Chemistry 843 "Advanced NMR Spectroscopy" © Gerd Gemmecker, 1999

This course will cover the theory required to understand and successfully implement the methods of state-of-the-art NMR spectroscopy, with the stress laid on structure elucidation by multidimensional (essentially 2D) NMR techniques.

What will be covered?

⇒ Introduction to the principles of NMR (including build-up of an NMR spectrometer, general features of Fourier transform, relaxation, folding, sensitivity etc.)
⇒ theory required for the understanding of important experiments (Cartesian product operators)
⇒ a selection of the most widely-used 2D NMR techniques
⇒ interpretation of these spectra

and what not?

⇒ quantum mechanical treatment of NMR (although some equations will occur!!!)
⇒ solid state NMR
⇒ working with NMR data bases
⇒ empirical correlations for chemical shifts (increment systems)

What is required?

⇒ knowledge of 1D NMR, J coupling patterns, chemical shift etc., e.g., Chemistry 605 or 626
⇒ regular (!) attention of the course, since most "individual sections" require an understanding of the previous ones.
⇒ "re-reading" (and "re-thinking"!) of the material on a regular basis, and working out your own solutions to the problems given in the course – to make sure that you have really grasped the concepts and developed a working knowledge!

Credits / Grades:

For credit, a report is required on an aspect of this course relevant to one's own research, or a research proposal.
Some literature recommendations

Monographs

  (physics, very gut & very difficult to understand, the "old testament" of NMR)

  (physical chemistry, very exact & very difficult, the "new testament")

  (the original article about product operators, but very readable! – if you skip some paragraphs)

  (easily readable introduction to basic concepts, no modern techniques)

  (stress on biomolecular NMR, incl. proteins & nucleic acids, but also including a compact, yet concise introduction, nice book, reasonably priced)

  (good review on all 2D techniques, incl. product operator explanation, still up to date)

  (mixture of introductory and application chapters, on heteronuclear spectroscopy etc., expensive)

  (good on principle and features of FT, otherwise outdated)
  (introduction into principles and applications of 2D NMR, not much 2D theory)

  (no product operator description, but very good description of applications for 2D techniques, incl. example spectra).

  (Lots of theory, quantum-mechanics & product operators, FT, relaxation measurements, despite title large section on 2D methods)

Journals

  (technical & theoretical developments, also solid state & imaging)

  (applications and data on compounds; review-like papers on practical aspects of NMR techniques, processing etc.)

- J. Biomol. NMR
  (methods development & biomolecular applications)
"First Exam"

1. What do the following acronyms stand for?
   - NMR
   - FT
   - COSY
   - NOE

2. Please make a sketch of the $^1\text{H}$ 1D spectrum of diethyl ether:

   ![Spectrum Sketch]

3. What's the size of the H1-H2 and the H2-H3 $^3$J couplings?

4. What do you expect to learn in this course?

5. Do you have any specific subjects that you would like to be treated here?
Applications of NMR

in synthesis
for checking the results in a fast and efficient way, concern. connectivity purity.

determination of solution structure
with similar accuracy as x-ray analysis, allowing to detect differences between crystall and solution structure, as well as influence of solvent.
currently limited to ca. 10 kDa without isotopic labeling, ca. 30-40 kDa with isotope $^{13}$C, $^{15}$N (and $^2$H) labeling (proteins & nucleic acids).

investigating intermolecular interactions
mostly for biologically active compounds, e.g.,

- enzyme - inhibitor
- DNA - intercalator or repressor
- receptor - hormon oder substrate
- antibody - antigen

important, since all biological functions are based on intermolecular interactions, quite often in a very complex way (complexes higher than binary)

molecular dynamics
from relaxation measurements, the dynamic behaviour of molecules can be derived on various time scales – important for understanding chemical & biochemical reactivity, protein folding etc.

General course of an NMR study
from simple to increasingly complex models, e.g.,
1. selecting the nucleus to be studied (mostly $^1$H or $^{13}$C), often limited by the availability of larger amounts of the substanceand solubility (isotopic labeling).
2. optimizing measurement conditions (temperature, solvent, etc. - often skipped in routine NMR for organic synthesis)
3. assigning the resonances to the individual atom positions; for less complex molecules this can be done from 1D spectra considering the following parameters:
a) "signal intensities" (integrals!) proportional to number of nuclei
b) characteristic chemical shifts
c) $J$ coupling patterns (to find neighbouring positions connected by bonds)
d) line widths (dependent on local flexibility, chemical exchange, proximity to quadrupolar nuclei or paramagnetic species)

A complete assignment is a reliable proof for the postulated connectivity / formula;

4. after that, conformationally sensitive parameters can be used to derive information about the 3D arrangement, mostly $J$ couplings and NOE effects.
5. additional experiments for measuring relaxation and exchange rates give additional information on dynamic aspects.

<table>
<thead>
<tr>
<th><strong>Structural theory</strong></th>
<th><strong>NMR equivalent</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>alchemy</td>
<td>qualitative composition</td>
</tr>
<tr>
<td>Liebig</td>
<td>quantitative composition</td>
</tr>
<tr>
<td>Gerhard &amp; Laurent</td>
<td>functional groups</td>
</tr>
<tr>
<td>Kekulé &amp; Couper</td>
<td>connectivity</td>
</tr>
<tr>
<td>Van't Hoff &amp; Barton</td>
<td>spacial arrangement of atoms</td>
</tr>
<tr>
<td>Karplus</td>
<td>dynamics</td>
</tr>
</tbody>
</table>