

## Week 2

# Project 1 Presentations

### 2.1 Introduction to Proton, Carbon, Nitrogen, and Phosphorus

2/11:

- Our presentation.
- $^{13}\text{C}$  NMR presentation (Angel, Nate).
  - Broadband decoupled  $^{13}\text{C}$  NMR gives no coupling with protons, so the number of peaks is the number of distinct carbons.
  - Low abundance of  $^{13}\text{C}$  gives 100 times weaker signal than  $^1\text{H}$ .
  - Gyromagnetic ratio  $\gamma$  is 1/4 that of  $^1\text{H}$ .
    - The signal intensity is proportional to  $\gamma^3$ , so overall, proton signal is about 6400 times stronger than  $^{13}\text{C}$ .
  - Solution: Increase sample concentration, longer relaxation delay (d1), higher field strength NMR (600 MHz), DEPT, 2D NMR.
  - Chemical shifts: 0-220 ppm.
    - Two regions: Above and below 100 ppm.
    - Aliphatic: 0-50 ppm.
    - EWG-substituted aliphatic: 50-100 ppm.
    - Aromatic: 100-150 ppm.
    - Since carbon is more electronegative than hydrogen, adding carbon substituents shifts signals downfield.
    - Resonance structures and partial charges can help predict shifts.
    - Steric effects: Up to 10 ppm shifts from van der Waals interactions of atoms being near each other, especially in rigid molecules.
  - Impurities.
    - $\text{CDCl}_3$  has an equally heighted triplet at 77 ppm due to the spin 1 deuteron splitting the carbon peak into 3 peaks of equal height.
  - Functional groups (shifts and couplings).
    - Alkenes: 100-150 ppm.
      - One-bond coupling of about 150 Hz.
    - Alkynes: 70-90 ppm.
      - Results from differences in electronic configuration around the carbon nuclei.
      - One-bond coupling to proton in acetylene of about 249 Hz (*sp*-hybridized carbons have huge couplings; shorter bonds!).
      - Two-bond coupling to other proton of about 49 Hz.

- Aldehydes.
- Halides.
  - Big bulky electron density on iodine pushes shift for alkyl iodides to  $-20$  to  $-40$  ppm.
- Why isn't  $^{13}\text{C}$  NMR quantitative?
  - We'll talk about it, but it might have something to do with NOESY.
  - Polarization transfer can amplify signals *and* decouple.
  - Turning off NOE, very long relaxation delay, and can make  $^{13}\text{C}$  NMR quantitative!
- For  $^1\text{H}$ , we don't have an issue with chemical shift anisotropy. For almost any heteroatom (and carbon), we will have this issue. And it increases with the square of the field strength, so there's an ideal field strength range for carbon NMR whereas for proton, you can go as high as they make them.
- $^{15}\text{N}$  and  $^{31}\text{P}$  NMR (Natalie, Rosalind).
  - For both nuclei: Typical chemical shifts, proton-heteroatom coupling constants, and what this can look like in biomolecular NMR.
  - $^{15}\text{N}$ .
    - Spin  $1/2$ .
    - 0.37% abundant.
    - Low  $\gamma$ .
    - $> 1000$  ppm range of chemical shifts.
    - Most groups fall within 0-500 ppm. Metal nitrosyl (M-NO) complexes are roughly 300-1200 ppm, but this is helpful for identifying metal complexes (such as iron sulfur complexes, i.e., metalloproteins which store or transport NO)!
    - Proton-nitrogen couplings are difficult to detect. Magnitude affected by solvent used as well as intermolecular interactions (e.g., hydrogen bonding).
    - A variety of techniques be used to study biomolecules (e.g., at MIT in Mei Hong's lab). HSQC experiments, solid-state, isotopic labeling, and many more.
    - DNA is only made of four simple nitrogen-containing heterocycles, so looking at isolated nucleotides can be very helpful.
    - Shifts affected by post-translational modifications, DNA shape, protonation, etc.
    - 100-130 ppm for backbone nitrogens in proteins, varies drastically for side chains (30-220 ppm).
    - HSQC is a protein fingerprint, as well as the gateway into deuterium exchange experiments. Can be used to study the folding of proteins.
  - $^{31}\text{P}$ .
    - Spin  $1/2$  and 100% isotopic abundance. Thus, very easy to measure!
    - 2000 ppm shift range.
      - Upfield defined by  $\text{P}_4$  at  $-527$  ppm.
      - Downfield defined by...
    - Proton-phosphorus  $J$ -coupling allows us to tell how far part phosphorus and hydrogen atoms are. Very useful tool!
      - Great examples in the slides.
    - Chirality determination with a chiral phosphorus reagent and  $^{31}\text{P}$  NMR.
    - $^{31}\text{P}$  NMR in DNA.
      - Gives information about backbone conformation (e.g., A vs. B vs. Z).
      - Dickerson dodecamer backbone; researchers were able to correlate  $^{31}\text{P}$  NMR shift with the percent of a certain conformation in the sample.
    - Cummins and Radosevich labs will have a lot to say on  $^{31}\text{P}$ - $^{31}\text{P}$  couplings!
  - These nuclei are also not often studied at higher fields; you lose stuff even at 600 MHz.

## 2.2 Miscellaneous Nuclei

2/13:

- Announcements.
  - We don't have class next Tuesday; only next Thursday.
- $^{19}\text{F}$  NMR (Yifan, Francesca).
  - Quite similar to proton!
    - Natural abundance: 100%.
    - Nuclear spin of  $1/2$ .
    - $\gamma_{\text{F}} \approx \gamma_{\text{H}}$ .
    - Reliable integration.
    - Broad range of chemical shifts.
    - Standard reference:  $\text{CFCl}_3$ .
  - However, shielding is more paramagnetic; proton shielding is more diamagnetic.
    - Consequence: OChem proton NMR intuition goes out the window.
    - It's harder to predict shift based on functional groups.
    - Magnetic anisotropy ring currents have less effect (overlapping aromatic and aliphatic regions).
  - Some tables of shielding and deshielding effects.
  - Steric deshielding.
  - Talking about isotope effects and satellites.
  - Not very sensitive to solvent effects, unlike proton where benzene- $d_6$  has a big effect.
  - $^{19}\text{F}$ - $^{19}\text{F}$ ,  $^{19}\text{F}$ - $^1\text{H}$ , and  $^{19}\text{F}$ - $^{13}\text{C}$  couplings are most common.
    - Very similar to proton-proton couplings, because both nuclei have  $I = 1/2$ .
    - Proton NMR may couple to both nuclei! Quartet of quartets possible from 3 protons and 3 fluorines nearby (in 1,1,1-trifluoropropane).
    - Coupling constants decrease with more electronegative substituents nearby.
    - Karplus-type effects are still there: *trans* vs. *cis* coupling constants.
    - Geminal fluorine coupling constants increase with more electronegative groups.
    - Carbon couplings can be huge.
    - Long-range couplings are especially noticable with fluorine NMR.
    - Coupling can be transferred through quadrupolar interactions with benzene.
  - Applications of  $^{19}\text{F}$  NMR.
    - Reaction time courses, method optimization, and mechanistic investigation.
    - Deconstruction C–F bonds is really big rn.
    - Fluorine is rather bioorthogonal, so you can put fluorine-substituted amino acids into proteins!
    - Chemical shift of fluorine is very sensitive to the local chemical environment, so it can be used to reconstruct how proteins fold!
    - Confirms the presence of weakly coordinating anions (e.g.,  $\text{BArF}$ ).
    - Swager does a lot of PFAS sensing, especially with porous polymers and  $^{19}\text{F}$  NMR, which can be much more reliable than the EPA's current LCMS methods.
  - There is also a fluorine NMR background from teflon in almost all NMR probes.
- Main group NMR nuclei (Sunny, Kwanwoo, Georgia).
  - $^{11}\text{B}$  NMR.
    - $^{11}\text{B}$  has a spin of  $3/2$ , 80% abundance, higher  $\gamma$ , lower quadrupole moment.

- Borosilicate glass within the NMR probe gives a hump from  $-30 - 30$  ppm.
  - Can do a number of things to reduce this.
- Can reduce the issue of tubes with quartz NMR tubes.
- Heisenberg uncertainty principle leads to more uncertainty and greater broadening. Strong quadrupolar moment also gives shorter relaxation time.
- Chemical shift references.
- It's most common to do proton decoupling.
- B-F couplings are difficult to see; difference in electronegativity is cause??
- zgpg pulse sequence helps decouple the probe's peaks.
- $^{14}\text{N}$  NMR.
  - Nuclear spin number 1, hence quadrupolar and fast relaxation (so broader peaks).
  - Low  $\gamma$ .
  - Much more abundant, but more difficult to work with.
  - You can monitor the progress of a relaxation, but you have to know where to expect things.
  - Can be helpful for identifying heterocyclic isomers.
  - Conclusion: It's not the best, but you can determine isomeric structures. Since it's so abundant, you don't have to label your molecule or have specific growth media.
- $^{29}\text{Si}$  NMR.
  - $I = 1/2$ , negative  $\gamma$ , 5% abundance.
  - Really long relaxation time.
  - Does have some uses, though.
  - TMS is the reference standard for this.
  - Components of the probe and glass and other materials have silicon, so there's a large background peak around 100 ppm.
    - You can computationally subtract the background, or do some other things.
  - Example from soil science.
    - Dipolar decoupling and magic angle spinning in the solid state helped identify imogolite in different horizons of the soil.
- $^{27}\text{Al}$  NMR.
  - 100% natural abundance.
  - $I = 5/2$ , quadrupolar (interacts with not only the external magnetic field, but also the electric field gradient generated by its surrounding environment).
  - Highly sensitive.
  - Wide chemical shift range, and references.
  - $p$ -character explains why more electronegative atoms lead to *lower* chemical shifts.
  - You can monitor formation and degradation of a polyanion.
  - Solid-state aluminum NMR can study aluminum coordination in zeolites.
- $^{77}\text{Se}$  NMR.
  - $I = 1/2$ , 7.63% abundance, relatively low  $\gamma$ .
  - Sunny has worked with this recently!
  - Very broad chemical shift range.
  - Selenium-proton coupling is a thing.
  - Clear oxidation state shift.
  - Selenocysteine can be used in biology.
- $^{129}\text{Xe}$  and  $^{131}\text{Xe}$  NMR.
  - Huge chemical shift range.
  - You'll probably never use it, but it's cool.
  - Biological applications, but drawbacks in terms of practicality.

- More nuclei.
  - $^2\text{H}$  NMR.
    - You have to pump the system with an excessive amount of deuterium if you want to do it.
    - Low quadrupole moment, so poor resolution.
    - $I = 1$ .
    - Chemical shifts comparable for proton NMR, so you can use this side-by-side with proton NMR to really see what's going on in your reaction/molecule.
    - Good for deuterium labeling studies.
    - Example: Adamantanone homo-enolization.
      - *exo*- vs. *endo*-hydrogen abstraction determined by comparing  $^1\text{H}$  and  $^2\text{H}$  NMR.
      - Shifting reagents make proton and deuterium have very similar chemical shift ranges.
    - Example: Chemical biology.
      - Study of the lipid bilayer with deuterated lipids.
      - Used to study the order of the molecules.
  - $^6\text{Li}$  NMR.
    - $I = 1$ , 8% abundant.
    - Chemical shift range of about 28 ppm; some inorganic species have dramatically different shifts.
    - Coupling with proton, carbon, or nitrogen can be used.
    - Can be used to understand the behavior of organolithium species.
      - Reveals monomeric and dimeric phenyl lithiates!
      - Isotopically labeling a nearby nitrogen reveals several possible dimer conformations.
  - $^7\text{Li}$  NMR.
    - $I = 3/2$ , 92% abundant.
    - Broad peaks and very little coupling.
  - $^{23}\text{Na}$  NMR.
    - $I = 3/2$ , 100% abundant.
    - 110 ppm range in solution; varies greatly in the solid state.
    - Implications in biology.
    - Sodium contamination is common in empty NMR tubes!
    - Application: Electrochemistry.
      - Characterizing sodium ion battery degradation mechanisms.
    - Application: Frozen seawater and how large bodies of water freeze.
      - Studied brine freezing.
      - $\text{NaCl}_{(\text{s})}$  has a characteristic broad peak, becomes thin when dissolved in water, and gets messier when you go to lower temperatures.
  - $^{35}\text{Cl}$  NMR.
    - $I = 3/2$ , 75.5% abundant.
    - Resolution isn't as bad as deuterium labeling, but not great due to quadrupole moment.
    - Fairly big chemical shift range.
    - Solvents give broad peaks; inorganic/salt phase is better.
    - Application: Solid-state  $^{35}\text{Cl}$  NMR for hydrochloride salt concentration determination of pharmaceuticals.
      - Salt structure can be characterized.
      - Much better for solid-state dynamics than  $^{13}\text{C}$  NMR.
    - Proton decoupling is important for chlorine NMR.