Understanding Temperature Dependent Hydrogen Bonding in Solids from Chemical shifts: Experimental and Periodic DFT Approaches

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Outline of the presentation

- Solid State Nuclear Magnetic Resonance (SS NMR) Spectroscopy as a valuable probe of local molecular structure, in particular because of its ability to accurately identify close proximities between specific nuclei.

- Density Functional Theory (DFT) as an approach to interacting many-body problem: The advantage of CASTEP - a DFT approach is that, it uses a periodic calculation.

- Worked examples of small organic crystalline molecules to explain effect of temperature on hydrogen-bonded systems

Aim of the project

- Application of SS NMR and CASTEP to study the temperature dependent hydrogen bonding in organic molecular crystals.

CAmbridge Serial Total Energy Package (CASTEP)
Solid-State Nuclear Magnetic Resonance Spectroscopy

Impact of Structural Order on NMR Spectrum

• lack of motion and modulation of dipole-dipole interaction
  • mutual spin flips occurring between pairs of spins
    ➢ Each nucleus is “fixed” in the crystal lattice

➢ Each nucleus produces a rotating magnetic field as it precesses in the applied magnetic field → lifetime of spin state is reduced
➢ Each spin has a static field component that influences frequency of neighbors
  - Spin directions vary randomly
  - Range of frequencies that add to line-width
    ➢ Chemical shift anisotropy

- Chemical shift varies with orientation relative to $B_0$
- Contributes to line broadening
SS NMR can be used to obtain internuclear distances
Peak width can monitor motion within the crystal lattice

www.bionmr-c1.unl.edu/921/Lectures/chapter-11-solid-state-NMR
Proton Chemical Shifts from Magic Angle Spinning SS NMR

- Broad lines become narrower.
- Increasing the resolution for better identification and analysis of the spectrum.
- Nuclear interactions are averaged by MAS.
Density Functional Theory (DFT)

Why DFT?
Fast computation

CAMbridge Serial Total Energy Package (CASTEP)
- Periodic DFT code using plane waves
- Computes chemical shifts (CS) in solids
CASTEP is a software package which uses density functional theory to provide a good atomic-level description of all manner of materials and molecules.

A method to describe the exchange correlation interactions within density functional theory then has to be chosen, and we chose Perdew-Burke-Erznehof (PBE).
H Chemical Shift Calculations

Advantage of CASTEP:
uses a periodic calculation all around the crystal
- Gaussian uses only a single molecule

Courtesy: Chris Pickard, S. Ashbrook (St. Andrews, Scotland)
* Clark, S. J. et al. Z. Kristallogr. 2005, 220, 567
Motivation
Hydrogen bonding and its effects

Many organic acids can form dimers due to hydrogen bonding.

Certain organic molecules can also form an intra-molecular hydrogen bond.

The structures of proteins (folding), substances essential to life, are stabilized partly by hydrogen bonding.

Comparison
Calculated and Experimental $^1$H Chemical Shifts

Discrepancy between calculated & experimental Chemical Shifts (CS) for H-bonded proton observed!
Comparison
optimized & non-optimized structures

Good agreement between experimental and calculated CS for geometry optimized ibuprofen structure
Methodology
Variable temperature NMR experiments

NMR chemical shielding computation using CASTEP (0 K)

Conversion of chemical shielding into chemical shifts

Comparison between the experimental and calculated $^1$H chemical shifts with respect to temperature
Case studies

Case Studies on Ibuprofen, Flurbiprofen, Indomethacin, and Paracetamol will be discussed in this presentation.

An example: Acetic acid (dimer)
Ibuprofen

Source: Cambridge Structural Database
Reference code: IBPRAC
Experimental details: X-Ray Diffraction
@ Temperature = 283 – 303 K

Experiments at various temperatures
Experimental chemical shifts are extrapolated to 0 K

Molecular Formula $\text{C}_{13}\text{H}_{18}\text{O}_2$
Melting Point 76 °C

$^1\text{H}$ Spectrum of ibuprofen
(NMR 700 MHz, at 270 K, under MAS at 33 kHz)

The proton NMR chemical shift for hydrogen-bonded proton tends to go upfield (lower ppm) with increase in temperature.

This change is more noticeable than that for the other hydrogens.
Comparison: Experimental (extrapolated to 0 K) & Calculated (0 K) $^1$H CS

The geometry optimized structure shows better agreement between expt. (extrapolated 0 K) CS and cal. CS (using CASTEP)

Fig. 1 | Before the partial geometry optimization

Fig. 2 | After partial geometry optimization
Comparison: Calculated and Experimental $^1$H CS for Iburprofen

Root-mean square deviation (RMSD) at 0 K is better than RMSD at high temperature.
Flurbiprofen

Source: Cambridge Structural Database
Reference Code: FLUBIP
Experimental details: X-Ray Diffraction
@ Temperature = 283 – 303 K

Molecular Formula $C_{15}H_{13}FO_2$
Melting Point 117 °C

$^1H$ Spectrum of flurbiprofen
(NMR 700 MHz, at 270 K, under MAS at 33 kHz)
The proton NMR chemical shift for hydrogen-bonded proton tends to go upfield (lower ppm) with increase in temperature.
Comparison: Calculated and Experimental $^1$H CS for Flurbiprofen

calculated and experimental CS show better agreement at 0 K

RMSD at 0 K is better than RMSD at high temperature.
Indomethacin

Source: Cambridge Structural Database
Reference code: INDMET
Experimental details: X-Ray Diffraction
@ Temperature = 283-303

Molecular Formula C_{19}H_{16}ClNO_{4}
Melting Point 155-161 °C
Experimental $^1$H CS for Indomethacin

Variation in cooling systems during experiments

Variation in $^1$H CS is only because of temperature effect
Comparison: Calculated and Experimental $^1$H CS for Indomethacin

Calculated and experimental CS show better agreement at 0 K
Paracetamol

Source: Cambridge Structural Database
Reference Code: HXACAN
Experimental details: Neutron diffraction
@ Temperature = 20, 80, 100, 150, 200, 250, and 330 K

Molecular Formula $\text{C}_8\text{H}_9\text{NO}_2$
Melting Point $169 \, ^\circ\text{C}$

$^1\text{H}$ Spectrum of paracetamol
(NMR 900 MHz, at 247 K, under MAS at 60 kHz)

Chick Wilson Z. Kristallogr. 2000, 215, 693
The close contact shown for the H-bonded atoms in paracetamol structures at two different temperatures (blue: 20 K; red: 330 K) studied under neutron radiations.

Prominent change in (hydrogen bond) structures is observed with respect to change in temperature.
Paracetamol: Neutron structures obtained at various temperatures

- Chemical shifts of hydrogen bonding protons decrease as temperature increases.
- H-bond strength decreasing ......... ?
Relationship among bond distances, temperature, and calculated $^1$H chemical shifts

**OH...O**

- Proton chemical shift vs. OH...O distance
- Temperature vs. OH...O distance

**NH...O**

- Proton chemical shift vs. NH...O distance
- Temperature vs. NH...O distance
Conclusion

- Experimental $^1$H chemical shifts vary with temperature
- Larger variation, $^1$H chemical shifts for H-bond
- Relationship among temperature, bond distance and $^1$H chemical shifts
- SS NMR experiments at variable temperatures accounts for the vibrational, thermal motions of protons. This is NOT reproduced in CASTEP calculations; but when the experimental chemical shifts are extrapolated to 0 K, we get good agreement between the calculated and experimental CS
- a combined use of experimental and DFT calculation approach produces a far more reliable indicator of hydrogen bonding and the $^1$H-chemical shifts than either alone

Development of an application of CASTEP to study the temperature dependence of $^1$H chemical shifts
Conclusion

- The temperature dependence of hydrogen bonding is an important factor that explains the evolution of $^1$H chemical shifts

- SS NMR and CASTEP
  - an interdisciplinary approach
  - a great promise to turn CASTEP into a more accessible tool for organic / structural chemistry and crystal engineering

Validation of neutron / XRD structures of crystalline organic (small) Molecules.
(For SS NMR is in many ways complementary to X-Ray diffraction studies of solids - It does not require the use of single crystals.)
References


This work in literature

- EU Master thesis, Bibliotheque, Ecole normale superieure de Lyon, France
  http://www.academia.edu/33623369/Understanding_Temperature_Dependent_Hydrogen_Bonding_in_Solids_from_NMR_Chemical_Shifts_Experimental_and_Periodic_DFT_Approaches
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Education and Culture