Intermolecular Hydrogen-Bonding Effects on the Amide Oxygen Electric-Field-Gradient and Chemical Shielding Tensors of Benzamide

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Recent advances in experimental solid-state nuclear magnetic resonance (NMR) and computational chemistry have made it possible to establish the correlation between second-rank NMR tensors and molecular structure.1-5 Several studies have demonstrated the influence of intermolecular interactions on chemical shielding tensors for 1H, 13C, and 15N nuclei.6-13 However, relatively little is known about 17O chemical shielding tensors, despite the enormous importance of oxygen-containing functional groups in chemistry and biology. In this contribution we report a new experimental determination of the 17O electric-field-gradient (EFG) and chemical shielding (CS) tensors for an amide functional group. We also demonstrate the importance of including intermolecular hydrogen-bonding (HB) interactions in quantum chemical calculations of 17O EFG and CS tensors.

Figure 1 shows the 17O magic-angle spinning (MAS) and stationary NMR spectra of [17O]benzamide.16 From the analysis of the 17O MAS spectrum, we obtained the following NMR parameters: δiso = 300.0 ± 0.5 ppm, χ = e2QVRe/h = 8.40 ± 0.05 MHz, and ηQ = 0.37, where VRe is the largest principal component of the EFG tensor, |VRe| > |Vx| > |Vy|, and ηQ is the asymmetry parameter defined as ηQ = (Vx - Vy)/VRe. Following the standard procedure,17 we were able to analyze the stationary 17O NMR spectra shown in Figure 1 and obtain the principal components of the 17O CS tensor: δ1 = 000.0 ± 2.0, δ2 = 400.0 ± 2.0, and δ3 = 0 ± 2.0 ppm, α = 6 ± 4°, β = 90 ± 1°, and γ = 72 ± 1°. These results indicate that the direction of the strongest

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Figure 1. Experimental (upper trace) and calculated (lower trace) solid-state 17O NMR spectra of [17O]benzamide: (A) MAS, 11.75 T, sample spinning frequency = 15 kHz, (B) stationary, 11.75 T, and (C) stationary, 9.40 T.

shielding, δ331°, is approximately parallel to Vxx, and that the angle between δ1 and Vxx is 72°. It is important to point out that one must exercise caution in interpreting stationary 17O NMR spectra because, in many cases, multiple solutions may exist. This ambiguity is easily removed by obtaining stationary 17O NMR spectra at multiple magnetic fields.

It is well-known that analysis of solid-state 17O NMR spectra yields only the relative orientation between the EFG and CS tensors. To determine tensor orientations in the molecular frame of reference, we decided to perform quantum chemical calculations for the 17O EFG and CS tensors in benzamide. Although several groups have reported reasonably good agreement between experimental and calculated 17O isotropic chemical shifts,18-24

(16) Benzoic acid-17O was obtained by reacting 0.3850 g (2.0 mmol) of o-acetophenone with 0.0720 g (4.0 mmol) of H2O2. (50.8% 17O atom purchased from ISOTEC, Miamisburg, Ohio) in a sealed tube at approximately 120°C for 15 h. HCl gas was removed after cooling the sealed tube to room temperature. The remaining white crystalline product was recrystallized from acetone/petroleum ether. Yield: 93%. [17O]Benzoic chloride was obtained by refluxing thionyl chloride and benzoic acid-17O (molar ratio of 1:1.1) for 1 h, and subsequently removing the excess thionyl chloride by distillation. To [17O]benzoic chloride was added dropwise a cold ammonia–methanol solution until the temperature was stabilized, and the solution was stirred at room temperature for 3 h. The solution was then poured into water and extracted with diethyl ether. The white product of [17O]benzamide (50.8% 17O atom) was obtained upon removal of the solvent. The melting point, solution NMR, and IR results are in agreement with the literature values. Solid-state 17O NMR spectra were recorded on Bruker Avance-500 and Avance-400 NMR spectrometers. In the static 17O NMR experiments, a Hahn-echo sequence was used to eliminate the acoustic ringing of the probe.

interactions also cause a more shielded environment at the amide oxygen nucleus (i.e., a smaller isotropic $^{17}$O chemical shift value). The principal component corresponding to the least shielding, $\delta_{11}$, exhibits a remarkable sensitivity (ca. 152 ppm) to the HB interaction, whereas the change in the most shielded component, $\delta_{33}$, is quite small, ca. 25 ppm. Since the changes in $\delta_{11}$ and $\delta_{33}$ are of the opposite signs, the span of the $^{17}$O chemical shift tensor exhibits a change of 177 ppm on going from the isolated molecule to the trimer. The calculated orientations of the $^{17}$O EFG and CS tensors are depicted in Figure 2B. Interestingly, the calculations indicate that the orientations of both the $^{17}$O EFG and CS tensors remain unchanged within 5° among the different models. This is consistent with a previous theoretical study on the hydration of glycyglycine.34 As also seen from Table 1, the calculated relative orientation between the $^{17}$O EFG and CS tensors is in excellent agreement with that determined experimentally.

It should be emphasized that the absolute $^{17}$O CS tensor orientation depicted in Figure 2B is quite different from that reported by Ando and co-workers for amide functional groups.35 In particular, based on solid-state $^{17}$O NMR and finite perturbation theory (FPT) MNDO-PM3 calculations, these authors concluded that $\delta_{11}$ of the $^{17}$O CS tensor for an amide oxygen is perpendicular to the C=O bond. However, for a carbonyl oxygen atom, the dominant contribution to the paramagnetic shielding is expected to be the $n^{\perp} \pi^*$ mixing. Consequently, the direction along the C=O bond should give rise to the least shielded environment at the oxygen nucleus. For example, a single-crystal $^{17}$O NMR study by Haeberlen and co-workers36 showed that $\delta_{11}$ of the $^{17}$O CS tensor in benzophenone, Ph=O, is along the direction of the C=O bond. The orientation of the $^{17}$O CS tensor for benzamidine reported in this study is also in good agreement with the DFT calculation for the complex of [13C, 17O]benzamide.37 All these studies support the tensor orientation depicted in Figure 2B.

In summary, we have presented new experimental and theoretical results on the magnitude and orientation of the $^{17}$O CS and EFG tensors in benzamide. We have also demonstrated that it is important to include a complete HB network in the quantum chemical $^{17}$O NMR calculations. The present study suggests that $^{17}$O is a remarkably sensitive nuclear probe to HB interactions, and is therefore potentially useful for structural studies of proteins. We are presently investigating the synthetizes, solid-state $^{17}$O NMR, and quantum chemical calculations of model peptides.

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Figure 2. (A) Hydrogen-bonding environment in benzamide determined by a neutron diffraction study.23 (B) Orientations of the $^{17}$O EFG and CS tensors in benzamide. Both $\delta_{33}$ and $\nu_{zz}$ are perpendicular to the amide plane.

Table 1. Calculated (B3LYP/D95**) and Experimental $^{17}$O CS and EFG Tensors of the Amide Oxygen in Crystalline Benzamidina,b

<table>
<thead>
<tr>
<th>System</th>
<th>$\delta_{33}$ (MHz)</th>
<th>$\nu_{zz}$ (MHz)</th>
<th>$\delta_{11}$ (deg)</th>
<th>$\delta_{22}$ (deg)</th>
<th>$\delta_{12}$ (deg)</th>
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<tr>
<td>Isolated Molecule</td>
<td>379</td>
<td>674</td>
<td>487</td>
<td>-24</td>
<td>10.19</td>
</tr>
<tr>
<td>Linear Dimer</td>
<td>351</td>
<td>608</td>
<td>455</td>
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<tr>
<td>Cyclic Dimer</td>
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<td>573</td>
<td>426</td>
<td>-13</td>
<td>9.17</td>
</tr>
<tr>
<td>Trimer</td>
<td>308</td>
<td>522</td>
<td>402</td>
<td>1</td>
<td>8.77</td>
</tr>
<tr>
<td>Exptl</td>
<td>300.0</td>
<td>500</td>
<td>400</td>
<td>0</td>
<td>8.40</td>
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a All chemical shifts are in ppm and relative to liquid water. Errors in the experimental principal components of the CS tensor are ±2 ppm.

b The computed absolute shielding values are converted to chemical shifts using $\sigma^{17}$O (H$_2$O, liquid, 300 K) = 307.9 ppm.31 The calculated values of $\nu_{zz}$ are converted to $\chi$ using $\chi$ [MHz] = 2.3496(Q[fm$^3$]V$_{zz}$)$^{-1}$. Where Q = -2.558 as recommended by Pykkö.32

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most authors did not comment on the accuracy of the calculated principal components. In the present study, we used several molecular cluster models in the calculations to evaluate the influence of intermolecular HB interactions on $^{17}$O NMR tensors. The first cluster model is a linear dimer consisting of Mol1 and Mol2 as defined in Figure 2A. The second cluster is a cyclic dimer, Mol1 and Mol3. The third model is a trimer formed by Mol1, Mol2, and Mol3. The experimental neutron diffusion structure of benzamide33 was used in all the models.

The calculated $^{17}$O NMR results26 are summarized in Table 1. The value of $\chi(17O)$ shows a strong dependence on the HB environment. In general, the presence of the C=O···H—N hydrogen bonds causes a reduction in $\chi(17O)$. This is in qualitative agreement with previous $^{17}$O NQR studies.33 The strong HB