Approaches to Structure Elucidation

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Successful Structure Elucidation

• **Quick**
  – You cannot spend days on every structure. If it is a common compound you need to be able to ID it quickly.

• **Accurate**
  – The time you spend must be spent well. In order to make the most of your time you have to have a plan.
Best Use of Time

• Do you have your own personal NMR?
  – If not then consider the following:
    • Collect and examine the $^1$H NMR first.
    • If more spectra are needed what should you run?
      – $^{13}$C, COSY, TOCSY, HSQC/HMQC, HMBC, ROESY/NOESY, INADEQUATE, etc.

Do an NMR database search.

In most cases you only need:
- $^1$H
- COSY
- HSQC or HMQC
- HMBC
- ROESY or NOESY
Now You Have NMR Spectra, What Next?

• When it comes to structure elucidation you should remember:
  – Your compound is probably known.
  – If your compound is new it is probably related to a known compound.
  – All compounds are made from the same building blocks.
• The first place to go to identify your compound is not your spectra.
• Find out what has been reported from your organism.
  – Everything makes more sense when it is in context.
That Strange Plant in Your Roommate’s Closet

Tetrahydrocannabinol
Asterosaponin

Steven Pavlov

Your Roommate’s Aquarium
Something Your Roommate Left in the Fridge

Emodin

Paul Cannon
• Can be hard to obtain.
  – Trial and error
  – Borrow spectra from labmates for solved structures
  – Journal reading
    • Supporting Information
Triterpene Spectrum

Chemical Shift (ppm): 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5

Normalized Intensity:
- 0
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8

1 Alkene proton
1 Oxymethine
7 Methyl singlets
You Recognize the Compound Class.

Green Tea
Quick Assignment Based on Compound Class

- Do NMR database search.

- The chemical shift of H-3 (δ_H 5.53) indicates an ester group.
- The signals at δ_H 6.95 and δ_H 6.50 indicate galloyl groups.
- The signals at δ_H 5.96 indicates that the final two protons are equivalent.
- This does not seem to match the structure.
Your Compound Is Known.

- Refer back to the literature to check your assignments.
- Critically examine the assignments in the literature.
- Chemical shifts agree with literature values.
- Literature assignment is correct.
You Still Do Not Know What It Is

• The compound is not obvious.
• Now you must tackle the 2D spectra.
  – Go through the resonances one by one.
  – If you are disorderly you will become confused.
Make a List.

- Use the HSQC or HMQC to make a list of all of the $^1$H/$^{13}$C groups
  - CH$_3$, CH$_2$, CH, and C (if you have a $^{13}$C NMR spectrum).
  - Be careful:
    - Impurities can result in extra signals.
    - CH$_2$ can be tricky, use COSY correlations to help with them.

<table>
<thead>
<tr>
<th>CH$_3$</th>
<th>CH$_2$</th>
<th>C$_H$/shifts!</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.9</td>
<td>1.10 d</td>
<td>29.8</td>
</tr>
<tr>
<td>23.9</td>
<td>1.11 s</td>
<td>41.6</td>
</tr>
<tr>
<td>24.3</td>
<td>1.13 s</td>
<td>75.6</td>
</tr>
<tr>
<td>28.2</td>
<td>0.98 s</td>
<td>(6)</td>
</tr>
<tr>
<td>30.7</td>
<td>2.15 s</td>
<td>118.7</td>
</tr>
<tr>
<td>Acetone $^2$</td>
<td>30.2</td>
<td>2.43 d, 2.56d</td>
</tr>
<tr>
<td></td>
<td>32.2</td>
<td>1.90, 2.49</td>
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</table>
Assign the $^1$H Spin Systems With COSY

- The COSY data can quickly provide you with large fragments.

[Chemical structures and shifts diagram]
• If you get a nice large fragment that looks unique, go ahead and search for it.
  – 113 related structures.
  – Most common is jasplakinolide.
• There are some potential traps with COSY spectra.
  – Long range correlations are possible. Especially around double bonds.
  – Some expected correlations are not seen.
  – Overlap

If $J$ is very small you may not see a correlation.

If your $^1$H NMR contains a lump of overlapping proton signals you should not use those correlations.
Use HMBC to tie everything together

- HMBC can now be used to connect the COSY fragments and other pieces together.
  - HMBC can be confusing due to the presence of both 2 and 3 bond correlations.
    - Start with a group you already know something about.
Combine Fragments that Overlap
Look for a Few Additional Correlations

- From these large fragments only a few additional HMBC correlations are needed to finish the structure.
Check Your Work

• At this point you should have most if not all of the structure assembled.

• If your compound is new, look for similar compounds to compare chemical shifts.
Be Cautious

- Do not jump into the middle of the vast unknown, chip away at the edges.
- A note of caution, for rigid compounds, such as fused aromatic rings, 4 and 5 bond correlations are possible.
- Try not to base your structure on any one single correlation.

Start with Me groups and by trying to expand COSY fragments.
• If you have a chiral compound you should use ROESY or NOESY to assign the relative configuration.
  – This is not always straightforward. Use modeling software to minimize energies and verify interatomic distances.
  – ROESY and NOESY is also very helpful in assigning methoxy groups.
• Be careful avoid COSY correlations that are often present in ROESY and NOESY spectra.
  – They are usually out of phase, but over processing can obscure that.
Check Your Work

• Is your relative configuration reasonable compared to known compounds?
  – Differences must be supported.
Do You Have a New Compound?

• If your compound is new:
  – Compare shifts to similar compounds.
  – Check shifts with NMR prediction software.
    • $^{13}$C NMR shifts are usually best for this, as they are less influenced by solvent, concentration, temperature, etc.
Is Your Compound “Novel”

• If you are proposing an unprecedented structure, consider:
  – Is your structure chemically stable?
  – Is your structure biosynthetically possible?
• If not, expect to be challenged.

Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation
K. C. Nicolaou* and Scott A. Snyder

• After you have completed your assignment:
  – Ask one of your fellow group members to check your work.
    • It would be best if they did this without looking at your assignment to avoid bias.
Summary

- Reduce time spent on common known compounds.
- Quickly ID minor analogues of known compounds.
- Ease into complex spectra.
- Watch out for traps.
- Evaluate, evaluate, evaluate.