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1H NMR Relaxation in Urea

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Abstract:

Proton NMR spin-lattice relaxation times $T_1$ were measured for urea as a function of temperature. An activation energy of $46.3 \pm 4.7$ kJ/mol was extracted and compared with the range of 38-65 kJ/mol previously reported in the literature as measured by different magnetic resonance techniques. In addition, proton NMR spin-lattice relaxation times in the rotating frame $T_{1p}$ were measured as a function of temperature. These measurements provide acquisition conditions for the $^{13}$C and $^{15}$N CP/MAS spectra of pure urea in the crystalline phase.

Key Words:

NMR; $^1$H NMR; $^{13}$C CP/MAS; $^{15}$N CP/MAS; spin-lattice relaxation; $T_1$; $T_{1p}$; activation energy; urea.
Introduction

Urea is a natural product, being the principal nitrogen-containing decomposition product of proteins. Synthetic urea is widely used in making fertilizers and urea-formaldehyde resins and is also used as a feed supplement for livestock. It is produced commercially on the scale of $10^8$ tons per year. Desseyn and co-workers [1] provide an interesting overview of the scientific history of urea, including its isolation by Rouelle in 1773 and its synthesis from inorganic materials by Wöhler in 1828, along with a discussion of its many industrial uses.

Due to its scientific and commercial importance, the molecular structure and dynamics of urea have been investigated with a variety of techniques by numerous researchers since it was first isolated. An active research topic in the mid-twentieth century was establishing the planar structure of urea in the solid-state. The X-ray crystal structure [2] showed that the heavier C, N, and O atoms of each urea molecule lie in a plane with the position of the hydrogen atoms only inferred since these are too light to scatter X-rays. Spectroscopic evidence for the planar structure of urea in the solid state arose from the frequency analysis of infrared spectra of oriented urea crystals [3,4] obtained with plane-polarized radiation. Second moment analysis of proton nuclear magnetic resonance (NMR) spectra of oriented urea crystals [5] provided additional spectroscopic evidence for the planar structure. The planar structure has since been confirmed by both neutron [6] and synchrotron diffraction [7] studies.

An interesting aspect of this solid-state structure is the rare occurrence of a single O atom accepting four N-H···O hydrogen bonds. The packing of the molecules in the urea crystal is largely determined by this hydrogen bonding. The molecules are linked in a head-to-tail fashion along the tetragonal $c$-axis. This molecular chain is surrounded by four identical chains. Each of these is orthogonally oriented such that they point in the opposite sense along the $c$-axis. This results in a relatively open structure, as the chains form channels with a square cross-section of roughly 0.4 nm x 0.4 nm [2,6,7].

The molecular symmetry indicates that the two types of allowed rotations are reorientation about the C=O bond and reorientation of each -NH$_2$ group around the C-N bond. The effects of the $C_2$ rotation about the carbonyl bond direction are observed in the temperature dependence of magnetic resonance spectra. Activation energies reported for this motion are 38 kJ/mol, from analysis of the variation of the $^1$H NMR second moment with temperature [8], 46 ± 8 kJ/mol, from single-crystal $^2$H NMR [9], 49 ± 8 kJ/mol, from $^{14}$N nuclear quadrupole resonance (NQR) [10], and 65 ± 5 kJ/mol, from $^2$H NMR relaxation measurements [11]. On the other hand, the activation energy for rotation about the C-NH$_2$ bond has been reported to be 63 ± 13 kJ/mol from analysis of single-crystal $^2$H NMR line shapes [9], and 77 ± 8 kJ/mol from $^2$H NMR relaxation measurements [11].

The single-crystal $^2$H NMR line shape [9] indicates that, at room temperature, the molecule is static, whereas high-temperature spectra could be explained by assuming a thermally activated reorientation about the carbonyl bond. The $^{14}$N NQR study [10] also supports the presence of this reorientation about the carbonyl bond. The onset of reorientation around the C-N bond is not indicated at T < 110º C by the single-crystal $^2$H NMR study [9]. Urea melts (decomposes) around 135º C [11].

By measuring the line widths and second moments of $^1$H NMR spectra, Kromhout and Mouton [12] detected a dynamic transition in urea around 40-50º C. These changes
in line width and second moment were attributed to the onset of rotation of the -NH$_2$ groups about the C-N bond. Applying an extension of the Bloembergen, Purcell, and Pound theory [13], they determined an activation energy of 39.4 kJ/mol for this process. These authors argued that the reduction of the second moment by a factor of 0.33 is evidence that the transition involves the onset of rotation of the amine groups because this approximately equals the expected reduction factor of 0.25 for the onset of rapid reorientation about the C-N bond. No arguments were presented to rule out other motions, such as reorientation about the carbonyl bond.

Das [14] developed an analytic theory for the frequency of tunneling through high periodic barriers and applied it to various solid-state NMR data, including those of Kromhout and Mouton [12]. Applying his theory for hindered rotation through twofold barriers to their data yielded an activation energy of 53 kJ/mol. In Das' discussion of the barrier heights for the rotation of the -NH$_2$ group about the C-N bond, his calculated barrier for this rotation was so much higher that he presumed that the experimentally observed line narrowing was "caused by a rolling motion about the C-O axis which preserves the planarity of the whole molecule." However, Das later published an erratum [15] in which he corrected his theoretical calculation for this barrier and concluded that the height of the potential barrier hindering the motion of a -NH$_2$ group about the C-N bond is in good agreement with that obtained from the experimental data of Kromhout and Mouton [12].

Emsley and Smith [8], however, thought that other evidence from $^1$H NMR spectra and specific heat measurements suggested a different explanation of the dynamic changes in urea. The spectroscopic evidence [3-5] suggested that the equilibrium positions for the protons are in the molecular plane. Considering this, they noted that twofold reorientations about the C-N bond could not account for the large reduction in the second moment since such motions would change neither the magnitude nor the direction of the shortest interproton vector. Their study of the angular variation of the second moment of a single-crystal sample showed that the molecular motion responsible for the line-width transition in urea is hindered rotation about the carbonyl bond between two equilibrium positions related by the mirror plane perpendicular to the plane of the molecule.

The work of Emsley and Smith [8] clearly showed that reorientation about the C=O bond is the dominant molecular motion for the line-width transition in the range of 40-50°C. Chiba's single-crystal $^2$H NMR study [9] showed that reorientation around the C-N bond is important above 110º C. The onset of reorientation about the C=O bond around ambient temperature with reorientation around the C-N bond above 110º C is currently the generally accepted description of molecular motion within urea in the solid state.

Urea is still a subject of interest in various areas of research. For example, the structural, dynamic and chemical properties of "conventional" inclusion compounds formed between urea and guest molecules, as well as inclusion compounds formed from stoichiometric cocrystals of urea hydrogen-bonded with various dicyanobutanes [16], can be compared with the pure crystalline phase of urea. Urea is also a potential reducing agent for the selective catalytic reduction of NO$_x$ and has been studied when supported on various zeolites [17]. In addition, molecular interactions and motions of urea adsorbed on cotton cellulose have been investigated, "since this system may be of interest to both
the textile and detergent industries as urea is both used in fabric processing and is a constituent of human sweat and urine that interacts with carbon fibers” [18]. While solid-state NMR techniques are used to study such systems, the standard cross-polarization/magic angle spinning (CP/MAS) experiment applied directly to pure crystalline urea with natural isotopic abundances is challenging (Vide infra). In fact, reported NMR measurements for pure urea in such studies are often from solution NMR [17] or from isotopically labeled compounds [18], rather than from urea with natural isotopic abundance in the solid state.

Urea has also been used as a model compound for analysis of $^1$H-$^{14}$N polarization transfer experiments in molecular crystals [19]. While $^{14}$N NQR can be used to detect nitrogen (often in the form of nitro groups) found in most explosives, compounds such as trinitrotoluene (TNT) pose detection problems when the NQR frequencies are below 900 kHz [20,21]. As an alternative to NQR, $^1$H-$^{14}$N cross-relaxation is being investigated to increase detection sensitivity to such explosives.

The history of studies of urea provides three reasons to revisit urea and, in particular, to look at the $^1$H NMR relaxation. First, given the wide range of activation energies (38-65 kJ/mol) reported in the literature for motion involving $C_2$ rotation of the whole molecule about the carbonyl axis, use of a different magnetic resonance technique, i.e., $^1$H NMR spin-lattice relaxation, should provide a measurement that narrows the range of uncertainty in the activation energy. Second, analysis of proton relaxation provides suitable acquisition parameters for $^1$H cross-polarization transfer to rare-spin nuclei such as $^{13}$C and $^{15}$N in urea at natural isotopic abundance. Third, such data provide the basis for understanding the lattice dynamics and spin interactions, since relaxation processes were not included in the previous theoretical treatment [19].

Experimental

The NMR data were acquired with a Bruker Avance 300 spectrometer using a standard Bruker MAS probe with a 4 mm (outside diameter) zirconia rotor. The $^1$H spin-lattice relaxation ($T_1$) data were acquired with an inversion recovery sequence ($\pi - \tau - \pi/2 - \text{acquire}$) [22] while for the $^1$H spin-lattice relaxation in the rotation frame ($T_{1\rho}$), data were acquired with a spin-locking sequence ($\pi/2_x - (\text{spin lock})_y$) [22]. The $^1$H $\pi/2$ pulse width was 4 $\mu$s.

The $^{13}$C and $^{15}$N CP/MAS [23] spectra were acquired with a $^1$H $\pi/2$ pulse width of 4 $\mu$s, a contact time of 0.5 ms, a data acquisition time of 65 ms, and a recycle delay of 5 hours. The sample spin rate was 5 kHz. Sample temperatures were calibrated with $^{207}$Pb NMR of lead nitrate [24-26].

Results and Discussion

In the mid-twentieth century, there was interest in establishing the planar structure of urea in the solid state. It was around this time that NMR spectroscopy was being developed. Kubo and Tomita [27] provided an early formulation of the NMR phenomenon, including spin-lattice relaxation, in terms of rigorous quantum mechanics.
The theory specifically covered spin-lattice relaxation resulting from dipolar interactions under the influence of random reorientations of molecules or molecular groups in solids. Andrew and coworkers \[28\] recast their result for the rate of spin-lattice relaxation as

\[
\frac{1}{T_1} = C \left[ \frac{\tau_c}{1 + \omega^2 \tau_c^2} + \frac{4\tau_c}{1 + 4\omega^2 \tau_c^2} \right], \tag{1}
\]

where \(\tau_c\) is the correlation time for the motion, and \(\omega\) is the Larmor frequency. The constant \(C\), representing the magnitude of the dipolar interaction, has units of \(s^{-2}\). The correlation time is generally assumed to be thermally excited, with the form of equation (2):

\[
\tau_c(T) = \tau_0 \exp \left( \frac{E_a}{RT} \right), \tag{2}
\]

where \(E_a\) is the activation energy, \(R\) is the gas constant, and \(\tau_0\) is the pre-exponential factor. In the limit of slow motion at low temperature, \((\omega^2 \tau_c^2 >> 1)\), the \(T_1^{-1} \sim (\omega^2 \tau_c)^{-1}\). An activation energy \(E_a\) can be extracted in this limiting case from a plot of the natural logarithm of the spin-lattice relaxation time versus the inverse temperature. The linear fit to data in such a plot has a slope equal to \(\frac{E_a}{R}\). The result of such an analysis for the \(^1\)H spin-lattice relaxation time \(T_1\) for urea yields an activation energy of \(E_a = 46.3 \pm 4.7\) kJ/mol.

The processes which lead to spin-lattice relaxation of the longitudinal magnetization also affect the spin-lattice relaxation of spin-locked magnetization in the rotating frame. Look and Lowe \[29\] developed a model to calculate both spin-lattice relaxation times, \(T_1\) and \(T_{1\rho}\), due to the modulation of dipole-dipole interactions between spins belonging to a molecule undergoing hindered rotation and applied their results to the solid-state NMR data from a molecule of symmetry similar to that of urea, \(\text{H}_2\text{S}\) \[30\]. Their result for the spin-lattice relaxation time \(T_1\) has the same form as equation (1), although \(C\) can be a function of temperature. The temperature dependence of \(C\) reflects the model of finite jumps that Look and Lowe invoke. In addition, they have given an expression to describe the exponential decay of the magnetization under spin-lock conditions characterized by a relaxation time, \(T_{1\rho}\). The equation is similar in form to equation (1).

\[
\frac{1}{T_{1\rho}} = C \left[ \frac{5}{2} \frac{\tau_c}{1 + \omega_1^2 \tau_c^2} + \frac{\tau_c}{1 + 4\omega^2 \tau_c^2} + \frac{3}{2} \frac{\tau_c}{1 + \omega_1^2 \tau_c^2} \right], \tag{3}
\]

where \(\omega_1\) is the frequency corresponding to the strength of the spin-lock field, \(\gamma B_1\). The principal difference between equation (3) and equation (1) is the sensitivity of \(T_{1\rho}\) to motions with spectral density at \(\omega_1\). A system that exhibits low-frequency motion (in the range of \(1 – 100\) kHz) will exhibit spin-lattice relaxation in the rotating frame that is more efficient than spin-lattice relaxation of the longitudinal magnetization. In the limit that
the spectral density is that of white noise with a very short correlation time, the spin-lattice relaxation time in the rotating frame becomes equal to the spin-lattice relaxation time of the longitudinal relaxation, and there is no distinction between the two relaxation times. The data of Table 1 demonstrate that $T_1 \gg T_{1\rho}$ for urea, so one has to conclude that the dominant relaxation mode is modulation of the dipolar coupling with a correlation time near $5.8 \times 10^{-6}$ s at 300 K.

The experimental observation of a minimum in the $T_{1\rho}$ data allows the application of the full forms of equations (1) and (3) from the Look and Lowe model to $T_1$ and $T_{1\rho}$ data, as opposed to simply invoking the limiting case as done in applying the Kubo-Tomita model to the $T_1$ data. The temperature dependencies of the natural logarithms of both $T_1$ and $T_{1\rho}$ in urea are shown in Figure 1, along with the theoretical predictions of equations (1) and (3) from the Look and Lowe model, assuming a motion characterized by a single thermally activated (according to equation (2)) correlation time. The best fit to the data also indicates an activation energy of $E_a = 46.3 \pm 4.7$ kJ/mol, in agreement with that of the Kubo-Tomita model and also in reasonable agreement with the previous measurements of $46 \pm 8$ kJ/mol from single-crystal $^2$H NMR [9] and $49 \pm 8$ kJ/mol from $^{14}$N NQR [10]. This value of $E_a$ is significantly different from the 38 kJ/mol derived from the variation of the $^1$H NMR second moment with temperature [8]. However, accurate measurements of second moments are always challenging from a practical point of view. The greatest contributions come from the wings of the spectrum where the signal-to-noise (S/N) ratio is worst. High S/N ratios are also needed for accurate determination of the baseline for these measurements. In reporting this activation energy, Emsley and Smith noted that "the errors in these measurements are large." Williams and McDermott [11] noted that the value of $65 \pm 5$ kJ/mol from $^2$H NMR relaxation measurements was "slightly higher than the previous measured estimates [9,10] but within experimental error."

In the simulation of wide-line $^2$H spectra, it has been noted that "one may be left at the end of an extensive calculation with the uncomfortable possibility that even though the simulated spectra fit the experimental data, the motional trajectories used in the simulation may not be unique, or even particularly realistic [31]." That does not, however, appear to be an issue here as the motional model used by Williams and McDermott is the same one used in the other studies. In essence, the twofold rotation about the carbonyl leaves the orientation of the N-D bond unchanged relative to the applied magnetic field for the two trans deuterium nuclei, as these bonds are essentially parallel to the rotation axis. Hence, the quadrupolar interactions for the trans nuclei are unaffected by the quick hop between the two sites. However, the N-D bonds for the cis deuterium nuclei are oriented about 60º from the carbonyl axis. The twofold hop motionally averages the quadrupolar interaction for the cis deuterium nuclei. Simulation of the experimentally observed $^2$H line shape requires the superposition of an essentially static line shape for the trans nuclei with the motionally averaged line shape for the cis nuclei. As a result, the simulations of Williams and McDermott are complex due to a fit of two overlapping line shapes.

Williams and McDermott [11] also used molecular modeling results to look at the effect of a rotation about the carbonyl bond. Rotation about the carbonyl results in steric hindrance as the van der Waals radii of the hydrogen of the rotated urea molecule overlap with that of a hydrogen on an adjacent static molecule. Their modeling results suggested
that steric hindrance begins to develop at a rotation of around 40º and reaches a maximum at 90º, as this orthogonal orientation results in \( ^1\text{H}^1\text{H} \) distances of \(<0.18\) nm. However, they reported "a surprisingly flat potential along the rotation coordinate. The trans deuterons maintain their distance to their oxygen donor throughout the rotation while the cis deuterons form additional H bonds to the adjacent oxygen at the 90º orientation which approximately compensate for the loss of the ground-state hydrogen bonds."

It should also be noted that molecular modeling of urea indicates that the planar structure of urea arises as the C-O bond distance increases relative to that of the usual double bond, while the C-N bond distance decreases relative to that of the usual single bond [32]. This is consistent with forming some double-bond character in the C-N bonds, as noted by Williams and McDermott [11]. While steric hindrance is absent in the rotation of the \(-\text{NH}_2\) group about the C-N bond, the double-bond character provides a rationale for the very high activation energy for this motion.

The increased mass and typically shorter bond lengths associated with deuterium [33] give rise to the possibility that replacement of the protons with deuterium may affect the measured activation energy for rotation. A previous study [34] of such a highly hindered motion due to hydrogen bonding, i.e., a process having a high activation energy, suggests that there is likely no difference.

The \(^1\text{H} T_1\) and \(T_{1\rho}\) data for urea provide a striking example of the challenges of data acquisition in the solid state. A \(^1\text{H} T_1\) of 67 minutes is coupled with a relatively short \(T_{1\rho}\) at room temperature. Together these relaxation times conspire to make acquisition of \(^{13}\text{C}\) and \(^{15}\text{N}\) CP/MAS spectra at ambient temperature from urea containing carbon or nitrogen at natural isotopic abundance a difficult task. The natural abundance CP/MAS spectra for both \(^{13}\text{C}\) and \(^{15}\text{N}\) in urea, both taken with a contact time of 0.5 ms, are shown in Figure 2. Longer contact times result in a deterioration of the intensity.

Both \(^{13}\text{C}\) and \(^{15}\text{N}\) CP/MAS spectra in Figure 2 were acquired from the same 96.4 mg sample with a CP contact time of 0.5 ms. A single scan for the \(^{13}\text{C}\) CP/MAS experiment after a five-hour delay showed a single resonance at 162.7 ppm with a S/N ratio of 8. The full width at half maximum (FWHM) of the resonance was 211 Hz. Four scans with a five-hour recycle delay for the \(^{15}\text{N}\) CP/MAS experiment showed a single resonance at 80.9 ppm with a S/N of 4. The FWHM was 110 Hz. Most biochemical applications of \(^{15}\text{N}\) NMR have used liquid \(\text{NH}_3\) as a reference for \(^{15}\text{N}\) in aqueous solution, which is listed as a secondary reference for \(^{15}\text{N}\) by the International Union of Pure and Applied Chemistry [35]. This referencing has been used here rather than that based on nitromethane, which resonates at 382 ppm on this scale.

The implication of the \(^1\text{H} T_1\) and \(T_{1\rho}\) data for urea is that the low-frequency motion in the kHz regime is a very effective relaxation mechanism for the \(^1\text{H} T_{1\rho}\). \(^1\text{H}-^{14}\text{N}\) cross-relaxation experiments are typically performed at low magnetic fields where the \(^1\text{H}\) Larmor frequency matches the quadrupolar frequency for the \(^{14}\text{N}\). The short \(T_{1\rho}\) values suggest that the \(^1\text{H} T_1\) values at these low magnetic fields will be substantially shorter than those measured at high magnetic fields, as in the present study.
Conclusions

Analysis of the temperature dependence of the $^1$H spin-lattice relaxation times of the longitudinal and spin-locked magnetizations demonstrates that a low-frequency motion dominates the relaxation of protons in urea. From the analysis of the data, the motion is associated with an activation energy of 46.3 $\pm$ 4.7 kJ/mol, significantly narrowing the uncertainty previously reported in the literature for the whole body molecular reorientation about the carbonyl bond in urea. In addition, measurement of CP-MAS spectra of urea is demonstrated, but only if one uses a short contact time.

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References


32. Molecular simulations based on DFT, B3LYP, 6-311 +G**. In the gas phase, the angle between the CNH unit and the second hydrogen is 39.77 degrees. The angle of the hydrogen compared to the O=CN2 plane is 12.3 degrees.


### Table 1. $^1$H NMR Relaxation Times

<table>
<thead>
<tr>
<th>Temperature, K</th>
<th>$T_1$, minutes</th>
<th>$T_{1p}$, milliseconds</th>
<th>$\tau_c$, microseconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>295</td>
<td>67.1</td>
<td>2.8</td>
<td>7.9</td>
</tr>
<tr>
<td>323</td>
<td>15.7</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>348</td>
<td>3.5</td>
<td>0.7</td>
<td>0.45</td>
</tr>
<tr>
<td>373</td>
<td>1.4</td>
<td>1.7</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Figure 1: The natural logarithm of (○) the \(^1\)H spin-lattice relaxation time, \(T_1\), and (□) the \(^1\)H spin-lattice relaxation time in the rotating frame, \(T_{1\rho}\), of urea versus the inverse temperature. The lines fit of equations (1) and (3) to the data, as explained in the text.
Figure 2: The natural isotopic abundance $^{13}$C CP/MAS (A) and $^{15}$N CP/MAS (B) spectra of polycrystalline urea.