Oxygen-17 Nuclear Magnetic Resonance of Organic Solids

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We report solid-state ^{17}O NMR determinations of the oxygen chemical shift (CS) and electric field gradient (EFG) tensors for a series of ^{17}O-enriched organic compounds containing various functional groups. In several cases, analysis of the ^{17}O magic-angle-spinning (MAS) and static NMR spectra yields both the magnitude and relative orientations of the ^{17}O CS and EFG tensors. We also demonstrate the feasibility of solid-state ^{17}O NMR as a potentially useful technique for studying molecular structure and hydrogen bonding.

Key words: Oxygen-17; Solid State NMR; Organic Compounds; Chemical Shift Tensor; Quadrupole Coupling Constant.

1. Introduction

Oxygen is one of the most common elements in organic and biological molecules. Unlike other common elements such as hydrogen, carbon and nitrogen, oxygen does not have a stable spin-1/2 isotope. The only naturally occurring stable oxygen isotope with nonzero nuclear spin is ^{17}O (spin = 5/2, natural abundance = 0.037%, $\gamma = -3.6279 \times 10^7$ rad T^{-1} s^{-1}, $Q = -2.6 \times 10^{-30}$ m^2). These unfavorable nuclear properties of ^{17}O have made ^{17}O NMR quite difficult and therefore discouraged chemists from using ^{17}O NMR, despite the enormous importance of oxygen-containing compounds in chemistry and biology.

Most of the ^{17}O NMR studies so far reported deal with solution samples [1 - 3]. During the last decade, solid-state ^{17}O NMR has become increasingly important and accessible. While considerable attention has been devoted to solid-state ^{17}O NMR of various inorganic systems including high T_c superconductors [4 - 12], solid-state ^{17}O NMR studies of organic / biological solids have been scarce [13 - 18]. The major problem associated with solid-state ^{17}O NMR studies is that quadrupolar interactions are often several orders of magnitude larger than other nuclear spin interactions such as chemical shift and dipolar interactions. However, there are also tremendous advantages of carrying out ^{17}O NMR studies in the solid state. First, both the chemical shift and quadrupole interactions are *anisotropic* and can be best described by second-rank tensors. Characterization of the anisotropic nuclear spin interactions is capable of yielding more complete information about the three-dimensional electronic structures in the molecular systems under study. In the liquid state, only the averaged ^{17}O NMR parameters can be measured due to rapid molecular tumbling motion. Second, the rapid molecular tumbling in the liquid phase often causes efficient quadrupole relaxation thus poor intrinsic resolution – a consequence of very short lifetimes of the quadrupole energy levels. The situation becomes worse for large molecules exhibiting long rotational correlation times. Consequently, ^{17}O NMR of macromolecules is rather difficult in solutions. In contrast, the resolution of solid-state ^{17}O NMR spectra does not depend on the size of the molecules under study.

The two most important NMR parameters obtainable from solid-state ^{17}O NMR studies are the chemical shift and quadrupole tensors. To characterize a chemical shift tensor, the three principal components of the tensor, δ_{11}, δ_{22}, and δ_{33}, are often reported; but in some cases, the chemical shift anisotropy (CSA) is also given in the form of the span of the tensor, $\Omega = \delta_{11} - \delta_{33}$. To describe a traceless quadrupole tensor, however, one uses the nuclear quadrupolar coupling

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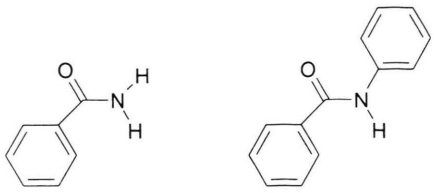


(**1**) (**2**)

constant ($\chi = e^2QV_{zz}/h$, where V_{zz} is the largest component of the electric field gradient tensor) and the asymmetry parameter, $\eta = (V_{xx} - V_{yy})/V_{zz}$. These NMR tensorial properties are sensitive to the chemical environment at the nucleus of interest. In this contribution, we wish to report the ^{17}O quadrupole and chemical shift tensors in typical organic compounds.

2. Results and Discussion

2.1. Amides

The amide functional group, $R_1C(O)NHR_2$, is of the greatest importance in peptide and protein chemistry. Although there have been a considerable number of solution ^{17}O NMR studies on amide oxygens [19 - 23], relatively little is known about the amide oxygen CS and EFG *tensors*. The only experimental solid-state ^{17}O NMR studies of amide oxygens were concerned with polypeptides [24, 25]. In this contribution, we report the ^{17}O CS and EFG tensors in two typical aromatic amides: [^{17}O]benzamide (**1**) and [^{17}O]benzanilide (**2**) (Scheme 1). Since compounds **1** and **2** exhibit very different hydrogen-bonding environment [26, 27], it is of interest to see whether or not solid-state ^{17}O NMR parameters can be useful in detecting such structural differences.

Figure 1 shows the MAS and static ^{17}O NMR spectra for **1**. The ^{17}O MAS spectrum exhibits a typical line shape arising from second-order quadrupolar interaction. At 11.75 T, the line width of the ^{17}O central transition is approximately 13.6 kHz. Analysis of the ^{17}O MAS spectrum shown in Figure 1A yields the following parameters for **1**: χ = 8.40 MHz, η = 0.40, and δ_{iso} = 300 ppm. Information about the ^{17}O CSA can usually be obtained from an analysis of NMR spectra from a stationary powder sample [28]. Figure 1B shows the static ^{17}O NMR spectrum of **1**. The frequency range of the static NMR spectrum is much

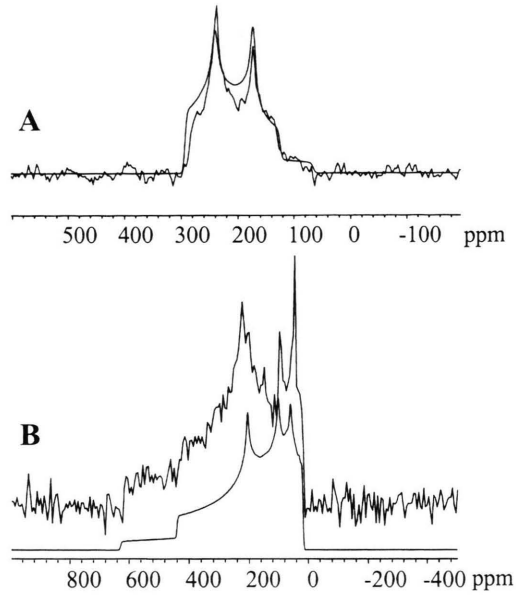


Fig. 1. Experimental and calculated ^{17}O MAS (A) and static (B) spectra of **1**. In (A), the sample spinning frequency was 15 kHz. 64 transients. 10 s recycle delay. In (B), 2202 transients. 10 s recycle delay.

larger than that of the MAS spectrum, indicating the presence of a substantial CSA. Analysis of the static NMR spectrum yields the principal components of the ^{17}O CS tensor for **1**: δ_{11} = 500 ± 3, δ_{22} = 400 ± 3 and δ_{33} = 0 ± 3 ppm. Another important piece of information from the analysis of static NMR spectra is the relative orientation between the ^{17}O CS and EFG tensors. It is found that the most shielded component, δ_{33}, is parallel to the smallest component of the EFG tensor, V_{xx}, and that the least shielded component, δ_{11}, deviates by 74° from the direction of the largest EFG component, V_{zz} (*vide infra*).

Figure 2 shows the MAS and static ^{17}O NMR spectra for **2**. Compared to the ^{17}O MAS spectrum of **1** (shown in Fig. 1A), significant spinning sideband intensities are observed in the ^{17}O MAS spectrum of **2**, indicating a much larger CSA. It is also clear from Fig. 2A that the highest MAS frequency achievable on our NMR spectrometer, 15 kHz, is comparable to the line width of the central transition, resulting in the incomplete separation between the central band and the first-order spinning sidebands. Nevertheless, it is still possible to analyze the ^{17}O MAS spectrum of **2** because the major feature of the central transition is clearly observed. From simulations of the MAS spectrum, we obtained the following ^{17}O NMR parameters

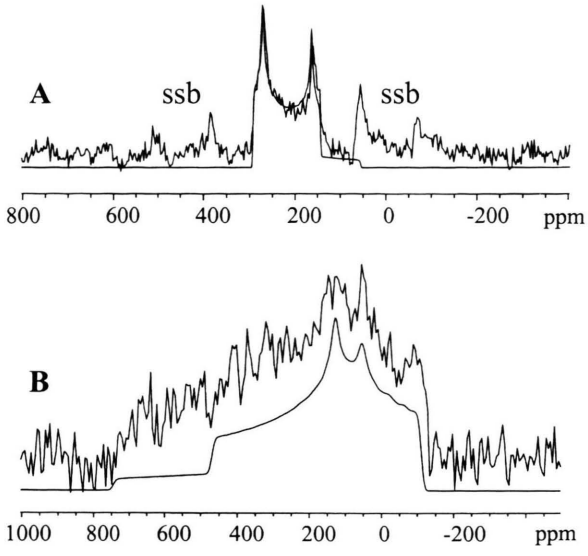


Fig. 2. Experimental and calculated ^{17}O MAS (A) and static (B) spectra of **2**. In (A), the sample spinning frequency was 15 kHz. 512 transients. 10 s recycle delay. In (B), 3950 transients. 10 s recycle delay.

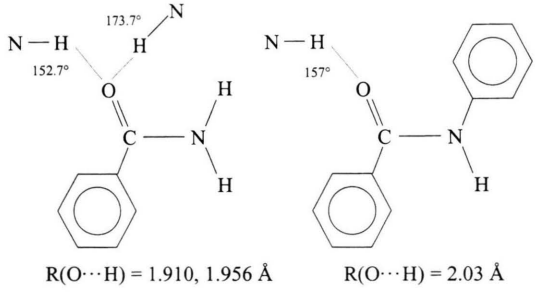
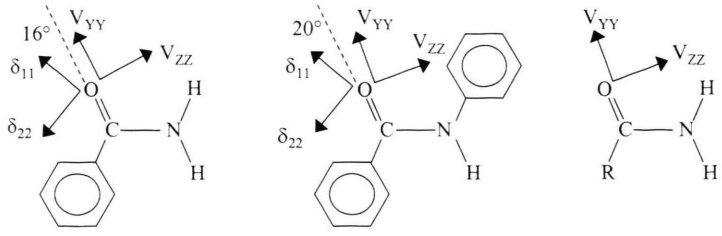


Fig. 3. The hydrogen bonding geometry in **1** and **2**.

for **2**: χ = 8.97 MHz, η = 0.15, and δ_{iso} = 320 ppm. Compared with **1**, compound **2** exhibits a larger ^{17}O quadrupolar coupling constant. In addition, the EFG tensor in **2** is closer to axial symmetry. As seen from Fig. 2B, the static ^{17}O NMR spectrum for **2** spans a range of 900 ppm (ca. 61 kHz at 11.75 T). Again, analysis of the static line shape yields the principal components of the ^{17}O CS tensor for **2**: $\delta_{11} = 580 \pm 5$, $\delta_{22} = 450 \pm 5$ and $\delta_{33} = -50 \pm 5$ ppm. The orientation of the ^{17}O CS tensor in **2** is found to be similar to that in **1**.

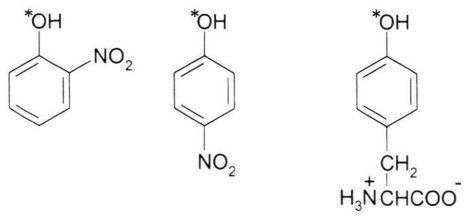
As mentioned earlier, compounds **1** and **2** have quite different hydrogen bonding geometry. As illustrated in Fig. 3, while the amide oxygen in **1** is involved in two O···H-N hydrogen bonds ($R_{O\cdots H}$ = 1.910, 1.956 Å), only a weak O···H-N hydrogen bond exists in **2** ($R_{O\cdots H}$ = 2.03 Å). This discrepancy is well reflected in the difference between the two χ values, 8.40 and 8.97 MHz, with the larger one associated with the weaker hydrogen bond. This trend is consistent with the general observation concerning ^{17}O quadrupole couplings and the hydrogen bond strength, as well as with previous results in solid polypeptides [24, 25].

Although it is possible to obtain relative orientation between the CS and EFG tensors from an analysis of static ^{17}O NMR spectra, information concerning the orientations of the two tensors in the molecular frame of reference is unavailable. Two approaches can be employed to obtain such information. The ideal approach is single crystal NMR. Unfortunately, no single-crystal ^{17}O NMR study has been reported for amides. Another approach is to rely on theoretical calculations on the orientation of the EFG tensor or the CS tensor. Since it is computationally easier to calculate ^{17}O EFG tensors than ^{17}O CS tensors, we chose to calculate the orientation of the ^{17}O EFG tensor for amide oxygens. A similar approach was used by Ando and coworkers in the studies of solid polypeptides [25]. Combining our experimental and theoretical results, we can tentatively assign the orientations of the ^{17}O CS and EFG tensors in **1** and **2**. The results are illustrated in Figure 4. In both cases, the most shielded component of the CS tensor coincides the smallest EFG component, both being perpendicular the amide plane. The least shielded CS tensor component lies in the amide plane and is 18° off the direction of the C=O bond. It is also worth noting that the span of the ^{17}O CS tensor in **2** is much larger than that in **1**, 630 versus 500 ppm. This may indicate that strong hydrogen bond interactions also tend to reduce the ^{17}O CSA of amide oxygens, which is in qualitative agreement with the theoretical results of Ando and coworkers [29]. However, there exists a discrepancy between our results and those by Ando and coworkers [25, 29] concerning the orientation of the amide oxygen CS tensor. Several recent MO shielding calculations indicated that δ_{11} of the amide oxygen CS tensor lies close to the C=O bond within 30° [30, 31]. Since it is known that hydrogen bonding can introduce large effects on chemical shift tensors [32], the apparent discrepancy may arise from the different hydrogen bonding models used in various MO calculations. In any event, a complete understanding about the relationship between ^{17}O NMR parameters (CS and EFG tensors) and hydrogen bond geometry



A **B** **C**

Fig. 4. Orientations of the ^{17}O CS and EFG tensors in **1** (A), **2** (B) and formamide (C).



(**3**) (**4**) (**5**)

requires further experimental and theoretical NMR studies. We are presently investigating the orientation of the ^{17}O CS tensors in simple amides and peptides by performing high-level MO calculations.

2.2. *Phenols*

The phenolic oxygen is also an important functional group often found in protein side chains (e.g., tyrosine). To the best of our knowledge, no solid-state ^{17}O NMR report has appeared in the literature on phenolic oxygens. Here we report observations of solid-state ^{17}O NMR spectra of 2-nitro-[^{17}O]phenol (**3**), 4-nitro-[^{17}O]phenol (**4**) and [^{17}O]tyrosine (**5**) (Scheme 2).

Figure 5 shows the static ^{17}O NMR spectra of compounds **3** - **5**. The ^{17}O NMR spectra of **3** and **4** are much wider than those obtained for amides, indicating larger ^{17}O quadrupole coupling constants. A common feature of the ^{17}O NMR spectra for **3** - **5** is that the detailed NMR line shapes arise primarily from the second-order quadrupolar interaction. From analysis of the static ^{17}O NMR line shapes, we obtain the following ^{17}O NMR parameters: for **3**, χ = 9.9 MHz, η = 0.8, δ_{iso} = 63 ppm, and Ω = 170 ppm; for **4**, χ = 9.7 MHz, η = 0.85, δ_{iso} = 80 ppm, and Ω = 120 ppm; for **5**, χ = 8.1 MHz, η = 1.0, δ_{iso} = 117 ppm,

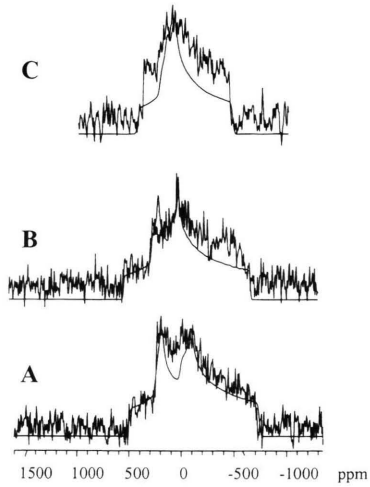


Fig. 5. Experimental and calculated ^{17}O static spectra of **3** (A), **4** (B) and **5** (C). In (A), 6181 transients; 5 s recycle delay. In (B), 7193 transients; 5 s recycle delay. In (C), 7152 transients; 10 s recycle delay.

and Ω = 100 ppm. The χ values found in **3** and **4** are much larger than that in **5**. The χ value for the latter compound is comparable to those observed in chlorophenols from ^{17}O NQR studies [33]. The phenolic C-O bond lengths in **3** and **4** are rather similar, 1.343 and 1.351 Å, but are slightly shorter than that in **5**, 1.371 Å [34]. However, the three phenols have quite different hydrogen bonding environment. In **3**, the phenolic oxygen is linked to the 2-nitro group forming an intramolecular hydrogen bond, $R_{O\cdots O}$ = 2.602 Å [34a]. In **4**, the hydrogen bond is between the phenolic oxygen and the nitro group of the neighbor molecule, $R_{O\cdots O}$ = 2.818 Å [34b]. The phenolic oxygen in **5** is however involved in two hydrogen bonds, $R_{O\cdots O}$ = 2.668 Å and $R_{O\cdots N}$ = 2.875 Å [34c]. It is unclear at this time whether the large difference in ^{17}O χ values found in compounds **3** - **5** is due to electronic effects or hydrogen bonding effects. However, these preliminary results are encouraging, since

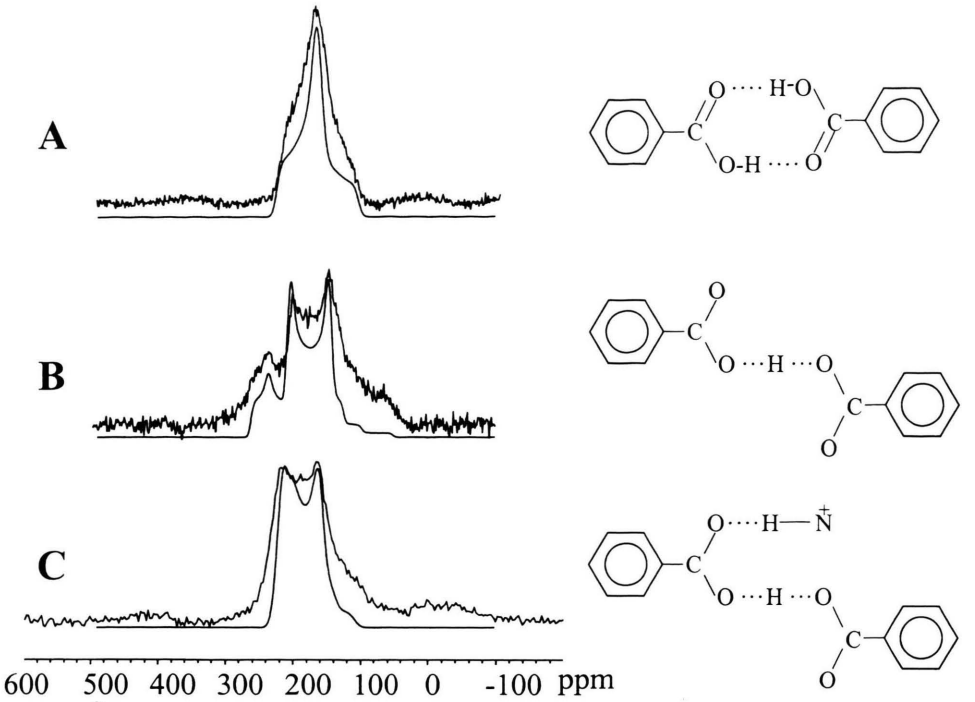


Fig. 6. Left: Experimental and calculated ^{17}O MAS spectra of **6** (A), **7** (B), and **8** (C). Right: The hydrogen bonding environment in **6** - **8**.

they demonstrate that oxygen sites with large χ values (ca. 10 MHz) are readily accessible by solid-state ^{17}O NMR even at a relatively low ^{17}O enrichment level, 25%. Unfortunately, for compounds **3** - **5**, MAS spectra obtained at practically achievable spinning frequencies inevitably exhibit complex features due to the presence of a large number of spinning sidebands. It would be interesting to see whether ^{17}O CS and EFG tensors are sensitive to the protonation/deprotonation of the phenolic oxygen. This may become a useful means of detecting protonation state of protein side chains. Research in this direction is underway in our laboratory.

2.3. Carboxylic Acids and Acid Salts

Carboxylic acids and their acid salts have been extensively studied by ^{17}O NQR [35]. The only solid-state ^{17}O NMR report on carboxylic acids is a single-crystal NMR study [36]. The main interest in these previous studies is the proton dynamics in carboxylic acid dimers. Since the carboxyl group represents an important functional group, it is desirable to test the feasibility of solid-state ^{17}O NMR in studying this class of compounds in the form of powders. Here we report solid-state ^{17}O NMR results for [^{17}O]benzoic acid (**6**), potassium hydrogen [^{17}O]dibenzoate (**7**) and ammonium hydrogen [^{17}O]dibenzoate (**8**).

Figure 6 shows the ^{17}O MAS NMR spectra of **6** - **8**. From analysis of the ^{17}O MAS spectra, we obtained the following ^{17}O NMR parameters: for **6**, χ = 5.7 MHz, η = 1.0, δ_{iso} = 230 ppm; for **7**, O1(C-O), χ = 8.5 MHz, η = 0.20, δ_{iso} = 290 ppm, O2(C-O···H), χ = 6.3 MHz, η = 0.10, δ_{iso} = 230 ppm; for **8**, O1(C-O···H), χ = 6.3 MHz, η = 0.40, δ_{iso} = 240 ppm, O2(C-O···H-N), χ = 6.3 MHz, η = 0.0, δ_{iso} = 242 ppm. For compound **6**, the two oxygen atoms are equivalent on the ^{17}O NMR time scale as a result of the dynamical proton disorder. Therefore, only one oxygen site is observed in the ^{17}O MAS spectrum of **6**. The value of χ is 5.7 MHz, which is in agreement with the determination from ^{17}O NQR [35a]. The crystal structure of **7** indicates that the two oxygen atoms of the carboxyl group have quite different environment [37]. As illustrated in Fig. 6, one oxygen atom is involved in a symmetrical hydrogen bond, $R_{O\cdots H\cdots O}$ = 2.51 Å, but the other one is not in any hydrogen bond. The ^{17}O MAS spectrum of **7** exhibits two overlapping features

associated with the two inequivalent oxygen sites. The oxygen site with a large χ is assigned to C-O···H since it is known that the strong hydrogen bonding often causes reduction of the ^{17}O quadrupole coupling constant and increase in the ^{17}O chemical shielding. The χ value for C-O···H, 6.3 MHz, is consistent with the NQR result, 6.165 MHz [35b]; however, the asymmetry parameter for this oxygen site, $\eta = 0.10$, differs considerably from that obtained in the NQR study, $\eta = 0.591$. Compound **8** is practically isostructural with **7**, except for the formation of an additional O···H-N hydrogen bond [38]. Interestingly, the formation of the strong O···H-N hydrogen bond removes the difference between the two oxygen atoms. As a result, the two oxygen atoms in **8** exhibit very similar ^{17}O NMR parameters. Again, the ^{17}O χ values and the isotropic chemical shifts are all consistent with the carboxyl oxygens involved in strong hydrogen bonds. For **8**, it appears that ^{17}O NMR parameters are not too useful in distinguishing between O···H···O and O···H-N hydrogen bonds.

2.4. [^{17}O]Toluenesulfonic Acid Monohydrate (**9**)

In an early ^{17}O NQR study, Cheng and Brown reported the ^{17}O quadrupole parameters in a series of compounds containing S-O bonds, i. e., sulfones and sulfoxies [39]. But solid-state ^{17}O NMR data for the sulfonate group, RSO_3^-, has not been reported. As a part of our research on the interactions between sulfonyl derivatives and peptides, we were interested in finding the best way of introducing the ^{17}O isotope into the sulfonyl group. Here we report solid-state ^{17}O NMR spectra of [^{17}O]toluenesulfonic acid monohydrate.

Figure 7 shows the ^{17}O MAS spectrum of **9**. The narrow line width immediately suggests that the χ value is quite small for **9**. The ^{17}O MAS spectrum also indicates the presence of only one type of oxygen environment. Since compound **9** exists as an oxonium salt in the solid state, the three oxygen atoms of the sulfonate group are nearly identical and each is hydrogen bonded to an oxonium ion, H_3O^+ [40]. The three S-O bond distances are practically the same: 1.456 ± 0.002, 1.450 ± 0.002 and 1.452 Å ± 0.002. From the ^{17}O MAS spectrum shown in Fig. 7, we obtained that $\chi = 4.79$ MHz, $\eta = 1.0$ and $\delta_{iso} = 140$ ppm. The small χ value in **9** is somewhat surprising, considering that the χ values for sulfones and sulfoxides are *ca.* 7 and 9 MHz, respectively [39]. The S-O bond

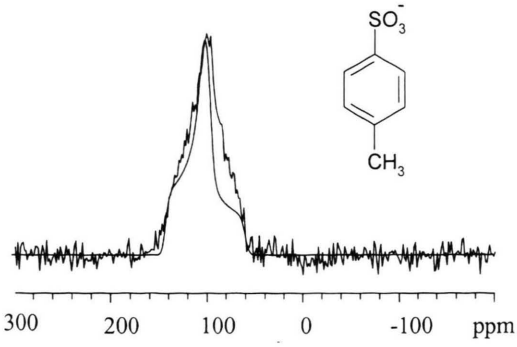


Fig. 7. Experimental and calculated ^{17}O MAS spectra of **9**. The sample spinning frequency was 10 kHz. 64 transients. 5 s recycle time.

length in aryl sulfoxides is in the range of 1.47 - 1.48 Å, while slightly shorter S-O distances are usually found in aryl sulfones. The S-O distances in **9** cannot provide an explanation for the observed value of the ^{17}O quadrupolar coupling constant. Another important feature of the crystal structure of **9** is the presence of three strong hydrogen bonds between the sulfonate oxygen atoms and the oxonium ions. The $O^{\delta-}$···H-O^+ distances are 2.525, 2.530 and 2.535 Å. The formation of these strong hydrogen bonds might be responsible for a small χ observed in **9**.

3. Experimental Section

3.1. Sample Synthesis

Water at 50.8% and 25.2% ^{17}O atom was purchased from ISOTEC (Miamisburger, Ohio) and Trace Science International Corp. (Toronto, Ontario), respectively. Benzoic acid-$^{17}O_2$ (**6**) was obtained by reacting 0.3850 g (2.0 mol) α,α,α-trichlorotoluene with 0.0720 g (4.0 mmol) H_2O^* (50.8% ^{17}O atom) 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 products were recrystallized from acetone / petroether. Yield: 93%. [^{17}O]Benzoyl chloride was obtained by refluxing thionyl chloride and benzoic acid-$^{17}O_2$ (molar ratio of 1.1:1) for 1 h, and subsequently removing the excessive thionyl chloride by distillation.

[^{17}O]Benzamide (1). To [^{17}O]benzoyl chloride was added dropwise a cold ammonia-methanol solution until temperature is stabilized, and the solution

was stirred at room temperature for 3 h. The solution was then poured into water followed by extraction with ethyl ether. The white product was obtained upon removal of the solvent.

[^{17}O]Benzanilide (2). Compound **2** was synthesized by the same procedure as for **1**, except that a cold phenylamine-methanol solution was used.

2-Nitro-[^{17}O]phenol (3). 0.028 g (1.56 mmol) H_2O* (25.2% ^{17}O atom) and 0.060 g (1.54 mmol) potassium metal were added to 2.0 ml anhydrous THF. The solution was stirred at room temperature until no potassium metal is left. Subsequently, 0.21 g (1.52 mmol) 2-fluoronitrobenzene and a grain of 18-crown-6 were added, sealed and stirred at 80 °C for 11 h. After cooling, excessive HCl (aq) was added to the solution. Compound **3** was obtained by recrystallizing from THF/acetone. Yield: 81%. During the reaction, argon was applied as the protective gas.

4-Nitro-[^{17}O]phenol (4). The procedure is the same as the preparation for **3**, except that 4-fluoronitrobenzene was used.

***dl*-[^{17}O]Tyrosine (5).** 0.18 g *p*-aminophenylalanine were dissolved in 0.3 ml H_2O* (50.8% ^{17}O atom) and the solution was acidified with 0.1 ml concentrated H_2SO_4. A solution of 70 mg $NaNO_2$ in 0.2 ml H_2O* (50.8% ^{17}O atom) was added at –5 - 0 °C over a period of 30 min, and subsequently the solution was heated to 80 °C until no N_2 gas was evolved. Upon neutralizing with NH_3 gas, crude product precipitated. Compound **5** was crystallized from HCl (aq.) and neutralization with NH_3. Yield: 48%. Removal of the ^{17}O labeling on the carboxyl group was achieved by the back exchange with excess acidified unlabeled water at 100 °C for 2 h.

Potassium hydrogen [^{17}O]dibenzoate (7). 100 mg (0.82 mmol) benzoic acid-$^{17}O_2$ (**6**) and 0.20 mmol K_2CO_3 were dissolved in water to which was added a small amount of acetone. Compound **7** was recrystallized from acetone/water.

Ammonium hydrogen [^{17}O]dibenzoate (8). The procedure is the same as the preparation of **7**, except that ammonium hydroxide was used.

[^{17}O]Toluenesulfonic acid monohydrate (9). A tube containing 100 mg (0.53 mmol) toluenesulfonyl chloride and 0.01 ml (0.053 mmol) H_2O* (50.8% ^{17}O atom) was sealed and heated at 90 °C for 3 h. Upon cooling to room temperature, white crystal was obtained (HCl gas could be removed by applying N_2 gas).

3.2. Solid-state ^{17}O NMR

All solid-state ^{17}O NMR spectra were recorded on a Bruker Avance-500 spectrometer operating at 500.13 and 67.8 MHz for ^{1}H and ^{17}O nuclei, respectively. Polycrystalline samples were packed into zirconium oxide rotors (4 mm o.d.). A Bruker 4-mm MAS probe was used for both the ^{17}O static and MAS experiments. Typical sample spinning frequencies were 10 - 15 kHz. In the ^{17}O static experiments, the echo sequence of Oldfield et al. [41] was used to avoid probe ring down. Typical recycle delays were ranged from 2 to 30 s.

3.3. Ab initio Calculations

All molecular orbital (MO) calculations on EFG were performed on a Pentium II 400 MHz personal computer using the LINUX version of Gaussian 98 [42].

4. Conclusions

We have demonstrated that oxygen CS and EFG tensors can be directly determined by solid-state ^{17}O NMR spectroscopy. We have also shown that it is more advantageous to study the ^{17}O NMR tensors than their isotropic values alone. Both the ^{17}O CS tensors and EFG tensors are sensitive to hydrogen bonding environment, thus potentially useful for structural determinations. To fully understand the correlation between ^{17}O NMR tensors and hydrogen bonding geometry, more studies are clearly required. We are presently investigating the synthesis and solid-state ^{17}O NMR characterization of more complex organic and biological systems.

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