NMR Topics

Spin Systems • nOe and nOesy • HMBC and HMQC

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Chemistry Topics
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Pavia, D.L.; Lampman, G.M.; Kriz, G.S. Introduction to Spectroscopy
Silverstein, R.M.; Webster, F.X.; Kiemle, D.J. Spectrometric Identification of Organic Compounds
Proton NMR - Spin Systems

• Recall → 1.0 ppm = 100 Hz for a 100 MHz magnet
  • Resolution increases as a function of magnet strength

• Defining simple first-order multiplet
  • First-order if $\Delta \nu / J > 8$ (easier to achieve with bigger magnet)

    • $\Delta \nu$ is distance between midpoints of coupled multiplets (in Hz)
      and $J$ is coupling constant (Hz)

  • Follows n+1 rule

  ![Diagram showing multiplets with $\Delta \nu / J$ values from 1.0 to 5.0]

      | $\Delta \nu / J$ |
      |-----------------|
      | 5.0             |
      | 4.0             |
      | 3.0             |
      | 2.0             |
      | 1.0             |

  Chemical shift is no longer central between peaks
### Pople Notation

<table>
<thead>
<tr>
<th>$\Delta v/J$</th>
<th>Notation</th>
<th>Notes</th>
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<tbody>
<tr>
<td>10.0</td>
<td>AX</td>
<td>Proton sets in spin system are weakly coupled if $\Delta v/J &gt; 8$</td>
</tr>
<tr>
<td>4.0</td>
<td></td>
<td>- Termed <strong>AX</strong> system</td>
</tr>
<tr>
<td>3.0</td>
<td></td>
<td>When $\Delta v/J &lt; 8$ (higher order systems)</td>
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<tr>
<td>2.0</td>
<td>AB</td>
<td>- Termed <strong>AB</strong> system</td>
</tr>
<tr>
<td>1.0</td>
<td>AB</td>
<td>When three weakly coupled sets</td>
</tr>
<tr>
<td>0.0</td>
<td>$A_2$</td>
<td>Two strongly and one weakly coupled</td>
</tr>
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</table>

*Pople, J.A.; Schneider, W.G.; Bernstein, H.J. *High Resolution NMR* (1959), New York; McGraw-Hall*
Rigid vs. Free Rotation

If weakly coupled
- Termed $A_2X_2$ system
- Two triplets

If strongly coupled
- Termed $A_2B_2$ system
- Complex higher order

If weakly coupled
- Termed $AA'XX'$ system

If strongly coupled
- Termed $AA'BB'$ system
- Complex higher order

Conformational preferences and rigidity need to be taken into account
B₂, C₂, and D₂ are all strongly coupled
Together the “conglomerate” of spins couple to A₃

• At 300 MHz this leads to higher order system
  • Termed virtual coupling

• At 600 MHz Δν/J increases
  • Affords first order triplet
Three Coupling Constant Systems

AMX, ABX, and ABC systems

\[ \Delta \nu / J > 35 \text{ for all protons} \]

*Weakly coupled* – affords AMX system

Aromatic protons are a BB’ CC’ D system–higher order
Chemical-Shift and Magnetic Equivalence

If the protons in the same set couple equally to every other proton in the spin system they are magnetically equivalent.

Ha protons are *Chemical Shift Equivalent* but *NOT Magnetically Equivalent*.

*Not a simple first order spectrum—no matter what field strength used*.

Pople notation: AA’ XX’

Check for *Magnetic Equivalence* if protons are chemical-shift equivalent.

*Common in aromatic compounds*. 
Chemical-Shift and Magnetic Equivalence

Chemical Shift: $H_x = H_x'$ and $H_a = H_a'$.
Magnetic Equivalence: $H_x \neq H_x'$ and $H_a \neq H_a'$.

Note: $H_a$ and $H_a'$ do not couple the same with $H_x'$.

Pople notation: XX' AA' AXXX or X'2A'2A2X2

Recall: If protons are chemical-shift equivalent but are NOT magnetically equivalent the system is NOT first order and splitting is observed.

Corollary: In a first order system, chemical-shift-equivalent protons couple but do not lead to peak splitting.
Nuclear Overhauser Enhancement

Extension of Overhausers’ 1953 method to polarize nuclei of certain metals by Anderson and Freeman in 1962

• nOe can be heteronuclear
  • Between carbon and hydrogen atoms—directly bonded

• nOe can be homonuclear
  • Between hydrogen atoms—through space

• Time-averaged experiment
  • Lack of nOe is not proof of structure!

Heteronuclear nOe-Theory

• Irradiate one atom type while the NMR spectrum of the other type is determined
  • Enhancement occurs if intensities of non-irradiated atoms change
  • Effect can be positive or negative

• nOe occurs through space via spin-spin dipoles

• Magnitude decreases as function of the inverse of \( r^3 \)
  • \( r \) is radial distance from hydrogen of origin
Heteronuclear nOe-Theory

Cross Polarization

One spin can change per transition during excitation phase

Broadband irradiation of protons—population of $N_4 = N_2$ and $N_3 = N_1$
Disturbed from equilibrium populations

Relaxation restores equilibrium

Double quantum inversion allowed ($W_2$)
Increases carbon signals
Heteronuclear nOe

• Example – proton decoupled carbon spectrum
  • Positive effect for $^{13}\text{C}$ interacting with $^1\text{H}$
  • $\text{nOe}_{\text{max}} = \frac{1}{2} \left( \frac{\gamma_{\text{irr}}}{\gamma_{\text{obs}}} \right) = 1.988$ for $^1\text{H}$-decoupled $^{13}\text{C}$ spectrum
  • Effect is additive up to 200% enhancement
  • Total nOe increases $\text{C} < \text{CH} < \text{CH}_2 < \text{CH}_3$

\[
\text{Irradiation of formamide hydrogen leads to larger nOe of syn methyl group}
\]

- Formamide
  - $31.1 \text{ ppm}$
  - $36.2 \text{ ppm}$
Homonuclear nOe-Theory

Cross Polarization-through space

Uses a weaker irradiation frequency, $\nu_2$, than that used for decoupling

Leads to increase in population of the higher energy level in the nearby non-irradiated protons—energy transfer via dipolar mechanism

Excess population undergoes relaxation—increase in signal intensity

Effect decreases as $r^{-6}$, $r$ is distance between nuclei

Measurable effect up to 3–4 Å
nOe Difference Spectrometry

Obtain a $^1$H NMR spectrum with $\nu_2$ set at a non-interfering frequency

Set $\nu_2$ at a frequency to irradiate a desired resonance

Subtract the spectra from one another

Negative signal for irradiated resonance

Positive signals for nuclei that interact with irradiated resonance via dipolar mechanism—located within 3–4 Å

Signals of unaffected protons will be very weak or absent
nOe Difference Spectrometry

a: spectrum of 1e
b: nOe difference spectrum
c: spectrum of 1f
d: nOe difference spectrum

Taken from: Holzer, W. Tetrahedron, 1991, 47, 1393
**NOESY Spectrometry**

- 2D-variant of nOe experiment

- NOESY works best for small and large molecules:
  - For medium sized molecules—1000-2000 MW
  - ROESY (rotating-frame) can be applied

- Resembles a COSY spectrum
  - COSY peaks (spin-spin coupling) are present
  - May make interpretation cumbersome
HMQC Spectroscopy

- Result of one-bond couplings ($^{1}J_{CH}$)
  - Gives a correlation map of the coupled spins

- HMQC – Heteronuclear Multiple Quantum Coherence
  - Inversely detected experiment—detects $^{1}\text{H}$

- HETCOR experiment preceded HMQC
  - Directly detects $^{13}\text{C}$
  - 30-fold less sensitive

- HSQC – Heteronuclear Single Quantum Coherence
  - Provides better carbon resolution than HMQC
  - Very sensitive to pulse calibration and probe tuning
    - More susceptible to S/N loss
HMBC Spectroscopy

- Result of two and three-bond couplings ($^{2-3}J_{\text{CH}}$)
  - Indirectly gives carbon-carbon correlations

- HMBC – Heteronuclear Multiple Bond Coherence
  - Inversely detected experiment–detects $^1\text{H}$
  - Carbon detected experiment was COLOC

- Interpretation can be difficult
  - STRONGLY coupled $^1J_{\text{CH}}$ couplings present
  - $^2J_{\text{CH}}$, and $^3J_{\text{CH}}$ couplings may be absent
  - $^4J_{\text{CH}}$ couplings may be present
  - $^{13}\text{C}$ satellites of intense protons common (i.e. methyl)

- $J$-value of 10 Hz
  - $^2J_{\text{CH}}$, and $^3J_{\text{CH}}$

- $J$-value of 2 Hz
  - $^3J_{\text{CH}}$, and $^4J_{\text{CH}}$
Summary

• Instrument field strength will affect spin system appearance
  • Higher Order $\Rightarrow$ First Order
  • May depend upon shift and chemical equivalence

• Through space dipolar interactions can be used to aid in structure determination
  • NOE can be used to look at specific interactions
• 2D-version (NOESY) is useful for looking at all interactions

• HMQC and HSQC
  • Provides direct proton-carbon couplings

• HMBC – $J$-values set between 10 and 2 Hz
  • Together provides $^2J_{CH}$, $^3J_{CH}$, and $^4J_{CH}$ couplings
  • Indirect carbon-carbon coupling