Essential Techniques in Solid-state NMR

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Solid-state NMR

1945

Felix Bloch

Ed Purcell

proton NMR of paraffin wax

2005

nitrogen-15 NMR of VPU ion channel from HIV

structure from solid-state NMR
“We were physicists. We knew all the answers; we just didn’t know what the questions were.”
**Problems with NMR of solids**

**Poor Resolution**

* Anisotropic nuclear spin interactions result in powder patterns.
* Powder patterns from inequivalent sites overlap.
* Multiple anisotropic interactions result in broad featureless lineshapes.

**Low Sensitivity**

* NMR is inherently insensitive.
* Many useful nuclei, such as carbon-13, nitrogen-15 etc, have low natural abundance.
* Inefficient spin-lattice relaxation results in long experiment times.
Improving resolution

All internal Hamiltonians can be written as a product of two parts

* A **spatial part** which contains the variation of the interaction with orientation with respect to the $B_0$-field.

* A **spin part** which (in the secular approximation) contains angular momentum operators which are parallel to the $B_0$-field.

For example, the anisotropic part of the chemical shift Hamiltonian

$$H = \frac{1}{3} \left\{ \sum_{j=1}^{3} \sigma_j + \sum_{j=1}^{3} \left( 3 \cos^2 \theta_j - 1 \right) \sigma_j \right\} \gamma l_z B_0$$

contains a **spatial** term proportional to $3 \cos^2 \theta - 1$ and a **spin** term proportional to $l_z$. 
Motional averaging

Molecular motions can result in a **averaged** Hamiltonian which can be evaluated from the average over time for one spin or over orientation for many spins.

\[
\bar{H}_{\text{int}} = \frac{1}{\tau} \int_{0}^{\tau} H_{\text{int}}(\theta(t)) dt
\]

\[
\bar{H}_{\text{int}} = \int_{0}^{\pi} H_{\text{int}}(\theta) \sin \theta d\theta
\]

The techniques used to improve resolution in solid-state NMR subject the nuclear spins to some external motion in order to average interactions.

- **carbon-13 NMR of fullerene**
  - low temperature
  - room temperature
  - \(C_{60}\) tumbles isotropically
Two types of motions can be used:

* **Motions in sample space.** These require a mechanical rotation of the sample itself. This changes the spatial part of the Hamiltonian. An example is magic angle spinning.

* **Motions in spin space.** These require rotations of the magnetization by radiofrequency pulses. This changes the spin part of the Hamiltonian. An example is decoupling.

Note that in either case motional averaging is only effective when the motional frequency is greater than the broadening observed in the spectrum.
Magic angle spinning simulates the rapid isotropic tumbling motion of a molecule in solution by rotation of the sample at a frequency $v_R$ (up to 70 kHz) around an axis inclined at $\beta_R$ to the $B_0$-field.

* $\beta_R$ is a constant which can be varied mechanically.

* The axis $z_{\text{PAS}}$ moves on the surface of a cone with a half angle $\beta$ at the apex.

* In a powder all values of the angles $\beta$ and $\theta$ are present.

The motionally averaged Hamiltonian is

$$\overline{H} \propto \int_0^\pi \left(3\cos^2 \theta - 1\right) \sin \theta d\theta = \frac{1}{2} \left(3\cos^2 \beta_R - 1\right) \left(3\cos^2 \beta - 1\right)$$
Scaling anisotropic interactions with MAS

\[ H \propto \int_{0}^{\pi} \left( 3 \cos^2 \theta - 1 \right) \sin \theta \, d\theta = \frac{1}{2} \left( 3 \cos^2 \beta_R - 1 \right) \left( 3 \cos^2 \beta - 1 \right) \]

The term in $\beta_R$ acts as a constant scaling factor on the powder pattern.

* If $\beta_R = 0$ there is no effect on the spectrum.
* If $\beta_R = 90^\circ$ the width of the powder pattern is scaled by a factor $1/2$ and reversed in sign.
* When $\beta_R = 54.7^\circ$ (known as the “magic angle”) the term in $\beta$ is zero and MAS will scale the anisotropic part of the interaction to zero.
Magic angle spinning

Fast spinning limit

When $\nu_R \gg \zeta$

* the **anisotropic** part of the chemical shift is averaged to zero.

* the **isotropic** part is retained.

$$H = \frac{1}{3} \left[ \sum_{j=1}^{3} \sigma_j + \sum_{j=1}^{3} \left( 3 \cos^2 \theta_j - 1 \right) \sigma_j \right] \gamma_i B_0$$

**carbon-13 NMR of tyrosine**

with MAS
Slow spinning

When $\nu_R \ll \zeta$ the NMR precession frequency is modulated by the MAS

$$\nu(t; \Omega) = \sum_{m=-2}^{2} \nu^{(m)}(\Omega) \exp(i m \nu_R t)$$

As a consequence:

* contributions from different orientations refocus after $\tau_R$, resulting in “rotor echoes”.
* rotational sidebands separated by $\nu_R$ appear in the spectrum.
* sampling at the rotor echoes results in a spectrum of isotropic lines of restricted spectral width.
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Spinning sidebands

**Measuring shift tensor parameters**

* The envelope of the sideband intensities depends on the anisotropy $\zeta$ and the asymmetry $\eta$.

* This is the basis of the most common method for measuring these parameters.

**Identifying the isotropic line**

* The isotropic line corresponds to the chemical shift observed in solution.

* Note that the isotropic line is not always the most intense in the spectrum.

* It can be identified as the sideband which does not change frequency when the MAS rate changes.

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Choosing the MAS rate

Measuring shift tensor parameters

* To produce a solution-like spectrum with only isotropic lines the MAS rate must be greater than the largest shift anisotropy.

* To measure the shift anisotropy from the sideband pattern with optimal precision approximately 7 sidebands are required.

* To measure the asymmetry more than 10 sidebands are required.

Other considerations

* Molecular motions in the sample on a kHz timescale will interfere with the MAS averaging and cause sidebands to broaden.

* For abundant nuclei “rotational resonance conditions” where $\Delta \delta_{iso} = n \nu_R$ (n is a small integer) should be avoided.

Simulated MAS sideband patterns

Choosing the MAS rate

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TOSS (Total Suppression of Spinning Sidebands) uses a sequence of (five) carefully timed $\pi$ pulses synchronized with the MAS rotor.

- The phases of the sidebands depend in a new way on orientation.
- For an isotropic sample the sidebands from different orientations interfere destructively and cancel.

Note:

- The TOSS centreband is not quantitative.
- For small $\nu_R/\zeta$ the centreband can have negative intensity.

MAS and homonuclear dipolar couplings

There are two parts to the homonuclear dipolar Hamiltonian:

* an **inhomogeneous** part which shifts the energies of the Zeeman eigenstates

* a **homogeneous** part which mixes degenerate Zeeman states and causes line broadening

The homogeneous term also causes energy conserving “flip-flop” transitions between degenerate states at a rate which depends on the dipolar coupling.

\[ H_D \propto 3I_1 z I_2 z - I_1 \cdot I_2 = 2I_1 z I_2 z - \frac{1}{2} (I_1^+ I_2^- + I_1^- I_2^+) \]

![Diagram of energy levels and transitions](image)
The flip-flop transitions mean that the state of the spin system fluctuates and when $\nu_R/d$ is small this interferes with the MAS averaging.

The spinning sidebands for a homogeneously broadened line behave very differently from those associated with an inhomogeneous interaction.

An isolated proton-carbon-13 dipolar interaction is inhomogeneous, but if the proton is part of a homogeneous network then the overall behavior is homogeneous.
Decoupling uses an enforced motion in spin space to average heteronuclear dipolar couplings.

\[
H_D = -\frac{d}{2} \left( 3 \cos^2 \theta - 1 \right) 2 I_z S_z
\]

The spin part of the coupling Hamiltonian can be made to vary with time by continuous irradiation at the I-spin (proton) Larmor frequency while the S-spin (carbon-13) signal is observed.
Decoupling

* The radio-frequency radiation at the proton Larmor frequency causes the proton magnetization to precess at a rate in the yz-plane.
* In a rotating frame which follows the precessing magnetization the I-spin operator appears to rotate, and the spin part of the dipolar Hamiltonian becomes

\[
H_D(t) \propto \left( I_z \cos 2\pi \nu_1 t + I_y \sin 2\pi \nu_1 t \right) S_z
\]
* The oscillating I-spin operator terms cause the dipolar Hamiltonian to average to zero.
Setting the decoupler power

**Hardware considerations**

* To be effective the $B_1$ field must cause the spins to precess at a rate $\nu_1$ which is large compared to the IS dipolar coupling (about 20 kHz for $^{1}H$-$^{13}C$).

* When the I spins are homogeneous the rate must be comparable to the I spin homonuclear dipolar coupling (about 60 kHz for $^{1}H$).

* The amplitude of the decoupler $B_1$ field is limited by the probe (60 kHz for 7.5 mm MAS probe; 140 kHz for 3.2 mm MAS probe). Note: an I-spin $\pi/2$ pulse of 2.5 $\mu$s corresponds to $B_1 = 100$ kHz.

**Sample considerations**

* Large $B_1$ will cause sample heating.

* Molecular motions in the sample on a kHz timescale will interfere with the decoupling and cause lines to broaden.

* At high MAS rates the averaging by MAS interferes with the averaging by decoupling and the decoupling efficiency can fall.
A number of decoupling schemes have been proposed which give increased decoupling efficiency relative to CW for the same $B_1$ amplitude, especially at high $\nu_R$. These include **TPPM** (Two Pulse Phase Modulation) and **XiX**.

\[
\begin{array}{c|c|c}
\text{phase:} & 0^\circ & 180^\circ \\
\hline
\text{TPPM} & \phi & \phi + \sim 10^\circ \\
\end{array}
\]

\[
\begin{array}{c}
\text{XiX} \\
\end{array}
\]

Problems with NMR of solids

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**Low Sensitivity**

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* Many useful nuclei, such as carbon-13, nitrogen-15 etc, have low natural abundance.
* Inefficient spin-lattice relaxation results in long experiment times.
Improving sensitivity

**Sensitivity** can be improved by:

* increasing magnetization by polarization transfer from neighboring spins of higher magnetogyric ratio.
* increasing the repetition rate of successive scans, so that more signal averaging can take place, by polarization transfer from neighboring spins with more efficient spin-lattice relaxation.
Cross polarization

- Polarize the I spins at high field \((B_0 = \text{MHz})\).
- Cool the I spins to a low “spin temperature” in the rotating frame \((B_1 = \text{kHz})\).
Establish IS contact via the heteronuclear dipolar coupling and the Hartmann-Hahn match.

Allow S spins to heat I spins and vice versa, resulting in a growth of an enhanced S-spin magnetization along $B_1$.

\[
\gamma_H B_1(^1H) > \gamma_C B_1(^{13}C)
\]

Hartmann-Hahn match
Choosing CP parameters

**Experimental parameters**

* The I and S $B_1$ field are matched by observing maximum signal intensity for a suitable sample e.g. adamantane or hexamethylbenzene for carbon-13, kaolinite for silicon-29, glycine for nitrogen-15 etc.

* Choose the contact time which gives the highest overall intensity, since different chemical sites have different $T_{IS}$ and different I-spin $T_{1p}$.

**Sample considerations**

* Quarternary carbon sites require long contact times.

* Mobile systems can have short I-spin $T_{1p}$.

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The combination of cross polarization, MAS and heteronuclear decoupling is now the routine experimental method for recording high resolution NMR spectra of spin-1/2 nuclei.
Cross polarization and rapid MAS

MAS averages the heteronuclear dipolar coupling.

* When $\nu_R$ is rapid compared to $d_{IS}$ the Hartmann-Hahn matching condition splits into a set of spinning sidebands.

* The central matching condition has a slower $T_{IS}$ than the sideband matches.

\[
\gamma_f B_{1}(^{1}H) - \gamma_s B_{1}(^{13}C) \quad 2\pi \nu_R
\]

![Graph showing contact time vs Carbon-13 signal intensity for adamantane with and without MAS at 5 kHz.](image)
This problem can be overcome by ramping the amplitude of the cross polarization $B_1$ field.

For optimal signal:

- the ramp size should be approximately twice $\nu_R$
- the step size should be as small as possible

\[
\frac{\gamma_1 B_1(1^H) - \gamma_S B_1(13^C)}{2\pi \nu_R}
\]

Anisotropic nuclear spin interactions cause loss of resolution in NMR spectra of solids. **Magic angle spinning** can be used to average inhomogeneously broadened interactions, such as the chemical shift anisotropy. MAS uses a mechanical rotation in sample space to average the interaction.

For homogeneous interactions, averaging is best achieved by rotations in spin space using radiofrequency pulses. For example, to remove the heteronuclear dipolar interaction between carbon-13 and a proton which is itself part of a dipolar-coupled network **heteronuclear decoupling** is required.

Solid-state NMR spectroscopy is insensitive because of long spin-lattice relaxation times. **Cross polarization** can be used to enhance sensitivity by transferring polarization from neighboring spins with higher magnetogyreric ratio and more efficient spin-lattice relaxation.