Experimental and Theoretical Studies in Nuclear Magnetic Resonance

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EXPERIMENTAL AND THEORETICAL STUDIES IN

NUCLEAR MAGNETIC RESONANCE

by

John D. Persons

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EXPERIMENTAL AND THEORETICAL STUDIES IN
NUCLEAR MAGNETIC RESONANCE

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Nuclear Magnetic Resonance (NMR) has proven to be an excellent tool to probe the structure of molecules by gaining insight into nuclear interactions. Used in conjunction with theoretical calculations, NMR has the potential to elucidate these nuclear interactions and how they affect structure, bonding and dynamics on a molecular scale. The first two projects presented herein study the peroxide explosive hexamethylene triperoxide diamine (HMTD). In the first project, we use the characteristics of the solid-state NMR lineshape to determine the $^{14}$N quadrupole coupling constant ($C_Q$). The second project uses multi-dimensional solution-state NMR and chiral shift reagents to show that there are two enantiomeric pairs of HMTD conformers. The third project introduces the new two-dimensional NMR technique Slow Turning Reveals Enormous Quadrupole Interactions (STREAQI) to find the nuclear electronic parameters in one experiment, when ordinarily the very large $C_Q$ requires multiple experiments to obtain the entire lineshape. The final project studies the biological analog dimethylthiourea copper (I) chloride, in which the $C_Q$, chemical shift anisotropy ($\Delta \delta$) and isotropic chemical shift ($\delta_i$) are found using various experimental and theoretical methods.
This work is dedicated to:

my fiancé and best friend Monica Kinde,

my family and friends,

you know who you are and what you've done. 😊
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Chapter 1

Overview of Nuclear Magnetic Resonance

Summary

Since its development, Nuclear Magnetic Resonance (NMR) has quickly become one of the most important spectroscopic techniques in the physical sciences. Originally used to probe the chemical nature of small organic molecules in solution, it has been rapidly developed for use in the study of microcrystalline and single crystal solid materials, biological systems including proteins, peptides, and DNA, as well as a variety of other methodologies used to study dynamics and chemical kinetics. This first chapter seeks to demonstrate a general knowledge and underlying theory of NMR as a technique, the nuances of solid-state NMR, NMR probe circuitry and theoretical ab initio and density functional calculations.
1.1 Introduction and Background

The first experiments in what we would call today Nuclear Magnetic Resonance (NMR) were done independently in the mid-1940’s by Bloch and Purcell. These first NMR experiments on protons in water and paraffin built off the work of Rabi and others who laid the theoretical groundwork for NMR. In the time since many developments have been made in NMR. Today, NMR is used to determine structures from small organic molecules to proteins or crystal structures. It can be used to probe the nature of a hydrogen bond, or it can be used to look at dynamics.

Though liquid-state NMR is the most commonly used, solid-state NMR (SSNMR) has become an invaluable tool in many areas where liquid-state experiments do not work.

1.2 The NMR Experiment

Consider a sample (a collection of nuclei) that we place in a large magnetic field. All NMR active nuclei have a spin which comes with an associated angular momentum which depends on the spin ($I = \frac{1}{2}, 1, 3/2, 5/2$ and so on). The square of the total spin angular momentum ($I^2$) is given as:

$$I^2 = I(I + 1)$$ (1.1)

There are no known NMR active nuclei that have $I = 2$. This collection of spins is oriented randomly until they are placed in a large magnetic field ($B_0$), in which they
precess about the magnetic field at a frequency called the Larmor frequency \( (\nu_L) \) due to their angular momentum (Figure 1.1). The field also breaks the degeneracy of the energy levels of the spin-angular momentum, splitting into \((2I + 1)\) energy levels. For example, a spin ½ nucleus will have 2 energy levels \((\pm 1/2)\) with 1 transition frequency, and a spin 3/2 nucleus will have 4 energy levels \((\pm 1/2, \pm 3/2)\) with 3 allowed transitions.

In early continuous-wave (CW) NMR experiments, the sample was irradiated at a fixed radio frequency, and the magnetic field was swept until a transition frequency was observed. These methods have all but completely been replaced by modern pulsed NMR. Instead of changing the field, we hold the magnetic field static, and use the frequency of light that excites the transition at that field strength. We ‘pulse’ the sample with a specific frequency of radio waves. This RF pulse causes the spins in the sample to reorient 90°, after which the spins ‘relax’ back to the z-axis. This relaxation is then recorded in the form of time domain data called a free-induction decay (FID). This time domain data is processed by Fourier transformation to the frequency domain, which is the type of NMR spectrum most NMR users would recognize.
Figure 1.1. Spin-1/2 nuclei in a static magnetic field, $\mathbf{B}_0$. The angular momenta of the nuclei precess about the magnetic field and the orientation with respect to the magnetic field depends on the spin quantum number, $m_s$. 
Pulse sequences are very important in NMR. There are countless ways to pulse a sample, but the simplest pulse sequence is a 90° pulse, followed by a delay to allow the system to relax. This simple experiment is shown as figure 1.2. A very common pulse sequence for solids-state NMR is the Hahn Echo\(^6,\text{7}\), or the spin-echo pulse sequence (figure 1.3(a)). This consists of an initial 90° pulse followed by a delay during which the magnetization is allowed to precess, then a 180° pulse which refocuses the magnetization, followed by a second delay, and then the acquisition of the echo. During the second delay precession again occurs. The second delay is such that by the end of the delay, the magnetization is refocused and the echo can be observed. This is illustrated in figure 1.3 (b-f). There are many ways to structure NMR pulse sequences depending on the desired result.

Relaxation has two mechanisms: spin-lattice (or longitudinal) relaxation and spin-spin (or transverse) relaxation. Longitudinal relaxation, governed by the value \(T_1\), is the process of the populations to return to thermal equilibrium from a perturbed state (returning to the z-axis from the x-y plane). Transverse relaxation has to do with the decay of coherences, and is governed by the time constant \(T_2\). Both types of relaxation can have practical implications in the collection of spectra. For example, in many hydrogen bonded systems, \(T_1\) times can be quite long (on the order of minutes to hours). In other systems the \(T_1\) can be on the millisecond timescale. If \(T_2\) is short, the coherence dies before it can be observed. A way to combat this is to sample faster, but this involves much more data processing than a typical spectrum would.
Figure 1.2. The most basic pulsed NMR experiment. (a) shows the equilibrium magnetization, perturbed by the RF pulse. (b) the magnetization recovers back to equilibrium state (c).
Figure 1.3. The Hahn Echo pulse sequence. (a) Shows the Hahn echo pulse sequence, (b) the initial magnetization, (c) the magnetization after the first pulse. The magnetization is allowed to precess (d) and then is refocused to (e), where it is allowed to precess for a delay just long enough to get state (f) and observe the echo.
Depending on the chemical environment around the nucleus we will get a spectrum consisting of one or more lines. The number, shape, and placement of these lines can give us great detail of the spin system and the environment that it is in.

1.3 The NMR Hamiltonian

The total sum of NMR interactions can be written in the form of a Hamiltonian operator, given as equation 1.2. The Hamiltonian can be used to describe all things that will affect the system. These include, but are not limited to the interaction with a static magnetic field (Zeeman interaction), the interaction with a radiofrequency pulse, chemical shielding (\( \sigma \)), dipole-dipole interactions, \( J \)-coupling, and quadrupolar coupling\(^\text{17}\).

\[
\mathcal{H}_{\text{total}} = \mathcal{H}_Z + \mathcal{H}_{RF} + \mathcal{H}_{CS} + \mathcal{H}_D + \mathcal{H}_Q
\]  

(1.2)

Each of these interactions has a different effect on the spin system, and we can deduce what effect each may have on the spectrum and lineshape. The Zeeman and RF Hamiltonians represent what is sometimes called the external Hamiltonian, meaning that they are external to the system being studied. This is in contrast to quadrupolar, chemical shift, dipolar, and \( J \)-couplings, which are part of the system being studied, and are sometimes called the internal Hamiltonian.
1.3.1 The Zeeman and RF Hamiltonians. The largest interaction in an NMR experiment is the Zeeman interaction. It is so large in fact that all other parts of the total Hamiltonian are generally treated as perturbations of it. The Zeeman interaction arises from the interaction between a spin and the static magnetic field, represented by the equation:

$$\mathcal{H}_Z = -\gamma B_0 I_z$$  \hfill (1.3)$$

where $\gamma$ is the gyromagnetic ratio and $I_z$ is the component of the spin angular momentum along the $z$-axis, which is coincident with $B_0$. The gyromagnetic ratio is usually given in units of MHz/tesla, and the previously mentioned Larmor frequency is given as $\omega_L = -\gamma B_0$.

1.3.2 The quadrupolar Hamiltonian. While all of these things combine together to give a spectrum, the largest effect in the solid-state (if it is present) is due to the electric quadrupole moment of the nucleus. A quadrupole moment is the simplest way to represent this non-spherical charge distribution, represented by four poles, and is the same for each isotopomer. Higher-order moments are also possible, such as a hexadecapole, have been studied, but have never been shown to be different from zero. Any nucleus that has a spin of 1 or greater will have a quadrupole moment. If the quadrupole moment is oriented along the axis of symmetry, it will have a positive sign, if it is oriented perpendicular to the axis of symmetry, it will have a negative sign.

The quadrupolar Hamiltonian is given as follows:

$$\mathcal{H}_Q = \frac{eQ}{2I(2I-1)\hbar} \mathbf{I} \cdot \mathbf{V} \cdot \mathbf{I}$$  \hfill (1.4)$$
where $eQ$ is the electric quadrupole moment of the nucleus, $I$ is the spin of the nucleus, $\hat{I}$ is the nuclear spin vector, and $V$ is the electric field gradient tensor. The electric field gradient is a second rank tensor, and is shown in its full form in equation (1.5).

$$V = \begin{pmatrix} V_{xx} & V_{xy} & V_{xz} \\ V_{yx} & V_{yy} & V_{yz} \\ V_{zx} & V_{zy} & V_{zz} \end{pmatrix} \quad (1.5)$$

A frame of reference in which the electric field gradient is diagonal can also be defined. This is called the Principal Axis Frame (PAF)

$$V = \begin{pmatrix} V_{xx} & 0 & 0 \\ 0 & V_{yy} & 0 \\ 0 & 0 & V_{zz} \end{pmatrix} \quad (1.6)$$

Where by convention:

$$|V_{zz}| \geq |V_{xx}| \geq |V_{yy}| \quad (1.7)$$

Also, in its principal axis frame we can say that:

$$eQ = V_{zz} \quad (1.8)$$

The quadrupole moment couples to the gradient of the electric field, and the resulting value is called the quadrupole coupling constant ($C_Q$). It is represented by the following equation:
The quadrupole asymmetry parameter (\( \eta \)) describes the deviation from axially symmetry and can substantially contribute to the NMR lineshape. It is defined as:

\[
C_Q = \frac{e^2 q Q}{\hbar}
\]

(1.9)

The quadrupolar energy levels, although they are the largest term in the internal Hamiltonian, are still significantly smaller than the Zeeman term and therefore can be treated with perturbation theory. For nuclei with smaller quadrupole moments, first-order perturbation theory is often enough to describe the interaction. However, as the magnitude of the interaction increases, second-order perturbation theory is often necessary. Figure 1.4 shows how \( I = 3/2 \) energy levels change under Zeeman, first- and second-order quadrupole interactions. Under just the Zeeman interaction there are four degenerate states. Under first-order perturbation theory the central transition is shifted, but its frequency stays the same\(^{19} \), while the upper satellite is increased in frequency and the lower satellite is decreased in frequency.

\[
\eta = \left| \frac{V_{yy} - V_{xx}}{V_{zz}} \right|
\]

(1.10)

In the principal axis frame the Hamiltonian is given by:

\[
\mathcal{H}_Q = \frac{-e^2 q Q}{4I(2I-1)\hbar} \left[ 3I_{z,PAF}^2 - I^2 + \frac{1}{2} \eta (I_{x,PAF}^2 - I_{y,PAF}^2) \right]
\]

(1.11)
Figure 1.4. Energy levels of a spin $3/2$ nucleus showing first just the energy levels due to the Zeeman interaction, in the middle shows the first order quadrupole adjustment, and on the right is the second-order quadrupole.
If there is a need, as is the case for many spin-3/2 nuclei, we can apply second-order perturbation theory, which reduces the frequency of the central transition, and increases the frequency of both satellites. In the case of larger and higher-spin nuclei, it may be necessary to use higher orders of perturbation theory.

1.3.3 Chemical shielding. The chemical shielding term comes from the interaction of the RF-pulse with the electric field caused by the electrons in the system. When a spin system is pulsed, the current flowing in the coil induces a small magnetic field. This field then interacts with the magnetic dipole of the nucleus, but the effect is ‘shielded’ by the electrons of the atom. Each nucleus will be shielded differently depending on what its environment is. The chemical shielding Hamiltonian is given by:

\[ \mathcal{H}_{cs} = -\gamma B_0 \cdot \sigma \cdot I \]  

(1.12)

where \( \sigma \) is the second-rank chemical shielding tensor. As with the electric field gradient tensor, we can express the chemical shielding tensor in terms of a principal axis frame that yield the tensor diagonalized:

\[
\sigma^{PAF} = \begin{pmatrix}
\sigma^{PAF}_{xx} & 0 & 0 \\
0 & \sigma^{PAF}_{yy} & 0 \\
0 & 0 & \sigma^{PAF}_{zz}
\end{pmatrix}
\]  

(1.13)

We can also define several other quantities\(^\text{18}\): the isotropic chemical shielding (\( \sigma_{iso} \)), the chemical shielding anisotropy (\( \Delta \sigma \)), and the asymmetry parameter (\( \eta \)).
In an anisotropic liquid, the anisotropic part of the Hamiltonian is removed and the Hamiltonian simplifies to:

$$\mathcal{H}_{CS} = -\gamma B_0 \delta_{iso} I_z$$  \hspace{1cm} (1.17)

Chemical shieldings will change based upon field strength, so another value, chemical shift is usually used instead. Chemical shift ($\delta$) does not change based on field strength and allows direct comparison of results across different field strengths. The relationship between chemical shielding and chemical shift is shown in equation 1.18.

$$\delta = \frac{\sigma - \sigma_{ref}}{\omega_0}$$  \hspace{1cm} (1.18)

where $\delta$ is in parts per million, $\sigma$ and $\sigma_{ref}$ are in Hz and $\omega_0$ the spectrometer operating frequency in MHz.
1.3.4 Direct dipole-dipole coupling. This type of dipole-dipole interaction arises from the direct (through-space) coupling of a dipole from one nucleus to another. Because spins are magnetic, they induce a small, localized magnetic field. This magnetic field interacts with the other nuclear spin through space (as opposed to through the electron cloud). The Hamiltonian is expressed as follows:

\[
H_D = -\frac{\mu_0 \gamma_I \gamma_S \hbar}{4\pi r^3} \left[ 3(I_j \cdot r_{ik}) (I_k \cdot r_{jk}) - (I_j \cdot I_k) \right]
\]

(1.19)

Where \( \mu_0 = 4\pi \times 10^{-7} \text{ V s/(A m)} \) is the permeability of free space, \( \gamma_I \) and \( \gamma_S \) are the gyromagnetic ratios for spin \( I \) and spin \( S \) respectively. We can also write the Hamiltonian in terms of a tensor operator:

\[
H_D = -2I \cdot \begin{pmatrix}
-\frac{d}{2} & 0 & 0 \\
0 & -\frac{d}{2} & 0 \\
0 & 0 & d
\end{pmatrix} \cdot S
\]

(1.20)

where \( d \) is called the dipolar coupling constant, and is shown as below:

\[
d = \frac{\mu_0 \gamma_I \gamma_S \hbar}{4\pi r^3}
\]

(1.21)

If we write the secularly-approximated dipolar coupling Hamiltonian:

\[
H_D = -\frac{\mu_0 \gamma_I \gamma_S \hbar}{8\pi r^3} \left( 3\cos^2 \theta - 1 \right) \left[ 3(I_j \cdot I_{\perp}) - (I_j \cdot I_k) \right]
\]

(1.22)

we see that there is an orientation dependence introduced. The \( \theta \) in the \( 3\cos^2 \theta - 1 \) term is the angle between the static magnetic field and the vector between the two
spins. This orientation dependence causes significant broadening of the spectral lines, which results in the loss of isotropic information. On the other hand, the magnitude of the dipolar interaction depends on the inverse power of $r^3$, meaning that the magnitude of the dipolar interaction can be correlated to the distance between the two spins. At an angle of $\theta = 54.74^\circ$, $(3\cos^2 \theta - 1 = 0)$ the orientation dependence can be removed or lessened by rapid spinning. This technique called Magic Angle Spinning (section 1.4.1), significantly reduces linewidth and allows individual lines to be resolved.

1.3.5 J-coupling. The J-coupling interaction, like the direct dipole-dipole interaction, is a dipole interaction, but instead of being through-space, it goes through the electrons. Because it goes through the electrons, it can be used to help determine local structure and bonding. J-coupling may be written in terms of a second-rank tensor that looks very similar to the direct dipole-dipole Hamiltonian:

$$\mathcal{H}_J = -2\pi I \cdot \begin{pmatrix} J_{xx} & J_{xy} & J_{xz} \\ J_{yx} & J_{yy} & J_{yz} \\ J_{zx} & J_{zy} & J_{zz} \end{pmatrix} \cdot S$$

In the solid-state, J-coupling is usually ignored. This is because the quadrupolar, direct dipole-dipole and chemical shielding interactions are so much larger. However, in isotropic liquids the J-coupling can be quite useful, and because of this we can write the simplified isotropic J-coupling Hamiltonian:

$$\mathcal{H}_J = 2\pi \frac{J_{xx} + J_{yy} + J_{zz}}{3} I_j \cdot I_k$$
1.4 NMR Methods

There are many different techniques available to the NMR spectroscopist. These techniques vary based on the spin system and the nature of the sample. In this section I will discuss some commonly used techniques that will be mentioned in later chapters.

1.4.1 Magic angle spinning (MAS). Magic-Angle Spinning (MAS) is the most common technique used in solid-state NMR. The purpose of MAS NMR is to reduce broadening that occurs in the solid-state. Many of the orientation dependent effects in the solid state have a \((3\cos^2\theta - 1)\) term. If this term could be effectively removed, anisotropic interactions could be lessened or completely removed from the spectral lineshape, revealing isotropic interactions. Fortunately, if we spin at the angle where this term goes to zero we can remove much of the broadening. The faster we spin about this rotational axis, the more broadening can be removed. An artifact of spinning is to create spinning sidebands. These sidebands are spaced at the frequency of rotation. For example, a 10kHz MAS rate will have resonance lines flanking the main peak by integer multiples of 10 kHz. The spinning sideband pattern may be used to find \(C_\phi\), \(\eta\), and \(\Delta\sigma\).

1.4.2 Powder static NMR. NMR powder patterns can take on any number of shapes based on which interaction dominates the spectrum, which others are present, and by the symmetry of the system. The key feature of all static-NMR powder-patterns is the fact that powders contain crystallites of all possible orientations as shown in
Figure 1.5. With respect to the magnetic field, however, these crystallites have their principal axes anywhere from 0° to 90° from the z-axis. Singularities will appear at certain angles, which depend on the interaction(s) that are present. Figure 1.6(a) shows the spectrum of a spin−3/2, η = 0 with no chemical shift and a $C_0$ of 20 MHz. Figure 1.6(b) introduces an isotropic chemical shift of 100 ppm, and figure 1.6(c) has 100 ppm isotropic shift and 50 ppm $\Delta \delta$. The isotropic shift introduced in figure 1.6(b) simply shifts the entire central transition lineshape downfield, while the $\Delta \delta$ moves the sil (the central singularity) downfield toward the left-hand singularity, while adding minimal shift to the other two. The effect on the lineshape of a spin−3/2 central transition from $\Delta \delta$ is minimal compared to how the lineshape changes with the introduction of a non-zero asymmetry parameter. Figure 1.7 shows how a spin−3/2 central transition lineshape changes with increasing $\eta$.

A phenomenon that can occur when a second-order quadrupole interaction is present is called a magic-angle hole. In the previous section, magic angle spinning was discussed, and indeed a magic-angle hole occurs at the magic angle of $\theta = 54.7^\circ$ to the z-axis, but the reason is different. While the central transition frequency is not affected by first-order perturbation theory, the satellites are. Meaning, at this angle, we are not only hitting the central transition with the pulse, but the satellites as well. This changes the flip angle of the central transition, causing a ‘dip’ in the lineshape at that frequency. An example of this phenomenon is shown in the $^{65}$Cu central transition spectrum of the dimethylthiourea copper (I) chloride from chapter 5 (figure 5.3b).
**Figure 1.5.** Orientations of crystallites in a randomly ordered powder sample.
Figure 1.6. Simulated Hahn echo $I = 3/2$ with 2nd-order quadrupolar effects for a) $\eta = 0$, b) $\eta = 0$, $\delta_i = 100$ ppm, and c) $\eta = 0$, $\delta_i = 100$ ppm and $\Delta \delta = 50$ ppm. Simulated with SIMPSON 3.1\textsuperscript{11}. 
Figure 1.7. Spectra simulated in SIMPSON 3.1\textsuperscript{11} show changing $\eta$ affects the lineshape. Figure (a) has $\eta = 0$; (b) $\eta = 0.2$; (c) $\eta = 0.4$; (d) $\eta = 0.6$; (e) $\eta = 0.8$; (f) $\eta = 1.0$. All spectra are simulated with $C_Q = 20$ MHz, $\delta_i = 100$ ppm and $\Delta \delta = 50$ ppm.
1.4.4 Two-dimensional NMR experiments. Most of the projects in this dissertation use one-dimensional NMR experiments. However, some of them employ two-dimensional experiments. Multi-dimensional NMR has become very common in solution NMR and even solid-state NMR. There are many reasons to do multi-dimensional experiments. The complexity of many (especially) biochemical systems makes them nearly impossible to study with standard 1D NMR due to overlapping resonances. In chapter two, the Heteronuclear Single Quantum Coherence (HSQC) is used to correlate $^1$H and $^{13}$C in the peroxide explosive HMTD. The STREAQI experiment (Chapter 4) is another example of where a 2D spectrum has advantages. This experiment uses slow rotation, and the analysis of ellipsoids to determine the $C_Q$ and $\eta$ of a substance with a very large (greater than $\sim$20 MHz) $C_Q$ in one spectral window, as opposed to moving the transmitter to collect multiple experiments.

1.5 Probe electronics

There are many different parts that go into making an NMR spectrometer, but none are more important than the probe. The probe is the part of the instrument that transfers the radiofrequency pulse to the sample and then receives the signal from the sample and returns it to the console and computer for analysis. The basic probe circuit is a very simple circuit, and consists of two major parts: a capacitive element and an inductive element. Figure 1.8 (a) shows the most basic parallel NMR circuit
containing only a capacitor and an inductor and figure 1.8 (b) shows the most basic series circuit.

These can be arranged either in series or in parallel. The resonant frequency of this ‘LC’ circuit is:

\[ \omega = \frac{1}{\sqrt{LC}} \]  

Where \( L \) is the inductance of the coil in Henrys and \( C \) is the capacitance of the circuit in Farads. Common capacitances for an NMR probe range from 10-150 \( \mu F \). The capacitor is usually tunable, and the coil is static. All of the coils that are used for projects in this dissertation are solenoidal coils. It is hard to easily predict the inductance of a solenoid, unless you treat it in the limit of being infinitely long:

\[ L = \frac{\mu_0 n^2 A}{l} \]  

where \( L \) is the inductance of the coil near the center, \( \mu_0 \) is the permeability of free space, \( n \) is the number of turns, \( A \) is the cross-sectional area of the coil, and \( l \) is the length of the coil. This equation is best used for qualitative purposes. If one wants to lower the resonant frequency of the circuit, one either needs to increase the number of turns or the area, or decrease the length.

Tuning and matching are the two most important qualities of a probe (other circuit properties are significant as well). Tuning is setting your probe to the proper
Figure 1.8. (a) The most basic parallel circuit containing a capacitor and an inductor. (b) The most basic series circuit containing a capacitor and an inductor.
resonance frequency, like in a radio. Matching has to do with how much power goes into the sample versus how much gets reflected back at the receiver. Specifically, matching means impedance matching. The impedance of a circuit \((Z)\) is the sum of the resistance \((R)\) and the reactance \((iX)\).

\[
Z = R + iX
\]  

(1.27)

The impedance of a circuit is the sum of all the impedances of the elements in the circuit. For example, for the circuit pictured in figure 1.X(b), the impedance of the circuit would be equal to the sum of the inductive and capacitive impedances, where \(\omega\) is the resonant frequency of the circuit.

\[
Z = Z_L + Z_C
\]  

(1.28)

\[
Z = i\omega L + \frac{1}{i\omega C}
\]  

(1.29)

In the ideal case where the impedance of the circuit shown in figure 1.8 is matched to the standard 50 \(\Omega\) it can be used as is. However, this is never the case and some impedance matching must be done. There are three ways of doing this. Firstly, and as in most commercial probes, the matching comes from a tunable capacitor. This is a very good solution as it allows one to adjust the matching of the circuit quickly and easily to many different nuclei. The second way to match the circuit is to add a small inductor to the circuit. This method is cheap and effective, but the disadvantage is having to change inductors when changing nuclei, or at least having to remove the probe from the magnet to adjust the matching, which is not optimal because the matching will change from outside of the magnet to inside the
magnet. The third (and worst) way to match a probe is using a resistor. Usually, this would only be used while doing experiments outside of the magnet as in nuclear quadrupole resonance (NQR). The method that we have most commonly employed for impedance matching is the insertion of an inductive element (usually a small hairpin coil), in parallel to match the circuit.

Another important factor in an NMR probe is called the $Q$-factor, or quality factor and is found by:

$$ Q = \frac{\omega_0}{\Delta \omega} $$  \hspace{2cm} (1.29)

where $\Delta \omega$ is the width of the resonance at half-height. A high probe $Q$-factor means that the probe is highly resonant, and is characterized by a deep resonance that is very narrow. Decreasing the $Q$-factor of a probe makes the resonance shallower and wider. Usually this is undesirable, but in some cases one can ‘damp’ or lower the $Q$-factor of a probe by adding a resistance to increase the width of the resonance.

Most commercial probes are quite good, having high $Q$-factor as well as the ability to tune and match several different channels at one time. While these characteristics are indeed positive, they do not always meet the needs of a particular experiment. For example, running copper NMR on a commercial MAS probe, a large portion of the spectrum may be obscured by the peak from the copper metal. This is just one example of niche that exists for probe building: there may not be a commercial probe available to do what is needed.
1.6 Theoretical Calculations

Theoretical calculations are very useful in the prediction and analysis of NMR spectroscopic data. Three main methods are used throughout the following chapters: *ab initio* methods Hartree-Fock\(^1\) (HF) and Møller-Plesset second-order perturbation theory\(^3\) (MP2) as well as Density Functional Theory (DFT)\(^4\) calculations. DFT methods are built upon empirical evidence while *ab initio* calculations are derived from first principles. These methods all rely on some sort of approximation to be able to calculate solutions to the wavefunction.

Hartree-Fock methods represent one of the oldest and most commonly used *ab initio* methods has the advantage of being a method that can be used to get results quickly, due to its low computational cost. The drawback is the assumption of no electron correlation which is particularly problematic in systems that have heavy atoms with many electrons. HF uses a variational method to approximate solutions to the wavefunction: a trial wavefunction is selected, and the solutions are calculated. If the energy is not a minimum, a new wavefunction is selected, and the process repeats. HF calculations, however, lose out in accuracy to methods that use electron-correlation.

MP2 calculations are the next step in *ab initio* calculations after HF methods. MP2 uses the Hartree-Fock wavefunctions and adds electron correlation as a perturbation, providing more accurate results than HF methods alone. The drawback is higher computational cost. It should be noted that for molecules with heavier atoms, the addition of the electron correlation is especially useful.
The previous methods we have looked at have used wavefunctions to determine molecular properties. DFT is different than these in that it uses an empirical functional of the electron density to compute the contribution of electron correlation. The most commonly used functional is a hybrid exchange-correlation functional called B3LYP. This combines Becke’s 1988 exchange functional (B88)\textsuperscript{15}, the Lee-Yang-Parr correlation functional (LYP)\textsuperscript{16}, the Hartree-Fock exchange functional, and the Local Spin Density Approximation (LSDA) exchange and correlation functionals.

1.7 Conclusions

Chapters 2 and 3 will talk about the peroxide explosive hexamethylene-tetramine (HMTD). Chapter 2 focuses on HMTD in the solid-state while chapter 3 discusses the chirality of HMTD in solution. Chapter 4 will discuss a novel two-dimensional experiment developed for determining the $C_0$ and $\eta$ in one spectral window, as opposed to running multiple experiments at different frequencies and combining them. Chapter 5 talks about an experimental and theoretical study of the tris-dimethylthiourea copper (I) chloride complex, and examines relationships between isotopomers $^{63}\text{Cu}/^{65}\text{Cu}$ and $^{35}\text{Cl}/^{37}\text{Cl}$. 
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Chapter 2

The $^{14}\text{N}$ quadrupole coupling in Hexamethylene Triperoxide Diamine (HMTD)

Summary

Using high-field NMR, we have determined the magnitude of the nuclear quadrupole interaction in hexamethylene triperoxide diamine (HMTD), the explosive allegedly used in the London bombings of July 2005. The experimental quadrupolar coupling constant, 5.334 MHz, is in good agreement with quantum chemical calculations. The predicted single zero-field transition frequency should lie in a relatively empty part of the $^{14}\text{N}$ nuclear quadrupole resonance (NQR) spectrum; the spin relaxation rate is reasonably fast.
2.1 Introduction

Hexamethylene triperoxide diamine (HMTD), probably discovered at the end of the 19th century,\textsuperscript{1} languished in relative obscurity for 100 years, until its ease of preparation and stability relative to other organic peroxides, attracted the interest of terrorists, most notably the perpetrators of the London bombings of 2005.

HMTD is an interesting molecule to the physical chemist; it is helically chiral in solution\textsuperscript{2} but crystallizes with disorder\textsuperscript{3} in the achiral space group \(R3m\); the nitrogens lie on the crystallographic threefold axis. It possesses a comparatively planarized tertiary nitrogen, largely a result of the electron-withdrawing character of the peroxide groups ringing its molecular equator.\textsuperscript{5} Because of the local symmetry, the chemical shielding and electric field gradient (EFG) tensors are constrained to be axially symmetric, with the unique axis perpendicular to the pseudo-plane. Pure quadrupole resonance is an established method for the detection of explosives and other contraband, and characterizing the \(^{14}\text{N}\) HMTD NMR properties of HMTD is therefore a matter of more than academic interest. However, the desirability of working with small amounts of this unstable material, combined with the inherent low sensitivity of pure quadrupole resonance, led us to approach the initial characterization of the \(^{14}\text{N}\) resonance of this material by high-field NMR.
Figure 2.1. Structure of HMTD.
2.2 Experimental Methods

HMTD was prepared by standard methods. NMR experiments were conducted at 14 T in a Bruker Avance spectrometer equipped with high-power amplifiers for solids. The probe was homebuilt, with a 1.1 cm × 1 cm (diameter × length) coil, tunable over the range 35–90 MHz. The $^{14}$N $\pi/2$ pulse, measured for $^{14}$NH$_4$Cl at the Zeeman frequency, was 8 μs. Because the NMR signal of HMTD was expected greatly to exceed the bandwidth of the instrument, and thus only single transitions excited, an effective single transition $\pi/2$ pulse of 5.7 μs (~8 μs/$\sqrt{2}$) was used in all experiments. Although there are no reports that high radio frequency fields can induce detonation of this material, to guard against this possibility, the NMR probe, with the screws on the top removed to allow it to blow out, was placed behind an explosion-proof screen, and the sample subjected to 30 μs pulses, once per second for 10 min, at a power level 2 dB above operating levels, before it was inserted into the NMR magnet.

To detect signals of HMTD, a Hahn echo sequence ($\pi/2 - \tau - \pi - \tau -$ acquire) was employed, with $\tau$ delays of 80 μs and delays between acquisitions of 8 s; typically 1000 transients were averaged to obtain a spin echo. Echoes were obtained every 200 kHz over two regions, each spanning 1 MHz, at 1.9 MHz above and below the Zeeman frequency, where computations suggested the perpendicular edges of the Pake doublet were likely to lie. Once the peak intensities of the Pake doublet were located, higher quality spin-echo spectra were obtained centered at or near the estimated frequency. The relaxation behavior of HMTD was characterized
by progressive saturation; echo intensities were accumulated at the frequency of the upper parallel edge using the standard spin-echo sequence, and recycle delays between 1 and 32 s.

2.3 Results

Figure 2.2 shows the results of the echo sweep. Two pronounced maxima are apparent; the lower maximum, at 41.36 MHz is less intense than the upper maximum at 45.36 MHz, partly because of the relative Boltzmann polarizations and detection efficiencies of the two transitions, but more importantly because of the better coincidence of the upper transition maximum with the Pake-doublet perpendicular edge (see below). Such frequency sweep measurements are necessarily coarse-grained and limited in accuracy.

The spectra shown in figure 2.3(a) are Fourier transforms of spin-echo free-induction decays (FIDs) acquired at frequencies of 41.406241 and 45.406241 MHz, respectively. These spectra allow careful examination of the Pake-doublet perpendicular edge, and they were fit to simulated Pake doublets, computed to second order in perturbation theory, assuming an axially symmetric quadrupolar coupling tensor, using a finite pulse width correction for the spin-echo response using the measured 5.7 μs π/2 pulse length; fit parameters were $C_0 = 5.3346 \pm 0.001$ MHz, $T_2^* = 177$ μs, and $\sigma_\perp$ (offset of the HMTD perpendicular edge relative to NH$_4$Cl, presumably as a result of chemical shielding tensor of HMTD) = $+0.002 \pm 0.001$ MHz.
Figure 2.2. Intensity of the $^{14}$N Hahn spin echo signal obtained from HMTD, as a function of the spectrometer resonance frequency.
Figure 2.3. NMR spectrum of the two perpendicular edges of the HMTD $^{14}$N Pake doublet (a), obtained by Fourier transformation of the spin echoes, compared with simulated spectra (b), computed as described in the text.
In fact, the relative sparseness of the Hamiltonian allows us to derive an exact formula for the perpendicular edges.

\[ v_\perp = \sqrt{v_0^2 + \frac{9}{64} C_Q^2 + \frac{3}{8} C_Q} \]  

(2.1)

where \( v_0 \) is the nuclear Larmor frequency. At this orientation, there are no odd-order terms in \( C_Q \) except for the first-order; the fourth-order shift, the largest term omitted from the simulation, is predicted to be 24 Hz at the perpendicular edge.

Segments of the simulations corresponding to the same frequency ranges as the experimental spectra are shown in Figure 2.3(b). The simulations are quite satisfactory, but the experimental spectra appear to contain an approximately 10 KHz additional frequency dispersion, manifest as a rather flat-topped lineshape which is not accounted for in the simulation; the most probable explanation for this is a dispersion in quadrupole constants due to the known crystallographic disorder.

Using a \(^{14}\)N quadrupole moment \( eQ \) of 2.05 \( \pm \) 0.02 \( \text{fm}^2 \) and the conversion factor \( K_Q = 2\,349\,647.8 \text{ Hartree}^{-1} \text{Bohr}^2 \text{ fm}^{-2} \text{ s}^{-16} \); the \( zz \) element of the EFG tensor in atomic units (Hartree \( \text{Bohr}^2 \)) is given by \( V_{zz} = C_Q / (eQK_Q) = 1.107 \pm 0.01 \text{ au} \). HMTD calculations (Table 2.1) used the optimized \( D_3 \) structure published previously.\(^2\) In order to examine the effects of larger basis sets and/or higher levels of correlation, we also examined EFGs for the open-chain analog of HMTD, \( \text{tris(methylperoxy-methylene) amine (TMPMA)} \), using an optimized structure published previously\(^2\); trimethylamine (TMA) optimized at the B3LYP/6-311++G(2d,p) level; TMA optimized at the same level with the nitrogen constrained to 20 pm above the plane.
containing the carbon atoms (thus giving a more planar nitrogen with similar
genometry to TMPMA, and denoted by the abbreviation TMA-20); and ammonia.
Calculations used the augmented, correlation-consistent polarized valence multiple
zeta (aug-cc-pVnZ) basis set series of Dunning; unlike the Pople basis sets, these
allow a systematic comparison of EFGs calculated at different levels of theory,
converging to the complete basis set (CBS) result, which was obtained using the
formula of Woon and Dunning.

\[
V_\alpha(n) = V_\alpha(\infty) + B \exp(-nC)
\]  

(2.2)

This formula was chosen for reasons of simplicity, and because there is no empirical
or theoretical reason to choose more recent improvements. In any case, the exact
formula used for the extrapolation makes relatively little difference to the result.

Electron correlation was introduced using second-order Møller–Plesset
perturbation theory (MP2), as well as (where possible) coupled cluster-
singles/doubles methods (CCSD). The latter accounts for the effect of correlation on
EFGs very accurately. DFT calculations using the B3LYP functional are provided for
the purposes of comparison. Unfortunately, coupled cluster calculations were not
feasible for HMTD itself, but were run at the valence double-zeta (aug-cc-pVDZ)
level for TMA and TMA-20, and at the aug-cc-pVDZ and valence triple-zeta (aug-cc-
pVTZ) levels for ammonia.
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|          | TMPMA          |          |          |          |          |          |          |          |
|          | RHF           |          |          |          |          |          |          |          |
|          | aug-cc-pVDZ   | 1.290172 |          |          |          |          |          |          |
|          | aug-cc-pVTZ   | 1.313026 |          |          |          |          |          |          |
|          | aug-cc-pVQZ   |          |          |          |          |          |          |          |
|          | CBS           |          |          |          |          |          |          |          |

|          | TMA            |          |          |          |          |          |          |          |
|          | RHF           |          |          |          |          |          |          |          |
|          | aug-cc-pVDZ   | 1.234173 | 1.148088 | 1.055395 | 1.103184 |          |          |          |
|          | aug-cc-pVTZ   | 1.275131 | 1.217830 | 1.131875 |          |          |          |          |
|          | aug-cc-pVQZ   | 1.297480 | 1.243632 |          |          |          |          |          |
|          | aug-cc-pV5Z   | 1.299655 | 1.255766 |          |          |          |          |          |
|          | CBS           | 1.306267 | 1.262187 |          |          |          |          |          |

|          | TMA-20         |          |          |          |          |          |          |          |
|          | RHF           |          |          |          |          |          |          |          |
|          | aug-cc-pVDZ   | 1.464650 | 1.383545 | 1.279249 | 1.326223 |          |          |          |
|          | aug-cc-pVTZ   | 1.498449 | 1.450323 | 1.357437 |          |          |          |          |
|          | aug-cc-pVQZ   | 1.524153 | 1.480579 |          |          |          |          |          |
|          | aug-cc-pV5Z   | 1.526928 | 1.495514 |          |          |          |          |          |
|          | CBS           | 1.538490 | 1.507743 |          |          |          |          |          |

|          | NH₃            |          |          |          |          |          |          |          |
|          | RHF           |          |          |          |          |          |          |          |
|          | aug-cc-pVDZ   | 0.900208 | 0.828925 | 0.751733 | 0.795296 |          |          |          |
|          | aug-cc-pVTZ   | 0.922641 | 0.870354 | 0.800613 | 0.843492 |          |          |          |
|          | aug-cc-pVQZ   | 0.946155 | 0.896108 | 0.823014 |          |          |          |          |
|          | aug-cc-pV5Z   | 0.947340 | 0.904913 | 0.824235 |          |          |          |          |
|          | CBS           | 0.960873 | 0.918792 | 0.829434 |          |          |          |          |

Table 2.1. Computed values of $V_{zz}$, in atomic units, obtained as described in the text.
Increasing the basis set size systematically increased the EFG at nitrogen for all molecules at all levels of correlation. Unfortunately, the three Hartree–Fock calculations of HMTD are insufficient to do a CBS extrapolation. However, we were able to obtain CBS extrapolations for the Hartree–Fock results for TMA, TMA-20 and NH₃. The CBS result exceeds the aug-cc-pVTZ value by 0.0311, 0.0400 and 0.0382 respectively. It seems, therefore, reasonable to conclude that the CBS result for HMTD exceeds the aug-cc-pVTZ result by 0.0365 ± 0.0047. While this is not the case for smaller basis sets, results for TMA, TMA-20 and ammonia indicated that basis sets at the aug-cc-pVTZ level and higher, corrections for basis set incompleteness and electron correlation were largely additive. The difference between CCSD and MP2 EFGs fall in the range 0.0428–0.0469, with the lowest values being for ammonia.

The (CCSD – MP2) EFG appeared to be almost independent of basis set size, as one would expect if the corrections were additive. Therefore, we used an average of the four computations for which both CCSD and MP2 calculations were available, to estimate $V_{zz}(\text{CCSD}) - V_{zz}(\text{MP2}) = 0.0453 \pm 0.0025$.

Using these two corrections, we can now estimate a CCSD/CBS value for HMTD of $1.170 \pm 0.006$. For comparison, the same corrections applied to the MP2/aug-cc-pVTZ $V_{zz}$ of TMA lead to an estimated CCSD/CBS value of $1.215 \pm 0.006$, compared with the experimental gas phase value of $1.159 \pm 0.016$ (computed from the microwave spectroscopic value of $C_Q = 5.5002 \pm 0.0018$ MHz).
$^{14}$N spin relaxation under circumstances of single-transition excitation, as in the present case, is expected to be biexponential.\textsuperscript{10} We can write the polarization of the 0–1 transition as the difference in population of the two respective spin states:

$$I_{01} = p_0 - p_1$$

(2.3)

We can also write similar expressions for the Zeeman:

$$I_Z = p_{-1} - p_1$$

(2.4)

and quadrupolar polarization of the system:

$$I_Q = 2p_0 - p_1 - p_{-1}$$

(2.5)

Finally, solving these three equations gives:

$$I_{01} = \frac{I_Z + I_Q}{2}$$

(2.6)

In other words, the single-transition polarization is an equal admixture of Zeeman and quadrupolar polarization. The experimental progressive-saturation echo intensity (Fig. 2.4) gives an excellent fit to a biexponential decay with equal components; the two relaxation time constants are $T_{1Z} = 1.0$ s and $T_{1Q} = 8.0$ s; the shorter time constant is assumed to correspond to Zeeman order, since Zeeman and not quadrupolar order will be relaxed by fluctuations of the dominant quadrupolar interaction.
Figure 2.4. (Points) Intensity of the HMTD $^{14}$N spin echo, obtained at the upper Pake-doublet perpendicular edge, as a function of the relaxation delay; (line) best least-squares fit to a biexponential recovery, composed of two equal components with fit-time constants of 1.0 and 8.0 s.
2.6 Discussion and Conclusions

Observation of an axially symmetric Pake doublet from the $^{14}$N signal of HMTD confirms the threefold symmetry of the molecule required by the crystal structure, and the comparative narrowness of the perpendicular edge indicates that the crystallographic disorder has only a weak influence on the field gradient. Also, the very small inhomogeneous line width in this system has interesting consequences for the scheme used to detect the resonance signal. In the absence of line-broadening, theory requires that the intensity of the perpendicular edge of a Pake doublet diverges. While, in practice, no sample has zero intrinsic line width, in the present example the line width is about a factor of 3000 smaller than the total width of the pattern, and the result is that the spin-echo intensity at the perpendicular edge is almost 20 times the intensity in the center of the pattern. This has important consequences for the measurement of $^{14}$N quadrupole couplings, because it shows that the edges, from which the principal values can most accurately be determined, can be measured with much better sensitivity than the bulk of the pattern. Our data also indicate that the $^{14}$N nuclear quadrupole resonance (NQR) spectrum will be correspondingly narrow, which should favor detection of this species at zero field.

The short Zeeman $T_1$ and longer quadrupolar $T_1$, suggests that relaxation is dominated by fluctuations in the large quadrupole coupling constant. Given the axial symmetry of the system, only the quadrupolar $T_1$ will be directly observable at zero field. The $T_{1Q}$ value is quite long, presumably reflecting very limited dynamics in the crystal; however, it is probably not long enough to seriously inhibit zero-field
observation of this material.

The similarity of the EFG to that of TMA was somewhat surprising, since the nitrogen in HMTD is nearly planar, and planarization of TMA leads to a considerable increase in the EFG, as a result of the increase in the $p$-character of the nonbonding orbital. In earlier work\textsuperscript{2} we obtained an optimized structure of the open-chain analog of HMTD, TMPMA. Hartree–Fock EFGs for the optimized TMPMA structure were 1.2902 and 1.3130 at the aug-cc-pVDZ and aug-cc-pVTZ levels respectively, within 0.5% of those of HMTD at the same level of theory and much smaller than those at TMA-20, although the latter has the same degree of a planarity at the nitrogen. We therefore conclude that the increased $p$-character of the nonbonding electrons in HMTD, caused by planarization, is offset by electron withdrawal by the electronegative, peroxy groups. The comparable EFGs of HMTD and TMA, therefore, appear to be a result of the two competing and nearly equal, but oppositely signed, effects.

Assuming that we make the usual assumption that CCSD accurately accounts for electron correlation, the computed $C_Q$ values of both HMTD and TMA exceed the experimental values by 5–7%. There are probably two contributions to the deviation; vibrational averaging, particularly by the umbrella mode along the molecular $C_3$ axis, and the failure of standard basis sets to adequately allow Sternheimer polarization of the nitrogen K-shell.\textsuperscript{11} Comparing these results with those obtained with less accurate methods of correlation, it appears that in every instance, MP2 overestimates the correlation contribution to the EFG, by 33% to as much as 55%, while B3LYP underestimates the contribution by an even larger factor.
Neither method, therefore, seems to constitute a satisfactorily quantitative way of dealing with correlation at tertiary nitrogens of this sort, and use of CCSD or other higher-level EC methods seems to be mandatory for such systems.
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Chapter 3

Helical chirality in hexamethylene triperoxide diamine (HMTD)

Summary

The primary explosive hexamethyleneetriperoxide diamine has previously been found to exist in the solid state as a racemic mixture of helically chiral, threefold symmetric enantiomers; another enantiomeric pair of low-energy conformers has been predicted, but has never been observed. We show by solution 2D NMR at 14 T, in achiral solution and by addition of chiral shift reagents, that all four optically isomeric conformers coexist at slow equilibrium on the NMR timescale at room temperature, and can be observed. Calculations of the $^1$H and $^{13}$C NMR chemical shifts using gauge-including atomic orbital methods are in excellent agreement with experiment; thermochemical calculation of the free energies in solution are in somewhat worse agreement, but correctly predict the relative stability of the conformers. Analysis of the effects of chiral shift reagents on the NMR spectra suggests that discrimination between chiral isomers is primarily around the molecular equator, around which the enantiomeric gauche O–O linkages are arrayed.
3.1 Introduction

Hexamethylenetriperoxide diamine (HMTD) was possibly first synthesized by Legler in 1885, and proposed for use as a primary explosive by Taylor and Rinkenbach in 1924. Likely because it, like many peroxide explosives, is easily synthesized from commonly available materials, can be used as a primary explosive or detonator, and at the same time is somewhat more stable than most members of this class, it has been implicated in several recent terrorist incidents.

The first deduction of the chemical structure of HMTD has been attributed to Urbanski, and the compound has since been characterized by X-ray crystallography, infrared, Raman, and NMR spectroscopy, and computational methods employing density functional theory (DFT). Computation indicates the most stable conformation has $D_3$ symmetry and, remarkable for such a small molecule, is helically chiral (Fig. 3.1(a)); the enantiomers have been labeled P- and M-HMTD. The original X-ray study, which reported a disordered structure in the achiral crystallographic space group $R_{3m}$, was revised in light of the theoretical results to contain equal proportions of enantiomers disordered about the crystallographic mirror plane; the revised structure agreed with computations at the 6-31 + G(d) level.

Theory also predicted a second conformational minimum with $C_2$ symmetry (iso-HMTD). Spectroscopic work, however, detected only a single conformer. Moreover, the published NMR data are discordant, with the earlier studies obtained in solution in dimethylsulfoxide-$d_6$ (DMSO-$d_6$) reporting a strongly coupled quartet,
consistent with the two geminal diastereotopic protons expected from the $D_3$ conformer in solution; however, later workers (in CDCl$_3$) reported a singlet,$^4$ which could be consistent with that structure only in case of accidental chemical shift degeneracy of the diastereotopic protons, or rapid exchange of the two $D_3$ isomers. In fact, the rather broad quartet in DMSO does coalesce to a very broad singlet at elevated temperatures$^8$ (105 °C), though at these elevated temperatures the stability of HMTD in DMSO-$d_6$ might be questioned. Neither the NMR nor other spectroscopic work detected any other conformers besides $D_3$.

We therefore undertook a solution NMR study of HMTD, in conjunction with higher-level DFT calculations, in order to establish whether these conformers do in fact coexist in solution, and to determine their equilibrium constant.

### 3.2 Methods

#### 3.2.1 Experimental. HMTD was synthesized as follows:$^5$ 0.93g of hexamethylene-tetramine (purchased from Aldrich) was dissolved in 4.91 g of a 30% hydrogen peroxide solution (Aldrich). 1.31 g of citric acid (Aldrich) was then added to the solution slowly over a total period of about 5 min. This solution was mechanically stirred for 3 h in an ice bath, removed from the ice bath, and allowed to warm to room temperature and precipitate for about a day. Following vacuum filtration, the white crystals obtained were rinsed thoroughly with water and methanol. This preparation produced about 500 mg of HMTD. For NMR samples, 20 mg of HMTD was dissolved in about 0.5 ml of CD$_2$Cl$_2$ or DMSO-$d_6$. 
Solution NMR spectra were acquired at 14 T using a Bruker Avance spectrometer. Proton 1D NMR spectra were obtained at 600.179 MHz, using a single 4.3 µs π/3 pulse, 64 K points per free induction decay, and a spectral width of 10 ppm, centered at 5 ppm. Proton spectra were referenced to the lock signal of deuterium in CD$_2$Cl$_2$. $^{13}$C 1D-NMR spectra were obtained at 150.930 MHz, with WALTZ-16$^9$ proton decoupling at 600.179 MHz, using a 12.8 µs π/2 pulse, 32 K points per free induction decay, and a spectral width of 238 ppm, centered at 110 ppm. 2048 transients were accumulated at 5 s per acquisition.

Two-dimensional gradient-enhanced heteronuclear single-quantum coherence (HSQC) NMR spectroscopy,$^{10}$ implemented with the modifications introduced by Schleucher et al.$^{11}$ was used to acquire $^1$H–$^{13}$C correlation spectra at the same field and with the same probe and π/2 pulse lengths as already described. In order to minimize artifacts, a relaxation delay of 4.5 s was used between acquisitions; the spectral regions between 4 and 6 ppm, and between 85 and 95 ppm were observed in the $^1$H and $^{13}$C dimensions, respectively; 512 × 1024 time domain points were acquired. These parameters were chosen to maximize resolution, with the consequence that the signal arising from residual solvent protons was aliased in the $^{13}$C, but not in the $^1$H dimension.

3.2.2 Computations. Density functional calculations were carried out using the program GAMESS,$^{12}$ using a 6-311G + + (2d,p) basis set, with the B3LYP density functional, integrated over a 192 × 48 × 24 grid. Starting with approximate initial structures, the molecule was optimized under either a $D_3$ or a $C_2$ symmetry
constraint. The final optimized vacuum structures are shown in Figure 3.1. The $D_3$ structure is a trigonally distorted cylinder, with a nearly planar nitrogen: the nitrogen forms the apex and the carbons the base of a trigonal pyramid with a height of only 1.72 pm. The molecule is confirmed to be chiral, owing to the identical gauche torsion angle about the O–O bonds. This chiral twist also creates a diastereotopic inequivalence between the pairs of methylene protons, one becoming more axial and one more equatorial. The final $D_3$ structure agreed well with the X-ray structure in its heavy atom bond lengths ($r_{OO} = 145.51$ (computed), 146.96 (X-ray); $r_{CO} = 142.53$ (computed), 143.15, 144.38 (X-ray); $r_{CN} = 143.05$ (computed); 142.72, 142.42 (X-ray); all bond lengths in pm) and in overall shape; computed $r_{CH}$ values were 109.42 and 109.30 pm for the more axial and more equatorial hydrogen, respectively. In contrast to previous studies, there were some differences in the average bond lengths of the $C_2$ conformer ($r_{OO} = 145.59, 145.57$ (×2); $r_{CO} = 142.52, 142.54, 142.48$; $r_{CN} = 142.98, 142.78, 143.01$; all bond lengths in pm), reflecting the slight overall deformation of the molecule necessary to accommodate steric interactions around the reversed O–O bond. There was also considerable divergence in the C–H bond lengths between axial and equatorial protons in the $C_2$ conformer ($r_{CH,ax} = 109.73, 109.64, 109.51$ pm; $r_{CH,eq} = 109.10, 109.25, 109.16$ pm). The overall energies of the two structures were very similar, with the energy of the $C_2$ structure exceeding that of the $D_3$ by 2.2102 mHa, or 5.803 kJ/mol (1 Ha taken as
Figure 3.1. Optimized structures of the (a) $D_3$ and (b) $C_2$ conformers of HMTD, with atomic numbering used in the text.
equivalent to 2625.500 kJ/mol). The coordinates of both optimized structures are given in Table S1 of the supplemental material.

To explore the cause of the planarity of the nitrogen, the acyclic molecule tris-(methylperoxymethylene)amine (TMPMA) was optimized at the same level. We find the nitrogen to be somewhat more pyramidal than in HMTD (height of the C$_3$N trigonal pyramid is 11.8 pm (TMPMA); 1.7 pm (HMTD); CNC = 119.3° (TMPMA); 120.0° (HMTD)) but far less than in trimethylamine at the same level of theory (height 43.5 pm; CNC 111.4°).

Chemical shieldings and spin–spin couplings were computed using Gaussian 03,\textsuperscript{13} with the same basis set and functional, using tight SCF constraints without imposed symmetry. For the $D_3$ conformer, theory predicts chemical shifts of 4.607 and 4.659 ppm, with the axial proton being more shielded; and a two-bond $J$ coupling of -13.5 Hz for the diastereotopic protons. For the three pairs of diastereotopic protons in the $C_2$ conformer, larger chemical shift distances are predicted (Table 3.1).

Using GAMESS, we computed a full set of thermo-chemical data for the two conformations under a harmonic oscillator approximation, and found the energy and free energy difference between the two conformers at 298 K (Table 3.2). Interestingly, while the electronic energy of $C_2$ is 5.803 kJ/mol above $D_3$, the difference is much smaller for $\Delta G_{298}$, where $C_2$ is predicted to lie only 0.350 kJ/mol above $D_3$. The shift in $\Delta G$ is overwhelmingly entropic in origin; the lower symmetry
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<td>C$_3$</td>
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**Table 3.1.** Calculated and experimental chemical shifts and $^1\text{H}$$-^1\text{H}$ spin–spin couplings of the $C_2$ conformer of HMTD: to emphasize small differences, all chemical shifts are given relative to the chemical shift of the $D_3$ conformer, for both $^{13}\text{C}$ and $^1\text{H}$ (average of the axial and equatorial proton chemical shifts).
\[ \begin{array}{cccccc}
\Delta E_{\text{elect}} & \Delta H_{\text{vib}} & \Delta S_{\text{vib}} & \Delta H_{\text{rot}} & \Delta S_{\text{rot}} & \Delta G_{\text{total}} \\
298.15 \text{ K} & 298.15 \text{ K} & 298.15 \text{ K} & 298.15 \text{ K} & 298.15 \text{ K} \\
\hline
D_3 & 0 & 569.108 & 129.819 & 3.718 & 114.339 & 500.048 \\
C_2 & 5.803 & 567.886 & 134.553 & 3.718 & 123.737 & 500.398 \\
\end{array} \]

**Table 3.2.** Gas-phase thermochemical calculations for HMTD; enthalpies, energies and free energies are in kJ/mol, while entropies are in J/(mol.K).
of $C_2$ means that there are six equivalent conformations corresponding to only two $D_3$ conformations, while the higher vibrational entropy of $C_2$ appears to be due to the generally lower energy of the softest harmonic modes, which in turn is probably a result of the somewhat ‘looser’ structure of $C_2$. These are, of course, gas-phase calculations. To obtain some estimate of the effect of solvation, we ran computations using a polarizable continuum model (PCM), with standard parameters for the CH$_2$Cl$_2$ solvent. The result was a slightly higher energy of solvation of the $D_3$ conformer (46.233 kJ/mol for $D_3$ vs 44.936 kJ/mol for $C_2$). This has the net effect of stabilizing the $D_3$ conformer by 1.297 kJ/mol. Thus, our best computational estimate of $G_{298}(C_2) - G_{298}(D_3)$ in CH$_2$Cl$_2$ is 1.647 kJ/mol.

### 3.3 Results

As shown in Fig. 3.2(a), the main $^1$H NMR peak is indeed a strongly coupled AB quartet, consistent with a chiral $D_3$ structure interconverting slowly at the NMR timescale. Fitting this peak gave $\delta_A = 4.7679$ ppm; $\delta_B = 4.7988$ ppm; and $^2J_{AB} = \pm 13.50$ Hz. The chemical shift difference is 0.031 ppm (theory: 0.051 ppm); the measured $J$ coupling agrees exactly with calculations.

Careful inspection of the baseline (Fig. 3.2(b)) reveals the presence of additional AB multiplets, partially obscured by the proton resonance of the major conformer. These are assigned to the $C_2$ conformer. $^{13}$C NMR (Fig. 3.3(a)), in addition to the expected $D_3$ line at 90.73 ppm, shows three additional weak lines at 92.31, 90.98 and 89.88 ppm, from the minor conformer. In order to analyze the
Figure 3.2. (a) $^1$H NMR 14 T spectrum of HMTD (b) Simulated spectrum obtained as described in text.
Figure 3.3. (a) $^{13}$C NMR 14 T spectrum of HMTD (b) Simulated spectrum obtained as described in text.
proton NMR spectrum, we performed the pulsed field gradient variant of a HSQC
experiment. As shown in Fig. 3.4, this experiment successfully resolves the buried
proton resonances, and allows extraction of a full set of chemical shift and $J$ coupling
parameters (Table 3.1). Using these parameters, we can successfully fit the one-
dimensional proton spectrum (Fig. 3.2(b)).

The existence of chiral enantiomers, long lived on the NMR time scale, can be
beautifully demonstrated by addition of chiral shift reagents. Addition of
approximately 14 $\mu$mol of the chiral paramagnetic species europium(III)tris[3-(trifluoromethylhydroxymethylene)-D-camphorate] to a solution of 1 mg (4.8 $\mu$mol)
of HMTD in 0.5 ml of CD$_2$Cl$_2$ resolved the single quartet into a pair of quartets; at
lower shift reagent concentrations, the differential effect of the shift reagent on each
diastereotopic proton pair in fact had the disconcerting effect of collapsing each
quartet into a singlet, by reducing the chemical shift difference to zero. However,
higher concentrations of the reagent or lower temperatures restored the chemical
shift difference, this time with an inverted sign, and reinstated the expected pair of
quartets. Chemical shift values for the two enantiomers, obtained by least-squares
fitting of the $^1$H spectrum to a spectrum simulated assuming two AB quartets with
different chemical shifts but identical $J$ couplings, are $\delta_{A1} = 4.8005$, $\delta_{B1} = 4.8255$; $\delta_{A2}$
$= 4.8135$, $\delta_{B2} = 4.8355$.

As might be expected, use of the praseodymium reagent, which induces shifts
of the opposite sign, monotonically increased the diastereotopic difference. Similar
splittings of the enantiomeric $C_2$ signals is also observed. The effect of the shift
reagent was also increased substantially by lowering the temperature.
Figure 3.4. HSQC spectrum of HMTD. The complex multiplets at the same proton frequency as the main quartet and at a $^{13}$C frequency of ±0.5 ppm are artifacts of strong $^1$H–$^1$H coupling.
Figure 3.5 shows the pulse-field gradient HSQC spectrum of the chirally shifted solution of the composition described above at 278 K. Resolution of the enantiomeric pairs of carbons and equatorial proton signals is clear; no resolution of the axial proton signals is seen. The magnitude of these enantiomeric shift differences in the C₂ conformer are 0.0108 ppm for H₁eq, 0.0099 ppm for H₂eq, and 0.0088 ppm for H₃eq. For the carbon, the differences are 0.017 ppm for C₁ and 0.014 ppm for C₂ and C₃ of the C₂ conformer, and 0.027 ppm for the D₃ conformer. These shifts are all concentration dependent, and so only their relative magnitudes are meaningful.

From separate least-squares fits of the ¹H and ¹³C spectra, shown in Figs 3.1(b) and 3.2(b), we obtained two values of the equilibrium constant \( K = [C₂]/[D₃] = 0.17 \) and 0.23, respectively; the average of these two yields a \( \Delta G_{298} \) of 4.0 ± 0.4 kJ/mol for the reaction.

3.4 Discussion

The existence in normal (achiral) solution of two sets of ¹H and ¹³C resonances with the expected multiplicities, and the twofold further splitting of these resonances in the presence of the chiral shift reagents (since there are no enantiotopic pairs of protons in the molecule), are powerful evidence in favor of the predicted coexistence of two diastereoisomeric pairs of enantiomers, exchanging slowly on the NMR time scale, in solution at room temperature. Further support lies in a comparison of experimental and computed chemical shifts, which are in
Figure 3.5. HSQC spectrum of a solution of HMTD in CD$_2$Cl$_2$ containing a 3:1 molar ratio of the europium shift reagent.
remarkably good agreement, especially considering no corrections for vibration are being done.

Theory reproduces the experimental geminal $J$ couplings within 1%, and duplicates in magnitude the very small experimental difference between diastereotopic protons in the $D_3$ conformer. For the $C_2$, while it is impossible to make an absolute assignment of the three distinct methylenes in the structure to the three $^{13}$C$^1$H$_2$ spin clusters in the experimental data, the close agreement between the three sets of three measured parameters, and their computed values, makes our tentative assignment highly persuasive.

In every case, theory predicts the equatorial proton shift to lie downfield from the axial. There are no clear correlations between proton or carbon chemical shifts and bond lengths or angles, although the methylene with the largest carbon downfield shift and the largest difference between axial and equatorial proton shifts is the methylene adjacent to the ‘unique’ peroxide in the $C_2$ structure – i.e. that with the opposite O – O torsion angle from the other two. An examination of the effect of the chiral shift reagent indicates that the largest shift-reagent- induced difference between enantiomeric proton signals is in every case for the equatorial proton, and the largest differences are encountered for the ‘unique’ methylene. Significantly, there seems to be a correlation between the shift of this proton and the angle between the C – H vector and the N – N axis, with the unique methylene having the ‘most equatorial’ proton – the one with the largest angle – showing the largest chiral shift difference. This suggests that differential enantiomeric interaction between the shift reagent and HMTD is predominantly along the molecular equator. This
agrees with the molecular structure; ‘end-on’, the molecule is essentially achiral, while the band of peroxides around the equator is responsible for the chirality.

The energy difference between the two conformers, 5.9kJ/mol, is significantly greater than that computed by previous workers at a lower B3LYP/6-31G(d) level (0.3 kcal/mol or 1.3 kJ/mol). Inclusion of vibrational energies and entropies significantly reduces the difference between the two conformers, as does the $R \ln 3$ entropic contribution from the three equivalent $C_2$ structures, which is inherent in the ‘symmetry number’ of the gas-phase rotational entropy. PCM computations predict some differential stabilization of the $D_3$ conformer by solvation. While computations correctly predict that $D_3$ has a lower free energy than $C_2$, the agreement between computed and experimental free energy – 1.6 kJ/mol vs 4.0 kJ/mol – is not particularly good. (Note that the earlier energetic computations, in concert with the increased configurational entropy of $C_2$, would actually imply that it, and not $D_3$, is the stable conformer!) It is plausible that the $D_3$ form might have a 2 kJ/mol or so greater van der Waals energy of interaction with the solvent, and this could account for the computational under-estimation of the free energy difference between the two forms.

The above discussion, of course, assumes that the conformer has reached equilibrium at room temperature. In order to assure this, we attempted to obtain spectra upon rapid dissolution of the crystalline material. Although we were able to acquire data within a minute of dissolution of the material, unaltered proportions of the two conformers were detected; nor was any change in the relative intensities seen over several days at room temperature. This suggests that equilibrium is
rapidly achieved in solution at room temperature (although a possible alternative is that the crystal structure, which accommodates both $D_3$ enantiomers with 50% occupancy in an achiral lattice, can also accommodate the $C_2$ structure). It is notable that in DMSO above 40° C, the $C_2$ peaks disappear, apparently as a result of exchange with the $D_3$ form. The somewhat larger width of the $C_1$ and H1eq signals of the $C_2$ conformer, which are most distant from the $D_3$ resonances, in fact, appears to be a result of exchange on a time scale of hundreds of milliseconds, meaning that the exchange is not quite in the slow limit at room temperature. Calculations by Wierzbicki et al.,⁴ which are unfortunately given without much computational detail, give barriers of the order of 60 – 70 kJ/mol for the $C_2 - C_2$ and $C_2 - D_3$ exchange reactions, reasonable for a process that occurs on this timescale at room temperature, but more detailed kinetic studies are clearly needed.

One major disagreement of the present work with earlier computational studies lies in the origin of the nitrogen planarity. Wierzbicki and Cioffi,⁶ on the basis of a computed CNC of 117.7° for tris-(hydroperoxymethylene)amine (THPMA), concluded the planarity of the nitrogen in HMTD was a result of steric strain, since the nitrogen in THPMA is more pyramidal. Since the nitrogen in THPMA is nowhere near as pyramidal as that of trimethylamine, this conclusion is questionable in any case; but it is clear that calculations at our higher level of theory, and for a chemically somewhat superior acyclic model compound, result in a considerably more planar nitrogen than computed in the earlier work. In fact, the displacement of the nitrogen from the plane of the directly bonded carbons in TMPMA is only a quarter of that computed in trimethylamine. To a first approximation, this is a
planar, not a pyramidal nitrogen, and therefore we conclude that the major cause of nitrogen planarization in HMTD is electronic, not steric. This is not a particularly surprising observation; the difference in energies between planar and pyramidal amines is not large even in ammonia, and electron withdrawing substituents tend to stabilize the $sp^2$ hybridized planar conformation.

3.5 Conclusions

Solution NMR of achiral and chiral shift reagent containing solutions allows for the first time the spectroscopic observation of all four of the predicted helically chiral conformers of HMTD, which at room temperature in organic solvents appear to interchange on a timescale of the order of a few hundred milliseconds. DFT calculations reproduce the chemical shifts and $J$ couplings with good accuracy, lending support to the assignment of the spectra. Free-energy differences are reproduced less accurately but predict the relative stabilities correctly. The helical chirality is unusual in a molecule of this size, and it may aid in the identification of the otherwise rather simple NMR signal, particularly in the forensic examination of crude materials containing impurities.
References

2. Taylor CA, Rinkenbach WH. *Army Ordnance* 1924; **5**: 463.
Chapter 4

Slow turning reveals enormous quadrupolar interactions (STREAQI)

Summary

We introduce a new solid-state NMR method, which uses very slow sample rotation to visualize NMR spectra whose width exceeds feasible spectrometer bandwidths. It is based on the idea that if we reorient a tensor by a known angle about a known axis, the shifts in the NMR frequencies observed across the spectral width allow us to reconstruct the entire tensor. Called STREAQI (Slow Turning Reveals Enormous Anisotropic Quadrupolar Interactions), this method allows us to probe NMR nuclei that are intractable to current methods. To prove the concept and demonstrate its promise we have implemented the method for several $^{79}$Br containing samples with quadrupolar coupling constants in the range of 10–50 MHz.
4.1 Introduction

Quadrupolar half-integer-spin nuclei account for 68% of the NMR-active nuclei listed in the Handbook of Chemistry and Physics, and advances in NMR methodology over the last quarter century have made these nuclei more useful probes of the chemical and electrostatic environment in solids. Most experiments observe the central 1/2 to -1/2 transition of such nuclei, which is perturbed by the nuclear quadrupole coupling only to second (more properly even) orders. Narita et al.\textsuperscript{1} and Baugher et al.\textsuperscript{2} showed how the singularities of the second-order quadrupole perturbed central transition spectra could be used to determine the principal values of the quadrupole coupling tensor, and Kundla et al.\textsuperscript{3} computed how these powder patterns are narrowed but not eliminated under magic angle spinning. The advent of double rotation\textsuperscript{4,5}, dynamic angle spinning\textsuperscript{5,6}, MQMAS\textsuperscript{7}, and STMAS\textsuperscript{8} has provided a toolbox of useful experiments for narrowing these resonances to isotropic lines, and opened up a number of useful applications of high-resolution solid-state NMR of quadrupolar nuclei for the study of minerals, glasses, and other systems.

Unfortunately, however, there remains an extensive set of NMR nuclei whose quadrupolar couplings, even at the highest commonly accessible fields, are simply too large to be averaged by modern-line narrowing methods, or even to be contained within the effective bandwidth of modern NMR instruments. In general, such systems are still studied using static samples, and some variant of frequency sweeping. While some improvement in sensitivity has been gained by spikelet spin-
echo methods\textsuperscript{9}, in general these spectra require cumbersome acquisition of multiple free induction decays across the width of the central transition, which may be several MHz, exceeding the effective spectrometer bandwidth by a factor of ten or more. In many respects, these systems represent the last dogged holdouts, resisting the revolution in NMR that began with the implementation of Fourier transform and coherent averaging methods.

4.2 Theory

The expression for the second order quadrupolar coupling frequency for the central transition independently derived by Narita et al.\textsuperscript{1} and by Baugher et al.\textsuperscript{2} is given as equation 4.1; we will use the former authors’ angle convention:

\[
\nu_{Q}^{(2)} = \frac{9C_{Q}^{2}(2I + 3)}{16\nu_{0}I^{2}(2I - 1)}
\times \left[ \left( \frac{27}{8} - \frac{9}{4}\eta\cos 2\phi + \frac{3}{8}\eta^{2}\cos^{2} 2\phi \right)\cos^{4}\theta 
+ \left( -\frac{30}{8} + \frac{1}{4}\eta^{2} + 2\eta\cos 2\phi + \frac{3}{4}\eta^{2}\cos^{2} 2\phi \right)\cos^{2}\theta 
+ \left( \frac{3}{8} - \frac{1}{8}\eta^{2} + \frac{1}{4}\eta\cos 2\phi + \frac{3}{8}\eta^{2}\cos^{2} 2\phi \right) \right] \]  

(4.1)

with the quadrupole coupling constant \( C_{Q} = eQV_{zz} \) and the Zeeman frequency \( \omega_{0} = g\gamma B_{0} \). This formula makes clear the obvious relation between the quadrupolar-shifted transition frequency and the polar angles \( \theta, \varphi \), which define the direction of magnetic field in the frame of reference of the electric field gradient (EFG) at the nuclear site; as usual, \( V_{zz} \) and \( \eta \) are the largest principal value of the EFG tensor, and the asymmetry parameter of that tensor, respectively. Thus, the second-order shift
is directly dependent on the orientation of the EFG with respect to the field. Conversely, therefore, if one can measure the shift in the NMR frequency as a result of a defined change in EFG orientation, at more than one point in the spectrum, one can in principle infer the magnitudes of $C_Q$ and $\eta$.

Possible methods for changing the angles $\theta$ and $\phi$ include a discontinuous jump between two orientations, such has been used in dynamic-angle spinning$^{5,6}$ and magic-angle hopping$^{10}$; a field jump, implemented electronically; or slow continuous sample rotation over an extended interval, as has been implemented in the magic-angle turning experiment$^{11}$ and extensions of it$^{12}$. We have adopted the last method, largely for practical reasons: slow rotation is readily achieved using a magic-angle spinning probe; it can be carefully and precisely controlled without the wear-and-tear that results from fast, discrete jumps, and does not require shifting the direction of large magnetic fields. The disadvantage, of course, is that the experiment now departs from the ideal case discussed above, since the sample is now slowly rotating rather than static in the evolution and acquisition dimensions. In principle, the result will be to transform a single-crystallite spectrum in each dimension to a powder pattern, as was observed in the related STEAMER experiment of Hill and Yesinowski$^{13}$; Using numerical methods, we can explicitly include the effect of slow sample rotation in the evolution and acquisition dimensions. However, for heuristic reasons, we shall first consider the ‘ideal’ STREAQI experiment, in the limit of slow reorientation, by reducing the spinning speed and lengthening $t_s$, keeping the angular excursion during $t_s$ constant.
We begin our mathematical analysis of the experiment by defining the orientation of the EFG tensor with respect to the axis of reorientation, which is related to the field by the angle $\zeta$. The Euler angles relating the EFG principal axis system to the rotor frame (rotor axis along $z$; field in $xz$ plane) are $(\alpha, \beta, \gamma)$. If the sample is reoriented by an angle $\delta$ about the rotor axis, the sequence of reorientations taking the quadrupolar spin from the EFG frame to the laboratory frame (field along $z$; rotor axis in $xz$ plane) is $R_x(\alpha)R_y(\beta)R_z(\gamma)R_x(\delta)R_y(\zeta)$. If we restrict ourselves for the moment to reorientations about the magic angle ($\zeta = 54.7^\circ$), a little algebra gives us the Narita formula in terms of the new angles.

$$V_Q^{(2)} = \frac{C_Q^2(2I + 3)}{256\nu_0 I^2(2I - 1)} \times \left[ 9 - 30A_3 + 9A_3^2 - 2\eta(A_1 - A_2)(1 + 3A_3) \right] + \eta^2(-8 + (A_1 - A_2)^2 + 4A_3)$$

(4.2)

$$A_1 = \left[ \sqrt{2}(\sin x \cos \beta \cos \gamma + \cos x \sin \gamma) + \sin x \sin \beta \right]^2$$

(4.3)

$$A_2 = \left[ \sqrt{2}(\cos x \cos \beta \cos \gamma - \sin x \sin \gamma) + \cos x \sin \beta \right]^2$$

(4.4)

$$A_3 = \left( \cos \beta - \sqrt{2}\sin \beta \cos \gamma \right)^2$$

(4.5)

This describes the instantaneous frequency before the orientation. After the reorientation, the frequency is obtained with the same formula by replacing $\gamma$ with $(\gamma + \delta)$.

### 4.3 Methods

We have implemented a method for measuring this orientation-dependent shift using a standard three pulse sequence used in the EXSY/NOESY experiment\(^{14}\)
\( (90^\circ - t_1 - 90^\circ - t_s - 90^\circ - t_2) \) in which the central transition is excited, allowed to precess during \( t_s \), and alternate components of the phase-encoded magnetization stored along \( z \) using a TPPI based scheme. Following a delay \( t_s \) in which the sample orientation is changed, the changed frequencies are observed during \( t_2 \) following a third pulse. Two-dimensional Fourier transformation then maps the two frequencies onto each other.

Computed spectra using this idealized scheme are presented as surface plots in figure 4.1. Simulations assume a \( C_Q = 16 \) MHz, \( \nu_0 = 150 \) MHz, an angle jump of \( 2.4^\circ \), and asymmetry parameters of 0, 0.2, 0.4, 0.6, 0.8 and 1.0. We assume the jump is about the magic-angle; this is not an intrinsic requirement of the method, but allows the computations to be related to our experimental data, which were for practical reasons carried out in a standard MAS probe. Computed spectra consist of a series of overlapping ellipse-like ridges, with pronounced singularities at several positions along the diagonal, reminiscent of the two-dimensional exchange spectra reported by Spiess and co-workers\(^{15} \). Unlike the exchange case, however, careful mathematical analysis failed to reveal an analytical functional form \( f(\nu_1, \nu_2) \) for the ridges.
There is reasonably good correspondence with the computed spectrum, with the same pattern of singularities and pseudo-elliptical ridges.

In order to ascertain whether the differences between experiment and theory could be ascribed to the approximation of discrete jumps between static spectra in $t_1$ and $t_2$, we...

\[ \eta = 0.0 \quad 0.6 \]

\[ 0.2 \quad 0.8 \]

\[ 0.4 \quad 1.0 \]

\[ \text{Frequency (kHz)} \]

\[ 250 \quad 0 \quad -500 \]

Figure 4.1. Computed STREAQI spectra of a hypothetical substance with $C_0 = 16$ MHz, $\nu_0 = 150$ MHz, in the limit of slow-spinning at the magic angle, with a 2.4° jump during $\epsilon_s$. 
4.4 Results and Discussion

Figures 4.2(a) and (c) compare ideal and experimental STREAQI spectra of crystalline tyrosine hydrobromide, prepared by cooling a hot saturated solution of tyrosine in excess 2 M hydrobromic acid. $C_Q$ and $\eta$ were obtained by fitting the 1D powder pattern, giving $C_Q = 11.26$ MHz ($\eta = 0.86$), although it appears that in this sample there is a small chemical shielding anisotropy that affects the line- shape and positions of the singularities slightly. The two-dimensional STREAQI spectrum, obtained with the same 90° pulse length, a spinning speed of 300 Hz about the magic angle, a $t_s$ delay of 100 $\mu$s, corresponding to an angle excursion of 10.8°, and two-dimensional hypercomplex acquisition and processing\textsuperscript{16}, gave the spectrum shown. There is reasonably good correspondence with the computed spectrum, with the same pattern of singularities and pseudo-elliptical ridges.

In order to ascertain whether the differences between experiment and theory could be ascribed to the approximation of discrete jumps between static spectra in $t_1$ and $t_2$, we computed STREAQI spectra using the same parameters, but assuming continuous sample rotation during $t_1$ and $t_2$, using a fourth-order Runge–Kutta algorithm with 0.5 $\mu$s time increments to numerically evaluate the evolution of the spin system in the presence of a slowly rotating quadrupolar Hamiltonian. The result of such a simulation is shown in Figure 4.2(b).
Figure 4.2. $^{79}$Br STREAQI spectra of L-tyrosine hydrobromide, simulated using the assumption (a) of a discrete jump between two static orientations and (b) continuous sample rotation; compared with (c) an experimental spectrum, obtained as described in the text.
The agreement between simulated and experimental spectra is somewhat improved; in particular, the width of the pattern orthogonal to the main diagonal is increased in the continuous rotation simulation, compared with the discrete-jump simulation. Nonetheless, the simulated spectrum is qualitatively unchanged.

The sequence, however, likely to be most useful in circumstances where the second order pattern width is many times the spectrometer bandwidth. This is the case for leucine hydrobromide at 14 T, whose pure NQR frequency has been reported\(^\text{17}\) to be 25.35 MHz at 27 °C. Ordinary 1D NQR does not give an asymmetry parameter. However, the spin 3/2 NQR frequency

\[
v_Q = \frac{C_Q}{2} \left(1 + \frac{\eta^2}{3}\right)^{1/2}
\]

is a weak function of \(\eta\). Since \(\eta\) is likely to be similar to that of the isomorphous hydroiodide (\(\eta = 0.66\)), we expect a \(C_Q\) of around 50 MHz, relatively insensitive to error in \(\eta\). These two parameters are a good starting point for simulations.

**Figure 4.3** (c) shows the STREAQI spectrum of a sample of crystalline leucine hydrobromide, obtained by the same method used to prepare tyrosine hydrobromide, and with a spinning speed of 300 Hz, but with a STREAQI delay of 20 \(\mu\)s. This is clearly just a very small part of a 2D spectrum that extends over several MHz. Nonetheless, a clear pseudoellipse and a diagonal spine, ending in a singularity, are observed. Examination of simulated STREAQI patterns with \(C_Q\) and \(\eta\) values similar to those expected indicate that the frequencies \(v_3\) and \(v_4\), computed by Baugher et al.\(^\text{2}\) as
\[
\begin{align*}
\nu_3 &= \frac{C_Q^2 \eta^2}{48v_0} \\
\nu_4 &= \frac{C_Q^2 (1 - \eta^2)}{24v_0}
\end{align*}
\]

These likely correspond to the singularity, and the extremum of the ellipse, respectively. Using these two frequencies \(\nu_3 = 116\) kHz and \(\nu_4 = 434\) kHz, we obtained an estimated \(C_Q\) frequency of 49.0 MHz and an asymmetry parameter of 0.59. Using equation 4.6 we compute a pure NQR frequency of 25.88 MHz, in good agreement with the experimental 300 K value of 25.35 MHz. It can be seen from Figure 4.3(a), however, that the simulated STREAQI spectrum, using the ideal model, no longer gives a good fit to experimental data; clearly, the assumption of static evolution and detection periods spaced by an instantaneous jump breaks down for such large quadrupolar couplings. The spectrum simulated with continuous rotation (Figure 4.3(b)) is considerably improved, but agreement with the experimental data is still by no means perfect. This is unsurprising: the simulation does not allow for finite bandwidth or evolution during the pulses, which is likely to be a problem off-resonance. It is also likely that the implicit assumption of an isolated central transition breaks down for large quadrupole couplings, and the evolution of the full 4 \times 4 density matrix needs to be explicitly simulated.
Figure 4.3. $^{79}$Br STREAQI spectra of L-leucine hydrobromide, simulated using the assumption of (a) a discrete jump between two static orientations and (b) continuous sample rotation; compared with (c) an experimental spectrum, obtained as described in the text.
However, the location of the singularities is unchanged by these effects, and therefore a single on-resonance STREAQI pattern, or in worst cases two STREAQI patterns at different frequencies, should be adequate to determine the quadrupolar tensor magnitudes of materials whose spectral breadth greatly exceeds the spectrometer bandwidth.

4.5 Conclusions

Our analysis implicitly assumes the chemical shielding anisotropy is negligibly small; given the formally spherical bromide cation, it seems to be a reasonable assumption in the present instance, and certainly we find no evidence of a significant dispersion of isotropic or anisotropic shifts in the amino-acid hydrobromides. Inclusion of a comparable chemical shielding tensor, of course, considerably complicates the analysis. However, given the different angular dependence of the chemical shift and quadrupolar tensors, it may be possible to distinguish their influence by obtaining STREAQI spectra at different rotation angles, In fact, the 90° STREAQI experiment (rotating normal to the field), as was done in STEAMER\textsuperscript{13} and in an EPR experiment by Sierra and Schweiger\textsuperscript{18} poses some considerable theoretical advantages over magic-angle STREAQI, both in terms of sensitivity and the simplicity of the spectra. Consideration of this experiment must, however, await further research.
References

18] G.A. Sierra, A. Schweiger
Chapter 5

A Solid-State NMR and Theoretical study of Tris-dimethylthiourea Copper (I) Chloride

Summary

Copper is an important metal in many biological systems; however, very little copper NMR has been done on such systems.\textsuperscript{1,2} There is, however, a large amount of NQR and NMR data for copper in non-biological systems. Much of this is NQR data collected on high-temperature superconductor materials.\textsuperscript{3-7} Both copper and chlorine have two isotopes with spin 3/2 that are both NMR accessible, all having a high natural abundance and decent sensitivity. Having spectra of both isotopes can improve the parameters obtained from the NMR spectra because the ratios of the isotopomers of both copper and chlorine are well known.\textsuperscript{10} In this chapter, we determine the quadrupole coupling constant ($C_Q$), isotropic chemical shift ($\delta_i$) and chemical shift anisotropy ($\Delta \delta$) for the Tris-dimethylthiourea copper (I) chloride [(DMTU)\textsubscript{3}CuCl] complex for each isotopomer using first principles; an iterative ratio method that finds $C_Q$ and $\Delta \delta$, as well as quantum chemical calculations and lineshape fittings.
5.1 Introduction

Copper is an essential micronutrient for all aerobic organisms\textsuperscript{18} and is quite important in several different biological processes. These processes often involve the Cu\textsuperscript{+}/Cu\textsuperscript{2+} redox reaction in enzymes. Among the roles that copper plays in these enzymes, copper has been known to act as a chaperone to transport toxic metal\textsuperscript{18} and copper hemocyanins are used for oxygen transport in some organisms instead of iron.\textsuperscript{19} The primary importance of copper in biological systems appears in the form of oxidases.\textsuperscript{20,21} Among chief importance of these is cytochrome c oxidase, which reduces molecular oxygen to water as the last process in the respiratory chain.\textsuperscript{22} Although copper is important in many biochemical pathways, there is surprisingly little in the literature on copper NMR in biological, organic or organometallic systems, and the bulk of the information on NMR or Nuclear quadrupole resonance (NQR) in the literature is of high-temperature superconductor materials.

Copper has two naturally occurring isotopes, \(^{63}\text{Cu}\) (69.2 % abundant) and \(^{65}\text{Cu}\) (30.8 % abundant), both of which have relatively large quadrupole moments \((Q)\) of -22.0 and -20.4 fm\(^2\) and gyromagnetic ratios \((\gamma)\) of 11.2979 and 12.1027 MHz/Tesla, respectively.\textsuperscript{25} Due to its larger \(\gamma\) and smaller \(Q\), \(^{65}\text{Cu}\) is often the copper isotope of choice for high-field solid-state NMR experiments due to its smaller linewidth. However, \(^{63}\text{Cu}\) is often used as well due to its higher natural abundance, especially in NQR where the larger quadrupole moments do not cause the spectrum to have to be acquired in multiple steps. It is important to note that because copper (I) is
diamagnetic, copper (I) species are ‘silent’ to many forms of spectroscopy, thus NMR is one of the only spectroscopic tools to study them.

Early studies of $^{63/65}\text{Cu}$ NMR include solid-state studies of copper (I) halides\textsuperscript{28-30} and potassium tetracyanocuprate.\textsuperscript{31} Liquid state studies of copper (I) cyanides were studied and showed that the addition of ligands including thiourea, ammonia, chloride and urea gave an increased linewidth.\textsuperscript{32} Later studies of metal ligand binding using $^{63}\text{Cu}$ NMR showed that two- or three-coordinate copper compounds have broader lines than four-coordinate copper compounds.\textsuperscript{33}

Some of the most well studied compounds that have studied copper via NMR have been phosphines. Phosphine containing copper (I) halides have been studied by $^{31}\text{P}$ NMR and their $C_Q$s have been found indirectly by using the $^{31}\text{P}-^{63/65}\text{Cu}$ J-couplings via MAS NMR.\textsuperscript{23} Similar copper (I) nitrate derivatives of triphenylphosphine have been studied in much the same way.\textsuperscript{24,27} A study of potassium tetracyanocuprate by $^{63/65}\text{Cu}$ MAS NMR showed the first experimental evidence of an anisotropic chemical shielding in copper. It was also observed in these studies that the quadrupole coupling constant ratio of the copper isotopes ($^{63}\text{Cu}/^{65}\text{Cu}$) was 1.081, which is in agreement with the known value.\textsuperscript{34} Further solid-state NMR studies on a series of bis-triphenylphosphine copper (I) species using a frequency-stepped method with the WURST-QCPMG pulse sequence were conducted and $^{65}\text{Cu}$ NMR spectra were obtained, along with $C_Q$ and $\eta_Q$ values.\textsuperscript{35,36} In addition to phosphine derivatives, the coordination environment of copper was
probed by $^{63/65}\text{Cu}$ MAS NMR by using phosphorous-chalcogenide copper iodide coordination compounds.\textsuperscript{41}

Non-phosphorus containing organometallic copper compounds have been studied using the same WURST-QCPMG method, but both isotopes were used instead of just $^{65}\text{Cu}$. $^{63}\text{Cu}$ and $^{65}\text{Cu}$ SSNMR spectra were collected for organometallic copper complexes of different coordination numbers, and $C_Q$, $\eta$, and chemical shifts were found. $^{65}\text{Cu}$ MAS and powder static NMR studies were also conducted on copper (I) halide tert-butyl isocyanide adducts\textsuperscript{42}, and $^{63}\text{Cu}$ NMR was used to study the effects of the addition of CO to tridentate copper ligands.\textsuperscript{43} Kinetics has also been studied using time-resolved MAS $^{63}\text{Cu}$ NMR. The rate of interconversion of the $\alpha$- and $\beta$-phases of CuAlCl\textsubscript{4} was shown to be first-order and involve no intermediate phases.\textsuperscript{37}

The $[(\text{DMTU})_3\text{CuCl}]$ complex was first studied by NQR in the early 1970’s. The study found a ratio of $C_Q$s to be approximately 1.05 ($^{63}\text{Cu}/^{65}\text{Cu}$),\textsuperscript{8} which is in sharp contrast to the currently accepted value from microwave spectroscopy of 1.08.\textsuperscript{26}

The chemical shielding ($\sigma$) in Hertz for any given nucleus is proportional to the gyromagnetic ratio of said nucleus, while the $C_Q$ is proportional to a its quadrupole moment. These facts combine to give slightly different central-transition spectra of various isotopes of quadrupole nuclei. We have exploited this fact to extract values for the electric field gradient and chemical shielding tensor principal values at the copper and chlorine sites for the trigonal complex tris-dimethylthiourea copper (I) chloride $[\text{Cu(DMTU)}_3\text{Cl}]$. We can obtain these NMR parameters based on the
analysis of the characteristic singularities of the powder static spectra of various isotopes of $I = 3/2$ nuclei. This work represents solid-state NMR and theoretical studies of copper and chlorine in what can be considered a biological analogue and can be relevant to future studies of copper-containing biological molecules.

Detailed structural information for this complex can be found in figure 5.1(a), which shows an axial view of the complex (looking down the symmetry axis), and figure 5.1(b), which shows a side view of the complex. The three-fold symmetry of the complex dictates that it is axially symmetric and, therefore, the $\eta$ is equal to zero. This is relevant in that any deviations from the standard quadrupolar line shape one would expect from the powder static SSNMR pattern of a $I = 3/2$ nuclei will likely be attributed to influence from chemical shielding anisotropy.

High quality $^{63}\text{Cu}$, $^{65}\text{Cu}$, $^{35}\text{Cl}$ and $^{37}\text{Cl}$ central transition spectra were obtained and the line shapes analyzed through various means. From first principles we derived analytical expressions for the three frequency singularities ($\nu_0$, $\nu_{90}$, and $\nu_{\text{max}}$) of an $\eta = 0$ powder pattern, as a function of the isotropic chemical shift ($\delta$), the chemical shift anisotropy ($\Delta\delta$), and $C_Q$. Solving for these NMR parameters, we obtained equations that were dependent on the frequency of these line shape singularities. Employing a least squares fit method, we fit the singularities of each spectrum as a function of the angle $\theta$ to determine if the line shape had any significant deviation from a standard quadrupolar line shape. Due to the fact that we have three variables and three unknowns, a single spectrum is in principle sufficient to determine these values, significantly easing the interpretation of NMR line shapes.
However, the availability of two isotopes makes possible much better statistical rigor.

To confirm the results as obtained by this line shape analysis method, we employed the well-established fact that isotopes of a given quadrupole nucleus have well-known and oft published constant ratios of their quadrupole coupling parameters. An extensive literature search showed that the expected ratio for copper ($^{63}\text{Cu}/^{65}\text{Cu}$) is expected to be 1.08 while the chlorine ratio ($^{35}\text{Cl}/^{37}\text{Cl}$) is 1.27. Utilizing an equation we derived for the line shape fitting of the central transition ($\nu_0 - \nu_90$), we varied the magnitude of the chemical shielding anisotropy until the appropriate ratios of the quadrupole coupling constants were obtained. The results from this ratio method agreed within error to those obtained strictly by lineshape analysis.

In an attempt to provide theoretical NMR parameters that agreed well with our experimental results, we employed ab initio calculations. Despite maximizing the basis sets of the nuclei of interest and minimizing the basis sets of other non-contributing atoms in an attempt to reduce computational time, we were unable to obtain corresponding theoretical measurements of our NMR parameters. Obtaining theoretical NMR parameters that match well with those obtained experimentally has long been an issue in the field of NMR spectroscopy. This problem is only exacerbated in the analysis of nuclei with large electronic contributions (i.e. copper).
5.2 Experimental Methods

5.2.1 Sample preparation. Tris-dimethylthiourea copper (I) chloride was prepared by the method described by Amma, in which freshly prepared CuCl is suspended in a solution of dimethylthiourea and water. The resultant solution is filtered and dried. CuCl was prepared by heating CuCl₂ (Sigma-Aldrich) and copper granules in a hot solution of 12.1 M HCl until it turned clear. The liquid is decanted into a tall column of cold distilled water, where the white powder precipitates immediately. The crystals are then dried and stored over dry sulfuric acid until needed.

5.2.2 Solid-state NMR. Powder static NMR was performed on the central transition of ⁶³Cu, ⁶⁵Cu, ³⁵Cl and ³⁷Cl on a Bruker AVANCE spectrometer operating at 14 T, using a home-built probe with a silver coil for the copper spectra to avoid any signal coming from the coil itself. The frequencies of each isotope at this field strength are 159.03 MHz for ⁶³Cu, 170.37 MHz for ⁶⁵Cu, 58.79 MHz for ³⁵Cl and 48.93 MHz for ³⁷Cl. The 90° pulse length for this probe was found to be 1.5 μs for ⁶³Cu, 1.3 μs for ⁶⁵Cu, 2.4 μs for ³⁷Cl and 2.75 μs for ³⁵Cl. A Hahn echo pulse sequence was used with a recycle delay of 100 ms and delays of 40 μs between pulses and 30 μs after the refocusing pulse. Pulse lengths were reduced by a factor of 2 for all pulses. This is because the pulse length that corresponds to the maximum intensity for the central transition is shorter than the pulse length needed to excite all of the transitions. All four isotopes were referenced to CuCl and are shown in figures 2 and 3. Figures 5.2(a) and 5.2(b) show chlorine spectra, and figures 5.3(a) and 5.3(b) show copper spectra. A notable aspect of the ⁶³Cu central transition spectrum is the isotropic
Figure 5.1. (a) Shows a top-down view of the [(DMTU)$_3$CuCl] complex, while (b) shows a side view.
Figure 5.2. (a) The central transition of the \([\text{DMTU}]_3\text{CuCl}\) complex for \(^{35}\text{Cl}\). (b) The central transition of the \([\text{DMTU}]_3\text{CuCl}\) complex for \(^{37}\text{Cl}\).
Figure 5.3. (a) The central transition of the [(DMTU)$_3$CuCl] complex for $^{63}$Cu. (b) the central transition of the [(DMTU)$_3$CuCl] complex for $^{65}$Cu.
peak that occurs at about -300 kHz. This is due to sodium from the glass of the tube
the sample. $^{23}\text{Na}$ has a resonance frequency at 14T of about 158.71 MHz. This peak
has been ignored in all fits is not included in the figures.

5.2.3 **Theoretical calculations.** The (DMTU)$_3$CuCl complex was optimized using
GAMESS$^{12}$ with Gaussian$^{13}$ being used to calculate the field gradients and chemical
shieldings which were done at both the Self-Consistent Field (SCF) and Møller-
Plesset second order perturbation theory (MP2) levels of theory. The basis sets
used for all calculations was the following: AUG-cc-pVTZ for copper, AUG-cc-pVDZ
for chlorine and sulfur, 6-31G(d,p) for amino hydrogen atoms, 6-31G(d) for non-
methyl carbon atoms, 3-21G for nitrogen, methyl carbon atoms and methyl
hydrogen atoms. The basis sets were chosen this way (large basis sets for Cu, Cl,
and S, and smaller basis sets for atoms that are further away from Cu and Cl).

5.3 **Theory and Calculations**

$^{35,37}\text{Cl}$ and $^{63,65}\text{Cu}$ central transition spectra of the (DMTU)$_3$CuCl complex are
shown in figures 5.2 and 5.3 respectively. The most prominent features of these
spectra are the three singularities, which tell us that this complex is in fact $\eta = 0$. If $\eta$
were $\neq 0$, the lineshape would be more complicated, and feature more singularities.
These singularities each correspond to the angle that the principal axis a given
crystallite is at with respect to $B_0$. We can find these angles using the fact that the
spectrum is dominated by second order quadrupole and chemical shift interactions.
The angular dependence of a second order quadrupole interaction is:
whereas the angular dependence of the chemical shift varies as

\[ \sigma = \frac{\Delta \sigma}{2} (1 - 3 \cos^2 \theta) \]  

(5.2)

In fact, the chemical shift term is very small compared to the quadrupole, and thus has little contribution to the angle. To find the zeroes of the combined equations, we sum them to give equation 5.3, and the derivative is given as equation 5.4:

\[ (V_{1/2}^{(2)} + \sigma) = \frac{3C_Q^2}{64\omega_0} (1 - 10 \cos^2 \theta + 9 \cos^4 \theta) + \frac{\Delta \sigma}{2} (1 - 3 \cos^2 \theta) \]  

(5.3)

\[ \frac{d(V_{1/2}^{(2)} + \sigma)}{d\theta} = \left( \frac{15C_Q^2}{16\omega_0} + \frac{3}{2} \Delta \sigma \right) \sin \theta \cos \theta + \frac{27C_Q^2}{16\omega_0} \cos^3 \theta \sin \theta \]  

(5.4)

For a pure quadrupolar system \( \Delta \sigma = 0 \); setting the derivative equal to zero and solving gives crystallite angles of \( \theta = 0^\circ, 90^\circ, \) and \( 41.81^\circ \). Due to the small contribution of the chemical shift, we find that the when \( \Delta \sigma \) is included, the third angle deviates only slightly (\( 41.45^\circ \) vs. \( 41.81^\circ \)) from that observed with a pure second order quadrupole. Fits were slightly improved using this corrected angle.

### 5.3.1 First principles

From first principles we can construct a set of equations that correspond to the frequencies of the singularities of the spectrum. These are given as equations 5.5, 5.6 and 5.7, where each of the equations represent the frequency of a singularity.
Since the frequencies are known to us, what is more useful are the versions of these equations that are solved for \( C_Q \), \( \delta_i \) and \( \Delta \delta \), which are given as equations 5.8, 5.9 and 5.10 respectively.

\[
C_Q = \frac{64}{27} \left( \omega_0 v_{90} + v_0 - 2v_{\text{max}} \right) + \frac{128}{27} \sqrt{\omega_0^2 (v_{90}v_0 - v_{90}v_{\text{max}} + v_{\text{max}}^2)}
\]  \hspace{1cm} (5.8)

\[
\delta_{\text{iso}} = \frac{1}{27} \left( 16v_{90} + 7v_0 + 4v_{\text{max}} - 4\sqrt{(v_{90} - v_{\text{max}})(v_0 - v_{\text{max}})} \right)
\]  \hspace{1cm} (5.9)

\[
\Delta \delta = \frac{2}{9} \left( 4v_{90} - 5v_0 + v_{\text{max}} - \sqrt{(v_{90} - v_{\text{max}})(v_0 - v_{\text{max}})} \right)
\]  \hspace{1cm} (5.10)

The frequency values from the spectra can then be plugged into equations 5.8 – 5.10 along with the spectrometer frequency \( (\omega_0) \) to get the values of \( C_Q \), \( \delta_i \) and \( \Delta \delta \). These equations were used in a least squares fitting of the experimental data, as well as used in the ratio method.

**5.3.2 Ratio method.** In addition to an analytical solution given by the equations above, a second method using the aforementioned \( C_Q \) ratios for copper and chlorine was used to supplement the analytical solutions. In this method the width of the pattern (in kHz) is set equal to \( (v_{90} - v_{\text{max}}) \), with the isotropic shift cancelling. When
we subtract equation 5.7 \( (\nu_{\text{max}}) \) from equation 5.6 \( (\nu_{90}) \), we get the following equation for the difference.

\[
\nu_{90} - \nu_{\text{max}} = \frac{1}{3} \Delta \delta + \frac{3C_Q^2}{64\omega_0} + \frac{1}{108} \left( 24 \Delta \delta + \frac{64 \Delta \delta^2 \omega_0}{C_Q} + \frac{9C_Q^2}{\omega_0} \right)
\]

(5.11)

This leaves two free parameters \( C_Q \) and \( \Delta \delta \). We can plug in the numerical value for the splitting (for example 100 kHz) into equation 5.11 and solve for \( C_Q \). Equation 5.12 shows this where \( \nu_{90} - \nu_{\text{max}} = 100 \) kHz.

\[
C_Q = 19067.2 \sqrt{180,000 + 600\sqrt{90,000 - \Delta \delta - \Delta \delta}}
\]

(5.12)

A test value of \( \Delta \delta \) is chosen, and plugged into equation 5.12 generating a \( C_Q \) value for each isotopomer. The ratio of the each \( C_Q \) was found \( ^{63}\text{Cu} / ^{65}\text{Cu} \), and \( ^{35}\text{Cl} / ^{37}\text{Cl} \), and if the calculated ratio matched the correct ratio, the \( C_Q \) values are accepted, and if not the value of \( \Delta \delta \) is changed and the \( C_Q \)s are recalculated until the correct ratio of 1.08:1 for \( ^{63}\text{Cu} / ^{65}\text{Cu} \) or 1.27:1 for \( ^{35}\text{Cl} / ^{37}\text{Cl} \) is reached\(^{15,16}\).

**5.3.3 Lineshape fittings.** Experimental lineshapes were fit using a program by Massiot.\(^{14}\) The linefits for chlorine are shown in figures 5.4(a) and (b), and the linefits for copper are shown in figures 5.5(a) and (b). For the linefits two built-in functions of the program were used. The first called “Q stat-1/2” fits the lineshape of a half-integer quadrupolar spin system. This is a first-order quadrupolar spectrum that includes no chemical shift dependence. To correct this the method
“int2Quad” was used to fit the second order pattern and introduce a $\Delta \delta$ element.

Table 5.3 shows results for the line fits done by this method.

5.4 Results and Discussion

5.4.1 Least Squares Fit. $C_Q$ values for the experimental method came out to be 20.15 MHz and 18.67 MHz for $^{63}$Cu and $^{65}$Cu respectively, and 9.66 MHz and 7.54 MHz for $^{35}$Cl and $^{37}$Cl respectively. All values are given in table 5.1. As expected the isotropic chemical shifts for copper were very close with a value of 359.8 ppm for copper. The shift anisotropy for copper is 55.6 ppm. Chlorine has a large $\delta_i$ of about 502 ppm and a quite small $\Delta \delta$ of about 15 ppm. Although this calculated $\Delta \delta$ result shows some chemical shift anisotropy, in reality, the central singularity is obscured by an isotropic chloride peak, perhaps from HCl from the preparation of CuCl, and any $\Delta \delta$ for chlorine cannot be determined with any certainty.

5.4.2 The ratio method. The $C_Q$s for copper obtained from this method were 20.37 MHz for $^{63}$Cu and 18.86 MHz for $^{65}$Cu, with $\Delta \delta$ values of 25.1 and 23.5 ppm respectively. For chlorine the $C_Q$s were 9.65 MHz for $^{35}$Cl and 7.60 MHz for $^{37}$Cl and
Figure 5.4 (a) The linefit of the central transition of the [(DMTU)₃CuCl] complex for ⁳⁵Cl. (b) The linefit of the central transition of the [(DMTU)₃CuCl] complex for ⁴⁰Cl.
Figure 5.5(a) shows the linefit of the central transition of the \([(\text{DMTU})_3\text{CuCl}]\) complex for $^{63}\text{Cu}$. (b) The linefit of the central transition of the \([(\text{DMTU})_3\text{CuCl}]\) complex for $^{65}\text{Cu}$.
Table 5.1 Quadrupole coupling constant ($C_Q$), isotropic chemical shift and chemical shift anisotropy as calculated using a least squares fit.
the Δδ values were 34.0 and 40.9 ppm for $^{35}$Cl and $^{37}$Cl. This data is tabulated in Table 5.2.

5.4.3 Quantum calculations. $C_Q$ values computed using Hartree-Fock methods did not agree well with experiment, particularly for copper. The quantum calculation data is given in table 5.3. More rigorous computations employing Møller-Plesset second-order perturbation theory give quite good $C_Q$ values for both chlorine isotopes, but slightly worse values for copper. Isotropic shielding values for both copper and chlorine are significantly greater than experimental values, as are the anisotropies. Tables 5.5 and 5.6 show results of Hartree-Fock calculations for isotropic chemical shieldings at different basis sets.

5.4.4 Lineshape fittings. Line fitting analysis by the method of Massiot is somewhat consistent with the least squares fit and the ratio method. $C_Q$ values for chlorine are larger than either the ratio or least squares methods, as are the copper $C_Q$ values to a lesser degree. Lineshape fitting values for fit parameters are given in table 5.4. Both copper and chlorine isotropic shifts calculated by this method show fairly good agreement with those from the least squares method. Shift anisotropies for copper are all off by a sign, and chlorine shift anisotropies are indeterminate, due to the isotropic chloride peak. These results can be considered to be less accurate due to the fact that the whole lineshape is fit, instead of just the singularities as in the least squares method.
<table>
<thead>
<tr>
<th></th>
<th>$^{35}\text{Cl}$</th>
<th>$^{37}\text{Cl}$</th>
<th>$^{63}\text{Cu}$</th>
<th>$^{65}\text{Cu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_Q$ (MHz)</td>
<td>9.65</td>
<td>7.60</td>
<td>20.37</td>
<td>18.86</td>
</tr>
<tr>
<td>$\Delta\delta$ (ppm)</td>
<td>34.0</td>
<td>40.9</td>
<td>25.1</td>
<td>23.5</td>
</tr>
</tbody>
</table>

**Table 5.2** Quadrupole coupling constant ($C_Q$) and chemical shift anisotropy as calculated from the ratio method.
<table>
<thead>
<tr>
<th></th>
<th>$^{35}\text{Cl}$</th>
<th>$^{37}\text{Cl}$</th>
<th>$^{63}\text{Cu}$</th>
<th>$^{65}\text{Cu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_Q$ – HF (MHz)</td>
<td>4.82</td>
<td>3.8</td>
<td>27.0</td>
<td>25.1</td>
</tr>
<tr>
<td>$C_Q$ – MP2 (MHz)</td>
<td>10.0</td>
<td>7.9</td>
<td>28.4</td>
<td>26.3</td>
</tr>
<tr>
<td>$\Delta\sigma$ (ppm)</td>
<td>112</td>
<td>112</td>
<td>289</td>
<td>289</td>
</tr>
<tr>
<td>$\sigma$ (ppm)</td>
<td>1122</td>
<td>1122</td>
<td>590</td>
<td>590</td>
</tr>
</tbody>
</table>

**Table 5.3** Quadrupole coupling constant ($C_Q$), chemical shielding anisotropy and isotropic shielding as obtained from quantum chemical calculations.
<table>
<thead>
<tr>
<th></th>
<th>(^{35}\text{Cl})</th>
<th>(^{37}\text{Cl})</th>
<th>(^{63}\text{Cu})</th>
<th>(^{65}\text{Cu})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_Q) (MHz)</td>
<td>9.84</td>
<td>7.72</td>
<td>20.24</td>
<td>18.80</td>
</tr>
<tr>
<td>(\Delta \delta) (ppm)</td>
<td>-</td>
<td>-</td>
<td>-53.3</td>
<td>-50.0</td>
</tr>
<tr>
<td>(\delta_i) (ppm)</td>
<td>521.1</td>
<td>510.3</td>
<td>360.5</td>
<td>358.1</td>
</tr>
</tbody>
</table>

**Table 5.4.** Quadrupole coupling constant \((C_Q)\), isotropic chemical shift and chemical shift anisotropy as determined from lineshape fittings using the method of Massiot.
<table>
<thead>
<tr>
<th>Basis Set</th>
<th>Chlorine</th>
<th>Copper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUG-cc-pVDz</td>
<td>1099.2709</td>
<td>1010.7473</td>
</tr>
<tr>
<td>AUG-cc-pVTz</td>
<td>1096.8779</td>
<td>1041.2411</td>
</tr>
</tbody>
</table>

**Table 5.5** Isotropic chemical shielding in ppm calculated at the Hartree-Fock level with the given basis set for all atoms.

<table>
<thead>
<tr>
<th>Basis Set</th>
<th>Copper Isotropic Chemical Shielding (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUG-cc-pVTz</td>
<td>1066.0127</td>
</tr>
<tr>
<td>AUG-cc-pVQz</td>
<td>1060.0527</td>
</tr>
<tr>
<td>AUG-cc-pV5z</td>
<td>1063.7744</td>
</tr>
</tbody>
</table>

**Table 5.6** Copper isotropic chemical shielding calculated at the Hartree-Fock level with the given basis set for copper. Basis sets for other atoms as described in the text.
5.5 Conclusion

In summary, we have shown that the quadrupole coupling constant, and isotropic and anisotropic chemical shifts for all four isotopomers can be found for tris-dimethylthiourea copper (I) chloride using powder static solid-state NMR, with the use of several data analysis techniques to improve accuracy. MP2 calculations for the quadrupole coupling constant of chlorine isotopes showed good agreement with the NMR data, but calculated copper $C_Q$s were off by several MHz. $C_Q$ values between the other methods used agree quite well with each other, as do the $\delta_i$ values between Massiot’s method and the least squares method for copper. The isotropic shift for chlorine matches well between the least squares method and the lineshape fittings, however any chlorine shift anisotropies are indeterminate due to the obscured singularites.
References


Chapter 6

Conclusions and Summary

To conclude, NMR may be used to probe many molecular properties and give insight into the symmetry of a system being studied. This is particularly true in solids where anisotropic effects, which can be used to learn about the structure and bonding, may be obtained for a variety of systems. Also, NMR may be combined with theoretical methodologies to make predictions about a system and enhance results. Throughout this dissertation there are many different ways that NMR and computations are used. Both solid and liquid state NMR are used, and nuclei ranging from standard spin−1/2 nuclei (\(^1\)H, \(^{13}\)C) to spin−1 nuclei (\(^{14}\)N, \(^2\)H) to more exotic spin−3/2 nuclei (\(^{35}\)Cl, \(^{37}\)Cl, \(^{63}\)Cu, \(^{65}\)Cu, \(^{79}\)Br, \(^{81}\)Br and unintentionally \(^{23}\)Na). The computational techniques used include \textit{ab initio} and DFT calculations, as well as lineshape simulations and lineshape fittings. Together, these techniques combine to give better insight into nuclear properties and how they relate to the structure and function of molecules.

In chapter two, \(^{14}\)N solid-state NMR is used to study the peroxide explosive HMTD. This compound was allegedly used in the London train bombings in 2005. The frequency of the transmitter was moved to map out the Pake doublet, for which edges were found at approximately 41.406 and 45.406 MHz. The edges were fit to Pake doublets and the \(C_Q\) was found to be 5.3346 MHz using \(\eta = 0\) and calculating to second order quadrupole. The axial symmetry shows that HMTD does indeed have
3-fold symmetry, as shown by the crystal structure. Quantum chemical calculations for HMTD show good correlation with experiment at the MP2 level. Calculations on non-cyclic HMTD analogs, however, show that MP2 methods overestimate electron correlation while B3LYP underestimates it by an even larger factor, thus higher-level electron correlation methods should be used for $^{14}$N in these types of systems.

Chapter 3 treats the same compound, HMTD but in the liquid state instead of the solid. In the solid-state, HMTD is known to be a racemic mixture of helically-chiral $D_3$ enantiomers. However, in the liquid form there has been a pair of $C_2$ conformers predicted. In this chapter, it is shown through the use of 2D NMR and computational methods that both sets of conformers exist in solution at the same time. Using a $^1$H–$^{13}$C HSQC experiment and the introduction of chiral shift reagents, all four conformers were confirmed present in solution.

In chapter 4, we introduce a novel two-dimensional solid-state NMR experiment based on the combination of MAS-NMR and the NOESY pulse sequence, called STREAQI (Slow-Turning Reveals Enormous Quadrupole Interactions). A common issue when doing solid-state NMR of higher spin systems is that the spectrum is much wider than the probe response. The STREAQI method takes advantage of slow spinning to get such spectra in one window, instead of several. This can be done through the analysis of the ellipsoidal shape of the STREAQI spectrum and relating its frequencies to the singularities of a standard 1D lineshape. $^{79}$Br STREAQI spectra were collected for 3 different amino acid hydrobromides and show fairly good agreement with expected values. Lineshape simulations aided in
the analysis and showed fairly good correlation to experimental results. Overall, the
STREAQI method seems to work well for these systems, but further
experimentation is needed to see how well it would work for other systems.

Copper NMR data for copper in biological systems or analogs pales in
comparison to the amount of copper NMR and NQR that has been done on inorganic
systems. In chapter 5 the 3-fold symmetric dimethylthiourea copper (I) chloride
complex is used as an analog for copper in a biological system. Solid-state NMR of
the central transitions was collected for both isotopes of copper and chlorine.
These were analyzed in 3 different ways: first by use of a least squares method,
secondly using an iterative ratio method, and thirdly by doing line fitting analysis.
$C_Q$ values for all three of these methods agree fairly well, but the anisotropic
chemical shift values do not, especially for chlorine, where a large isotropic chloride
peak obscures the central singularity. Theoretical calculation results are mixed,
with some $C_Q$ values for chlorine showing good results. All calculated $C_Q$ values for
copper are high compared to experiment. To achieve better computational results,
higher electron correlation methods should be used in place of MP2 or HF
calculations, especially for copper.