correlate diffusion coefficient to weight, you have to understand the viscosity of the solvent, temperature, fluid effects, etc.
  - May need to convert data from 2D to a 1D stack, rephase, and rebaseline.
  - You can make MNova do a Bayesian transform.
  - Mixes of multiple molecules will give you two different diffusion coefficients!
    - This could help with identifying if my unknown sample in lab is multi-component or just one molecule!
    - I could also TLC/chromatograph the sample.
- PSet 4 will be assigned today, and we'll have a week to do it.
- The final project.
  - Propose a particular chemical synthesis that we're interested in, ask what I'd like to see come out at the other end, and how could I use the NMR experiments in class to distinguish between products?
- Chemical shift prediction (^{13}C, ^{15}N can guide our thought, but it shouldn't determine our assignments).
  - Aflotoxin's precisely-defined stereochemistry across the bridged ring will come in.
- PSet 3.
  - The carbons I couldn't identify are all exchange-broadened, in the 150-160 ppm.
  - Should have HMBCs to nearby protons.