

NUCLEAR MAGNETIC RESONANCE AND THEORETICAL
STUDIES IN STEREOCHEMISTRY

by

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Nuclear Magnetic Resonance and Theoretical Studies in Stereochemistry

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Nuclear magnetic resonance (NMR) has become one of the most widely used techniques to provide structural information in analytical chemistry, physical chemistry and biochemistry. In NMR, individual nuclei in a molecule can be recognized by their chemical shifts, through-bond J couplings and through-space distances. Molecular structures and NMR properties of the molecules in interest can also be studied by theoretical quantum chemical computations.

Ab initio and DFT calculations have been performed on a variety of amino acid and peptide hydrohalides. When generating the environment for the halide ion coordination, a simplified model is employed, using ammonium ions to replace $-\text{NH}_3^+$ and water to replace $-\text{OH}$ groups. From the calculations of electric field gradient on halide ion site, the QCC and η are obtained and compared with the available experimental results of halogen NMR.

Based on an approach analogous to COSY-based experiments in liquid-state NMR with coherences transferred via the weak scalar-coupling Hamiltonian, solid state double-quantum

filtered correlation spectroscopy (DQF-COSY) was performed to study the ^{13}C -enriched thymidine. The results have shown the DQF-COSY method can also be applied to solid state with success.

The effect of pseudorotation on carbon chemical shifts in tetrahydrofuran (THF) and 2,5-dimethyltetrahydrofuran (DMTHF) has been studied by theoretical quantum chemical calculations. Stable conformers along the pseudorotation pathway for THF and DMTHF were located using *ab initio* and DFT method under different basis sets. And the geometry and the chemical shift dependence on the pseudorotation angle for both molecules were analyzed.

Hexamethylenetriperoxide diamine (HMTD), triacetone triperoxide (TATP) and diacetone diperoxide (DADP) are among the cyclic peroxide explosives most favored by terrorists. With solution NMR experiments in conjunction with a high level DFT calculations, two different conformers of the symmetry D_3 and C_2 were found to be coexist in solution for HMTD and TATP, their equilibrium constant was also determined. The studies showed the power of modern computational methods in predicting important physical parameters about these dangerous materials.

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PREVIEW

Chapter 1

Overview and General Theory

Summary

Nuclear magnetic resonance (NMR) was first described and measured in molecular beams by Isidor Rabi in 1938.^[1] In 1946, the technique was implemented independently by Felix Bloch and Edward Mills Purcell^[2-4] on liquids and solids. They shared the Nobel Prize in Physics in 1952 for their work. After almost 60 years of development, NMR has become one of the most widely used techniques to provide structural information in analytical chemistry, physical chemistry and biochemistry. In the liquid state, individual nuclei in a molecule can be recognized by their chemical shift, through-bond J couplings and through-space distances. Multi-dimensional NMR experiments have been further developed into powerful tools for studying biomolecules in solution, particularly for the structure determination of proteins and nucleic acids. In many cases, however, the most appropriate physical state to study molecular structure and dynamics is

the solid. The first part of this chapter serves as a brief overview of the different solid-state NMR methods available in such cases. The second part of this chapter will briefly introduce *ab initio* and density functional quantum chemistry methods that were employed in this thesis to calculate the molecular structures and NMR properties of relevant molecules. The last part of this chapter briefly summarizes the remaining chapters in this thesis.

PREVIEW

1.1 Introduction of Solid State NMR

It is important, first of all, to understand how NMR samples in the solid state are different from those in the liquid state. Rapid molecular motions in the liquid state average out all the anisotropic interactions, and as a result NMR spectra have narrow line-widths, in many cases less than 1 Hz. Conversely, in the solid state, anisotropic interactions, including the chemical shift anisotropy (CSA), the dipolar coupling and the quadrupolar coupling, lead to substantial broadening of the resonances.^[5,6] These anisotropic interactions, on one hand, decrease the resolution of distinct sites and complicate the spectrum, but, on the other hand, they also contain abundant and valuable structural and dynamic information. Both the CSA and quadrupolar interactions provide insight into electronic structures and bonding environment, while the dipolar coupling offers direct access to internuclear distances. Moreover, all three anisotropic interactions are useful probes of dynamics. A number of approaches have been developed to study these anisotropic interactions and enhance the resolution.

We can first distinguish between spin half nuclei and quadrupolar nuclei. Nuclei with spin number $I > 1/2$ possess a quadrupole moment, and the corresponding spectra are dominated by the interaction between the quadrupole moment and the electric field gradient at the nucleus. Nuclei can be further classified according to their natural abundance: nuclei with over 99% natural abundance, e.g., ^1H , ^{19}F , and ^{31}P , are referred to as abundant, while nuclei with low natural abundances, e.g. ^2H , ^{13}C , and ^{15}N , are called dilute spins. For dilute nuclei, site selectivity can be achieved by selective isotopic labeling.

In an NMR experiment, the sensitivity is affected by the natural abundance; the gyromagnetic ratio γ , which determines the Larmor frequency of the nucleus at a particular magnetic field; and of course the strength of the field itself. Of all the naturally occurring nuclei, the proton ^1H has the best sensitivity. Though high natural abundance of protons means proton NMR in liquid state has great sensitivity, it severely complicates the solid-state spectra. The strongly dipolar-coupled proton networks in organic solids lead to static line broadenings of the order of 50 kHz, and, as a result, most attention in solid state NMR has rather focused on dilute spin-1/2 nuclei, e.g., ^{13}C and ^{15}N .

In solid-state NMR, the resonance frequency of a given nucleus within a particular crystallite depends on the orientation of the crystallite. The orientation dependence of the CSA, dipolar, and first-order quadrupolar interactions (the first order perturbation method truncates the quadrupole coupling Hamiltonian matrix at the diagonal terms) can all be represented by second-rank tensors. For such a second-rank tensor, there exists a principal axis system (PAS) in which only the diagonal elements of the matrix are non-zero. In the case of the chemical shift interaction, the chemically shifted Larmor frequency is given by

$$\omega_{CS} = \omega_0 \left(\sigma_{xx}^{PAS} \cos^2 \phi \sin^2 \theta + \sigma_{yy}^{PAS} \sin^2 \phi \sin^2 \theta + \sigma_{zz}^{PAS} \cos^2 \theta \right) \quad (1.1)$$

where ω_0 is the Larmor frequency, σ_{xx}^{PAS} , σ_{yy}^{PAS} and σ_{zz}^{PAS} are the three principal values in the PAS, and ϕ and θ are Euler angles that define a rotation from the PAS onto the laboratory frame defined by B_0 . The chemical shift is more commonly expressed as a sum of an isotropic and an anisotropic part. The isotropic chemical shift is given by

$$\sigma_{iso} = \frac{1}{3}(\sigma_{xx}^{PAS} + \sigma_{yy}^{PAS} + \sigma_{zz}^{PAS}) \quad (1.2)$$

while the anisotropic frequency is

$$\omega_{aniso} = \frac{\delta}{2}(3\cos^2\theta - 1 - \eta\sin^2\theta\cos 2\phi) \quad (1.3)$$

where δ and η describe the anisotropy and the asymmetry of the interaction, respectively.

Since the orientation dependence of the CSA, dipolar and first-order quadrupolar interactions can all be represented as second-rank tensors, Equation 1.3 can be considered as a general expression that applies to all three interactions. For the dipolar coupling between a pair of spins, the three principal values are $-D/2$, $-D/2$ and D . The interaction is axially symmetric and the tensor is traceless. Thus both the isotropic part and η are zero. D is the dipolar coupling constant:

$$D = \frac{\mu_0 \hbar \gamma_I \gamma_S}{4\pi r^3} \quad (1.4)$$

where r stands for the internuclear distance and γ is the gyromagnetic ratio.

For the first-order quadrupolar interaction,

$$\delta = \frac{3\pi C_Q}{2I(2I-1)} \quad (1.5)$$

where the quadrupolar coupling constant, C_Q is given by

$$C_Q = \frac{e^2 q Q}{h} \quad (1.6)$$

eq corresponds to the electric field gradient at the nucleus and eQ is the nuclear quadrupole moment.

Since the components of the second rank tensor for a given anisotropic interaction contain valuable chemical information about the electronic environment, several methods have been developed to determine these parameters in the solid state NMR. These approaches include single-crystal NMR, powder pattern analysis and magic-angle spinning NMR.

In a single-crystal NMR study, the most general method for determining the elements of this second rank tensor is by conducting three rotations of the crystal, normal to the field, about three mutually orthogonal axes. Each rotation provides two diagonal and one off-diagonal element and three rotations thus give, with some redundancy, all of the elements of the tensor. Recently, a more efficient approach, “Orientation of Single Crystals Using Linear Approximations to NMR Transits”(OSCULANT),^[7] uses the internal symmetry of the crystal to obtain the elements of the tensor by one off-axis rotation of a single crystal.

Sometimes, a single crystal of a size of several mm in each dimension is very hard to get, in solid state NMR, it is more usual to deal with a powder sample, in which molecular orientations are uniformly distributed. The NMR spectrum for a powdered sample, therefore, consists of a superposition of many lines, corresponding to all the possible resonance frequencies. Let's take deuterium powder sample as an example (Figure 1.1). The solid-state deuterium NMR spectrum is dominated by Zeeman and quadrupolar interactions. As a spin 1 nucleus, deuterium will have a two-fold degenerate Zeeman eigenstate. This degeneracy will be removed by the quadrupolar interactions and two transitions will be produced symmetrically about the Larmor frequency ν_0 , $\nu_0 + \nu_Q$ and $\nu_0 - \nu_Q$, where ν_Q is given by

$$\nu_Q = \frac{\omega_Q}{2} \left[(3\cos^2 \beta_{LP} - 1) + \eta \sin^2 \beta_{LP} \cos 2\gamma_{LP} \right] \quad (1.7)$$

where β_{LP} and γ_{LP} are the components of Euler angle Ω_{LP} in the Wigner rotation matrix. There will be three singularities in a deuterium powder pattern corresponding to certain unique orientations:

$$\begin{aligned} &\pm\omega_Q \quad \text{at } \beta_{LP} = 0 \\ &\mp \frac{\omega_Q}{2}(1+\eta) \quad \text{at } \beta_{LP} = 90^\circ \text{ and } \gamma_{LP} = 0 \\ &\mp \frac{\omega_Q}{2}(1-\eta) \quad \text{at } \beta_{LP} = 90^\circ \text{ and } \gamma_{LP} = 90^\circ \end{aligned} \quad (1.8)$$

The ^2H quadrupolar coupling is usually of the order of 200 kHz. In order to get excitation evenly across the lineshape and obtain undistorted spectra, a fast digitizer and high level of pulse power is required. This makes it rather difficult to acquire data immediately following the pulse. In practice, a standard quadrupole echo pulse sequence is used to record deuterium spectra from refocused signals.

From Equation 1.3, when the asymmetry parameter $\eta = 0$,

$$\omega_{aniso} = \frac{\delta}{2} (3\cos^2 \theta - 1) \quad (1.9)$$

So the anisotropic frequency will be zero if $(3\cos^2 \theta - 1) = 0$ which condition is achieved at $\theta = 54.7^\circ$. Thus a physical rotation of the whole sample around an axis inclined at an angle of 54.7° (referred to as the magic angle) to B_0 can average all the anisotropic interactions to zero.^[8,9] If the rate of the spinning is not fast enough comparing to the anisotropic interactions, a set of spinning sidebands will be produced. As the rate of the

spinning is increased such that it becomes large as compared to the static linewidth, the signal will be increasingly concentrated in the centreband position (Figure 1.2.). A purely isotropic spectrum without spinning sidebands can be achieved by employing a specially designed pulse sequence to suppress the spinning sidebands. Such methods include PASS^[10], TOSS^[11] and SELTICS^[12]. In principle, it is possible to extract the anisotropy and asymmetry of the CSA by fitting the observed MAS sideband intensities. This is referred to as a Herzfeld-Berger analysis^[13].

For solid-state NMR of a dilute spin 1/2 nucleus, e.g. ^{13}C , MAS is usually combined with the method of cross polarization (CP)^[14]. In this method, the sensitivity is enhanced by transferring polarization from an abundant nucleus with a high gyromagnetic ratio such as ^1H , to the lower-sensitivity nucleus. The combined approach is referred to as CPMAS NMR^[15]. High-power proton decoupling is usually applied during the acquisition to remove line broadenings due to dipolar couplings involving the protons.

For ^{13}C CPMAS NMR, a critical factor is the efficiency of ^1H decoupling. The simplest method, which is called continuous wave (CW) decoupling, involves the application of a continuous radiofrequency pulse of fixed phase for the duration of the acquisition of the FID^[16]. Recently, more sophisticated decoupling methods, such as TPPM^[17] have been introduced and these methods yield narrower ^{13}C linewidths than conventional CW decoupling. In simple terms, the efficiency of ^1H decoupling increases as the radiofrequency field strength increases. Experimentally, care must of course be taken to find the power level that gives the optimum decoupling performance without damaging the probe.

Two-dimensional (2D) NMR spectroscopy plays a very significant role in solid-state NMR. There will be a problem of assigning the spectrum if there are too many resolved ^{13}C peaks in a 1D MAS spectrum. In a homonuclear ^{13}C - ^{13}C 2D correlation experiment, a selection is usually made such that 2D peaks are only observed for pairs of directly-bonded carbons. In this way, it is possible to trace out the connectivity along the backbone of the organic molecule, and thus assign the ^{13}C resonance. As a consequence of the significant sensitivity problems associated with the very low probability of finding a pair of directly bonded ^{13}C nuclei in a sample at natural abundance, these experiments are usually performed on fully or partially ^{13}C enriched samples. DQF-COSY^[18] and INADEQUATE^[19] experiments are both based on the through-bond J coupling. For spin 1/2 nuclei, double quantum coherence (DQC) can only be created for coupled spin pairs and evolves during the t_1 dimension of the experiment. By using the J coupling, the observation of a pair of correlated peaks can only be due to directly-bonded ^{13}C nuclei.

1.2 *Ab initio* and DFT methods

Ab initio calculations (*ab initio* is from the Latin: “from first principles”) are based on the Schrödinger equation. The *ab initio* method solves the Schrödinger equation for a molecule and gives the molecule’s energy and wavefunction, which can be used to calculate the electron distribution. The Schrödinger equation cannot be solved exactly for any molecule with more than one electron. Approximations are instead used; the less approximation involved, the higher the level of the *ab initio* calculation is said to be. Regardless of its level, an *ab initio* calculation is based only on basic quantum mechanics and that’s where “from first principles” comes from.

Hartree Fock Methods

The most common type of *ab initio* calculation is called a Hartree Fock (HF) calculation. The HF method is typically used to solve the time-independent Schrödinger equation for a multi-electron atom or molecule described in the fixed-nuclei approximation by the electronic molecular Hamiltonian. Because of the complexity of the differential equations for any but the smallest systems, (hydrogen atom), the problem is usually impossible to solve analytically, and so the numerical technique of iteration is used. The method makes four major simplifications in order to deal with this task:

(1) The Born-Oppenheimer approximation is assumed. The true wavefunction is actually a function of the coordinates of the nuclei as well as the electrons. Born-Oppenheimer assumes that because the time scales of nuclear and electron motion are so different, the electronic wavefunction can be solved assuming static nuclear positions;