J. Am. Chem. Soc. **2000,** *122,* 4215−4216

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

Gang Wu,[*,†] Kazuhiko Yamada,[†] Shuan Dong,[†] and
Hiltrud Grondey[‡]

Department of Chemistry, Queen's University
Kingston, Ontario, Canada, K7L 3N6
Department of Chemistry, University of Toronto
Lash Miller Bldg., 80 St. George Street
Toronto, Ontario, Canada, M5S 3H6

Received November 12, 1999
Revised Manuscript Received February 15, 2000

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 ^{1}H, ^{13}C, and ^{15}N nuclei.[6−15] However, relatively little is known about ^{17}O 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 ^{17}O 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 ^{17}O EFG and CS tensors.

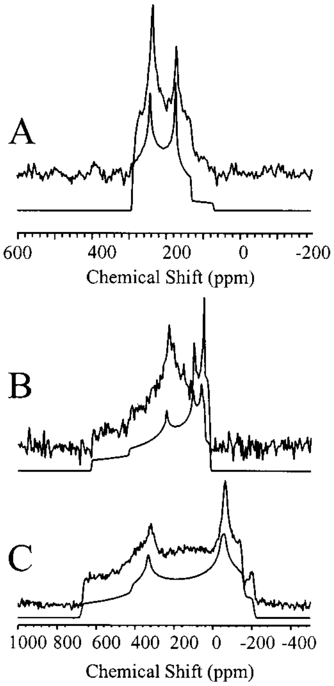

Figure 1. Experimental (upper trace) and calculated (lower trace) solid-state ^{17}O NMR spectra of [^{17}O]benzamide: (A) MAS, 11.75 T, sample spinning frequency = 15 kHz, (B) stationary, 11.75 T, and (C) stationary, 9.40 T.

Figure 1 shows the ^{17}O magic-angle spinning (MAS) and stationary NMR spectra of [^{17}O]benzamide.[16] From the analysis of the ^{17}O MAS spectrum, we obtained the following NMR parameters: $\delta_{\rm iso} = 300.0 \pm 0.5$ ppm, $\chi = e^2QV_{zz}/h = 8.40 \pm 0.05$ MHz, and $\eta_Q = 0.37$, where V_{zz} is the largest principal component of the EFG tensor, $|V_{zz}| > |V_{yy}| > |V_{xx}|$, and η_Q is the asymmetry parameter defined as $\eta_Q = (V_{xx} - V_{yy})/V_{zz}$. Following the standard procedure,[17] we were able to analyze the stationary ^{17}O NMR spectra shown in Figure 1 and obtain the principal components of the ^{17}O CS tensor: $\delta_{11} = 500 \pm 2$, $\delta_{22} = 400 \pm 2$, and $\delta_{33} = 0 \pm 2$ ppm, $\alpha = 6 \pm 4°$, $\beta = 90 \pm 1°$, and $\gamma = 72 \pm 1°$. These results indicate that the direction of the strongest shielding, δ_{33}, is approximately parallel to V_{xx}, and that the angle between δ_{11} and V_{zz} is 72°. It is important to point out that one must exercise caution in interpreting stationary ^{17}O NMR spectra because, in many cases, multiple solutions may exist. This ambiguity is easily removed by obtaining stationary ^{17}O NMR spectra at multiple magnetic fields.

It is well-known that analysis of solid-state ^{17}O 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 ^{17}O EFG and CS tensors in benzamide. Although several groups have reported reasonably good agreement between experimental and calculated ^{17}O *isotropic* chemical shifts,[18−24]

---

[*] Corresponding author. Phone: 613-533-2644. Fax: 613-533-6669. E-mail: gangwu@chem.queensu.ca.

[†] Queen's University.

[‡] University of Toronto.

(1) Tossell, J. A., Ed. *Nuclear Magnetic Shieldings and Molecular Structure*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1993.

(2) Jameson, C. J. In *Modeling NMR Chemical Shifts: Gaining Insight into Structure and Environment*; Facelli, J. C., de Dios, A. C., Eds.; ACS Symp. Ser. No. 732; Oxford University Press: Oxford, 1999.

(3) Sitkoff, D.; Case, D. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1998**, *32*, 165.

(4) Chesnut, D. B. *Annu. Rep. NMR Spectrosc.* **1989**, *21*, 51. Chesnut, D. B. *Annu. Rep. NMR Spectrosc.* **1994**, *29*, 71.

(5) Berglund, B.; Vaughan, R. W. *J. Chem. Phys.* **1980**, *73*, 2037.

(6) Wu, G.; Freure, C. J.; Verdurand, E. *J. Am. Chem. Soc.* **1998**, *120*, 13187.

(7) Asakawa, N.; Kameda, T.; Kuroki, S.; Kurosu, H.; Ando, S.; Ando, I.; Shoji, A. *Annu. Rep. NMR Spectrosc.* **1998**, *35*, 55 and references therein.

(8) de Dios, A. C.; Pearson, J. G.; Oldfield, E. *Science* **1993**, *260*, 1491.

(9) de Dios, A. C.; Laws, D. D.; Oldfield, E. *J. Am. Chem. Soc.* **1994**, *116*, 7784.

(10) de Dios, A. C.; Oldfield, E. *J. Am. Chem. Soc.* **1994**, *116*, 11485−11488.

(11) Malkin, V. G.; Malkina, O. L.; Salahub, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 3294.

(12) Anderson-Altmann, K. L.; Phung, C. G.; Mavromoustakos, S.; Zheng, Z.; Facelli, J. C.; Poulter, C. D.; Grant, D. M. *J. Phys. Chem.* **1995**, *99*, 10454.

(13) Facelli, J. C.; Pugmire, R. J.; Grant, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 5488−5489.

(14) Hu, J. Z.; Facelli, J. C.; Alderman, D. W.; Pugmire, R. J.; Grant, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 9863.

(15) Orendt, A. M.; Facelli, J. C.; Grant, D. M. *Chem. Phys. Lett.* **1999**, *302*, 499.

(16) Benzoic acid-^{17}O$_2$ was obtained by reacting 0.3850 g (2.0 mmol) of α,α,α-trichlorotoluene with 0.0720 g (4.0 mmol) of H$_2$O* (50.8% ^{17}O 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 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. To [^{17}O]benzoyl 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 followed by extraction with diethyl ether. The white product of [^{17}O]benzamide (50.8% ^{17}O 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 ^{17}O NMR spectra were recorded on Bruker Avance-500 and Avance-400 NMR spectrometers. In the static ^{17}O NMR experiments, a Hahn-echo sequence was used to eliminate the acoustic ringing of the probe.

(17) (a) Cheng, J. T.; Edwards, J. C.; Ellis, P. D. *J. Phys. Chem.* **1990**, *94*, 553. (b) Power, W. P.; Wasylishen, R. E.; Mooibroek, S.; Pettitt, B. A.; Danchura, W. *J. Phys. Chem.* **1990**, *94*, 591.

(18) Kaupp, M.; Malkin, V. G.; Malkina, O. L.; Salahub, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 1851.

(19) Schreckenbach, G.; Ziegler, T. *J. Phys. Chem.* **1995**, *99*, 606.

(20) (a) Gauss, J. *Chem. Phys. Lett.* **1992**, *191*, 614. (b) Gauss, J.; Stanton, J. F. *J. Chem. Phys.* **1996**, *104*, 2574.

(21) Barszczewicz, A.; Jaszunski, M.; Jackowski, K. *Chem. Phys. Lett.* **1993**, *203*, 404.

(22) Olah, G. A.; Burrichter, A.; Rasul, G.; Gnann, R.; Christe, K. O.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1997**, *119*, 8035.

10.1021/ja9939789 CCC: $19.00

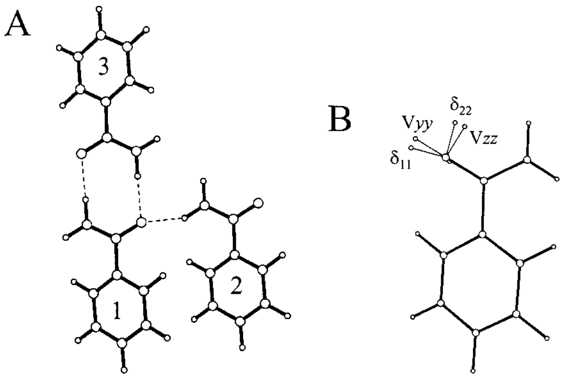

Figure 2. (A) Hydrogen-bonding environment in benzamide determined by a neutron diffraction study.[25] (B) Orientations of the ^{17}O EFG and CS tensors in benzamide. Both δ_{33} and V_{xx} are perpendicular to the amide plane.

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

system	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	χ/ MHz	η_Q	α/ deg	β/ deg	γ/ deg
isolated molecule	379	674	487	−24	10.19	0.24	7.7	88.7	77.7
linear dimer	351	608	455	−10	9.75	0.34	4.5	89.0	76.4
cyclic dimer	329	573	426	−13	9.17	0.43	6.4	89.0	75.0
trimer	308	522	402	1	8.77	0.53	4.3	89.6	73.3
exptl	300.0	500	400	0	8.40	0.37	6	90	72

[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. The computed absolute shielding values are converted to chemical shifts using $\sigma(^{17}\text{O}, \text{H}_2\text{O}, \text{liquid}, 300\ \text{K}) = 307.9$ ppm.[31] [b] The calculated values of V_{zz} are converted to χ using $\chi\ [\text{MHz}] = 2.3496Q[\text{fm}^2]V_{zz}[\text{au}]$, where $Q = -2.558$ as recommended by Pyykkö.[32]

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 diffraction structure of benzamide[25] was used in all the models.

The calculated ^{17}O NMR results[26] are summarized in Table 1. The value of $\chi(^{17}\text{O})$ shows a strong dependence on the HB environment. In general, the presence of the $\text{C}{=}\text{O}\cdots\text{H}{-}\text{N}$ hydrogen bonds causes a reduction in $\chi(^{17}\text{O})$. This is in qualitative agreement with previous ^{17}O NQR studies.[33] The strong HB 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, δ_{11}, exhibits a remarkable sensitivity (ca. 152 ppm) to the HB interaction, whereas the change in the most shielded component, δ_{33}, is quite small, ca. 25 ppm. Since the changes in δ_{11} and δ_{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 CS and EFG 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 glycylglycine.[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 δ_{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 $n \leftrightarrow \pi^*$ 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-workers[36] showed that δ_{11} of the ^{17}O CS tensor in benzophenone, $\text{Ph}_2\text{C}{=}\text{O}$, is along the direction of the C=O bond. The orientation of the ^{17}O CS tensor for benzamide reported in this study is also in good agreement with the DFT calculation for the complex of *N*-methylacetamide with two water molecules.[3] We have also performed numerous ^{17}O chemical shielding calculations on a number of model amides and dipeptides, and all the calculations predict ^{17}O CS tensor orientations similar to that of benzamide. This orientation is further confirmed by the results of a $^{13}\text{C}{-}^{17}\text{O}$ dipolar-chemical shift NMR study on $[^{13}\text{C},^{17}\text{O}]$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 syntheses, solid-state ^{17}O NMR, and quantum chemical calculations of model peptides.

Acknowledgment. This research was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada.

JA9939789

---

(23) Kaupp, M.; Malkina, O. L.; Malkin, V. G. *J. Chem. Phys*. **1997**, *106*, 9201.

(24) Kutzelnigg, W.; Fleischer, U.; Schindler, M. In *NMR−Basic Principles and Progress*; Springer-Verlag: Berlin, 1990; Vol. 23, p 165.

(25) Gao, Q.; Jeffrey, G. A.; Ruble, J. R.; McMullan, R. K. *Acta Crystallogr*. **1991**, *B47*, 742.

(26) The density functional theory (DFT) calculations were performed with the Gaussian 98 program.[27] The Dunning/Huzinaga full double-ζ basis set[28] including polarization functions, D95**, and the B3LYP exchange functional[29] were employed in the calculations. The Gauge-Included Atomic Orbital (GIAO) method[30] was used for the chemical shielding calculations. The experimental neutron diffraction structure of benzamide was used in all calculations.

(27) Gaussian 98, Revision A.6; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc.: Pittsburgh, PA, 1998.

(28) Dunning, T. H.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, H. F., Ed.; Plenum: New York, 1976; Vol. 3, p 1.

(29) (a) Becke, A. D. *Phys. Rev*. **1988**, *A38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev*. **1988**, *B37*, 785. (c) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648.

(30) (a) Ditchfield, R. *Mol. Phys*. **1974**, *27*, 789. (b) Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc*. **1990**, *112*, 8257.

(31) Wasylishen, R. E.; Mooibroek, S.; Macdonald, J. B. *J. Chem. Phys*. **1984**, *81*, 1057.

(32) Pyykkö, P. *Z. Naturforsch*. **1992**, *47A*, 189.

(33) (a) Gready, J. E. *J. Phys. Chem*. **1984**, *88*, 3497. (b) Butler, L. G.; Cheng, C. P.; Brown, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2738.

(34) Chesnut, D. B.; Phung, C. G. In *Nuclear Magnetic Shieldings and Molecular Structure*; Tossell, J. A., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1993; p 221.

(35) (a) Kuroki, S.; Takahashi, A.; Ando, I.; Shoji, A.; Ozaki, T. *J. Mol. Struct*. **1994**, *323*, 197. (b) Kuroki, S.; Ando, S.; Ando, I. *Chem. Phys*. **1995**, *195*, 107.

(36) Scheubel, W.; Zimmermann, H.; Haeberlen, U. *J. Magn. Reson*. **1985**, 63, 544.

(37) Wu, G.; Dong, S. To be submitted for publication.