Multidimensional NMR Experiments

Chem 4010/5326: Organic Spectroscopic Analysis
2D NMR Spectroscopy
General Information

– More complicated experiments to set up than $^1$H and $^{13}$C
– Changes in pulses (#, length, angles, mixing times, etc.)
– Observe effects based on relationship of nuclei
  **Can be homonuclear (same nuclei) (e.g. H–H) or heteronuclear (different nuclei) (e.g. H–C, H–P, etc.)**
– Will only go over the what the experiments tell you and how to interpret, and only for the most common and widely used for solving organic structures
  – DEPT, H–H COSY, HMQC (HETCOR), HMBC, INADEQUATE
– There is a whole alphabet soup of other experiments (both 1D and 2D)
  – EXSY, TOCSY, HOHAHA, INEPT, WATERGATE, and many more

http://www.chem.ox.ac.uk/spectroscopy/nmr/acropage.htm
2D NMR Spectroscopy

Number of Protons on Carbon

DEPT (*Distortionless Enhancement by Polarisation Transfer*)

– Used to be known as APT (*Attached Proton Test*)
  – DEPT is $^1$H-detected; APT is $^{13}$C-detected

– Tells you how many protons are attached to a particular carbon
  – negative peaks = CH$_2$
  – positive peaks = CH and CH$_3$ (distinguishable with further processing)
  – “missing” peaks = carbons w/o protons

– With a little help from IR and chemical shift of $^1$H and $^{13}$C, can get a rough idea of molecular weight
2D NMR Spectroscopy
Number of Protons on Carbon

DEPT (Distortionless Enhancement by Polarisation Transfer)

1 = Carbon spectrum
2 = ↓ CH$_2$
   ↑ CH, CH$_3$
3 = ↑ CH

90° pulse
135° pulse
2D NMR Spectroscopy

Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)

– Tells you which protons are coupled to one another
– Very useful when peaks are overlapping in $^1$H NMR and you are unable to calculate coupling constants, or when there are a lot of similar coupling constants
– Cross peaks are coupled to each other

![Graph showing $^1$H–$^1$H COSY](image)

– Newer method is DQF (Double Quantum Filtered)-COSY
  – same information, but looks “cleaner”
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)

– Overlapping protons and a lot of similar coupling constants

Raffinose—a trisaccharide
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)
2D NMR Spectroscopy
Who is Talking to Who?

$^1\text{H} - ^1\text{H}$ COSY (Correlation Spectroscopy)
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)

– DQF-COSY: Double Quantum Filtered COSY – cleans up the spectrum by reducing noncoupled systems (e.g. CH3 singlets)
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)

– DQF-COSY: Double Quantum Filtered COSY – cleans up the spectrum by reducing noncoupled systems (e.g. CH3 singlets)
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)

$\text{C}_6\text{H}_{10}\text{O}_2$
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^1$H COSY (Correlation Spectroscopy)
Recall...

$^1$H–$^1$H COSY

– Tells you which protons are coupled to one another
– Very useful when peaks are overlapping in $^1$H NMR and you are unable to calculate coupling constants, or when there are a lot of similar coupling constants
– Cross peaks are coupled to each other
Recall...

$^1$H–$^1$H COSY

– Tells you which protons are coupled to one another
– Very useful when peaks are overlapping in $^1$H NMR and you are unable to calculate coupling constants, or when there are a lot of similar coupling constants
– Cross peaks are coupled to each other

This can still cause ambiguities!
2D NMR Spectroscopy
Who is Talking to Who?

$^{1}$H–$^{1}$H TOCSY (Total Correlation Spectroscopy)

– Tells you which protons are in the same spin system (a continuous chain of spin-spin coupled protons)
– Magnetization from $H_A$ is transferred to $H_B$, which then transfers to $H_C$ and on down the line

– Can be run as either a 1D or 2D experiment
– Running as a 1D experiment greatly simplifies spectra with severe signal overlap
– Related experiment (HOHAHA) gives essentially the same information
– Can also observe one-bond $^{1}$H–$^{13}$C couplings (HMQC-TOCSY, hetero-TOCSY, HEHAHA) - will not discuss
1D TOCSY
Spin System Identification

$^1$H–$^1$H TOCSY (Total Correlation Spectroscopy)

- Irradiate at frequency of proton of interest
- Wait a period of time (typically 20 to 400 ms) and then collect 1D spectrum
- Only observe protons to which magnetization has been transferred
- Short periods of time (20 ms) will only give rise to “single step” transfers; longer periods of time allow magnetization to propagate further
1D TOCSY
Spin System Identification

Mixing time 400 ms β 1 irradiated

β6  β6'

Mixing time 120 ms

β5

Mixing time 80 ms

β4

Mixing time 40 ms

β3

Mixing time 20 ms

β2

'H NMR 600 MHz

3.9  3.8  3.7  3.6  3.5  3.4  3.3  ppm

β-lactose

H1 ⇌ 4.67 ppm
1D TOCSY

1D TOCSY

2D TOCSY
Spin System Identification

$^{1}$H–$^{1}$H TOCSY (Total Correlation Spectroscopy)

- Cross peaks are in the same spin system

2D TOCSY

- Cross peaks are in the same spin system

Intermediate in biomimetic synthesis of manzamine

2D TOCSY

- Cross peaks are in the same spin system

Intermediate in biomimetic synthesis of manzamine

2D TOCSY

- Cross peaks are in the same spin system

Intermediate in biomimetic synthesis of manzamine

New Developments
Deconvolution via MDEC

MDEC (Multi Frequency Homonuclear Decoupling)
– Conceptually the same as the homonuclear decoupling experiment mentioned earlier, but allows multiple frequencies to be decoupled at the same time

(a) $^1H$ NMR
(b) irr @ H-1
(c) irr @ H-1/H-7
(d) irr @ H-1/H-3a/H-7

J. Am. Chem. Soc. 2009, 131, 15994–15995
New Developments
Deconvolution via MDEC

1D-TOCSY-MDEC

(a) $^1$H NMR
(b) 1D-TOCSY
irr @ H-3
(c) 1D-TOCSY
irr @ H-3 with
MDEC @ H-1b, H-2b, H-3

J. Am. Chem. Soc. 2009, 131, 15994–15995
2D NMR Spectroscopy
Who is Talking to Who?

$^1$H–$^{13}$C COSY

– HETCOR (Heteronuclear Correlation)
  – older experiment; $^{13}$C-detected

– HMQC (Heteronuclear Multiple Quantum Correlation) and HSQC (Heteronuclear Single Quantum Correlation)
  – newer experiments; $^1$H-detected; largely replaced HETCOR

– Both give same information, experimentally very different

– Peaks have one-bond coupling (i.e. attached directly)

– Compliments DEPT

– Particularly useful for diastereotopic protons

1 bond H–C coupling
2D NMR Spectroscopy
Who is Talking to Who?

HMQC

F2

1 bond H–C coupling
2D NMR Spectroscopy
Who is Talking to Who?

HMQC

Diastereotopic Protons

1 bond H–C coupling
2D NMR Spectroscopy
Who is Talking to Who?

HMOC

Can “see into” multiplets

Caryophyllene Oxide
2D NMR Spectroscopy
Who is Talking to Who?

HMQC
2D NMR Spectroscopy

$^{13}$C/DEPT NMR 150.9 MHz
2D NMR Spectroscopy

[Diagram of NMR spectroscopy results with spectral lines and chemical structure]
2D NMR Spectroscopy
2D NMR Spectroscopy
Who is Talking to Who?

- COLOC (Correlated spectroscopy for Long range Couplings)
  - older experiment; $^{13}$C-detected
- HMBC (Heteronuclear Multiple Bond Coherence)
  - newer experiment; $^1$H-detected; completely replaced COLOC
  - Both give same information, experimentally very different
  - Peaks have two- or three-bond coupling
  - “Sees through” heteroatoms and quaternary carbons
  - Can be very complicated, but is very powerful
2D NMR Spectroscopy
Who is Talking to Who?

\(^1\text{H}–^{13}\text{C COSY (Long Range)}\)

- HETCOR (Heteronuclear Correlation)
  - older experiment; \(^{13}\text{C}\)-detected
- HMQC (Heteronuclear Multiple Quantum Correlation) and HSQC (Heteronuclear Single Quantum Correlation)
  - newer experiments; \(^1\text{H}\)-detected; largely replaced HETCOR
- Both give same information, experimentally very different
- Peaks have one-bond coupling (i.e. attached directly)
- Compliments DEPT
- Particularly useful for diastereotopic protons

\[\text{H} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{H}\]

1 bond H–C coupling
2D NMR Spectroscopy

Who is Talking to Who?

HMQC

1 bond H–C coupling
2D NMR Spectroscopy
Who is Talking to Who?

HMBC

2 and 3 bond H–C couplings
2D NMR Spectroscopy

Who is Talking to Who?

\[ ^{13}\text{C}/\text{DEPT NMR 150.9 MHz} \]

![Chemical structures](image)
2D NMR Spectroscopy
Who is Talking to Who?

[Diagram showing 2D NMR spectroscopy results with chemical structures and COSY 600 MHz data]
2D NMR Spectroscopy

Who is Talking to Who?

\[
\text{OH} \quad \text{or} \quad \text{OCH}_3
\]

HMQC 600 MHz
2D NMR Spectroscopy
Who is Talking to Who?

HMBC 600 MHz

[Chemical structures and NMR spectrum graph]
2D NMR Spectroscopy
Who is Talking to Who?

HMBC 600 MHz
2D NMR Spectroscopy
Who is Talking to Who?

\(^{13}\text{C}\)–\(^{13}\text{C}\) COSY

– INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment)
– tells what carbons are attached to each other
– if you know what type of carbon it is (C, C=O, CH, CH\(_2\), CH\(_3\), etc.)
  from DEPT, you can almost write down the entire gross structure by running two NMR experiments

– **BUT** it is \(^{13}\text{C}\)–\(^{13}\text{C}\) coupling
  – probability of one \(^{13}\text{C}\) is 0.01
  – two next to each other 0.01x0.01 = 0.0001
    (~1 molecule in 10,000)
– Need lots of sample and instrument time to overcome
– In our facility: 80% v/v, overnight, 500 MHz = nothing
2D NMR Spectroscopy
Who is Talking to Who?

INADEQUATE

INADEQUATE 150.9 MHz

1 bond C–C coupling
2D NMR Spectroscopy
Who is Talking to Who?

INADEQUATE

- Cross peaks show up as doublets = $J_{CC}$
- Diagonal is midway between the two doublets

![Diagram of 2D NMR Spectroscopy spectrum with labels and annotations]
2D NMR Spectroscopy

The diagram depicts a 2D NMR spectrum with peaks indicating various chemical shifts. The horizontal axis represents the chemical shifts in ppm, while the vertical axis represents the intensity in Hz. The spectrum shows several distinct peaks corresponding to different chemical groups such as CH, C, CH₂, C, and CH₃, CH₃, CH₂ CH₃.
2D NMR Spectroscopy
2D NMR Spectroscopy

**MASS**

```
<table>
<thead>
<tr>
<th>Mass (m/z)</th>
<th>% of Base Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td></td>
</tr>
<tr>
<td>151</td>
<td></td>
</tr>
<tr>
<td>230</td>
<td></td>
</tr>
<tr>
<td>232</td>
<td></td>
</tr>
</tbody>
</table>
```

**$^{13}$C/DEPT NMR 150.9 MHz**

```
<table>
<thead>
<tr>
<th>ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0</td>
</tr>
<tr>
<td>19.9</td>
</tr>
<tr>
<td>19.8</td>
</tr>
</tbody>
</table>
```
2D NMR Spectroscopy
2D NMR Spectroscopy
2D NMR Spectroscopy

Which Isomer?
2D NMR Spectroscopy
2D NMR Spectroscopy