COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Refinement of hydrogen atomic position in a hydrogen bond using a combination of solid-state NMR and computation

Robin K. Harris,*[a] Phuong Y. Ghi,[a] Robert B. Hammond,[b] Cai-Yun Ma[b] and Kevin J. Roberts[b]

[a] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE. E-mail: r.k.harris@durham.ac.uk; Fax: +44(0)191 384 4737; Tel: +44(0)191 334 2021*

[b] *Institute of Particle Science and Engineering, Department of Chemical Engineering, University of Leeds, Leeds, UK LS2 9JT. E-mail: cherbh@leeds.ac.uk; Fax: +44(0)113 3432405; Tel: +44(0)113 3432401*

Received (in Cambridge, UK) 4th August 2003, Accepted 29th September 2003
First published as an Advance Article on the web 20th October 2003

DFT computations of the proton chemical shift for the intermolecular hydrogen bond in the white form of methylnitroacetanilide, together with the experimental value obtained by high-speed magic-angle spinning NMR, enable the N–H distance to be determined as 1.03 ± 0.02 Å.

Hydrogen-bonding is ubiquitous in many areas of chemistry and vitally important for biochemistry. Although there is a vast amount of published research on characterising hydrogen bonds in solids, detailed information about the position of hydrogen atoms in hydrogen bonds for crystalline molecular organic compounds is not trivial to obtain. Although diffraction techniques are increasingly accurate in this respect, there is clearly room for alternative approaches. Since the advent of commercial high-speed (> 20 kHz) magic-angle spinning (MAS) rotors for NMR it has become much easier to locate chemical shifts of protons in hydrogen bonds. There are several publications[1–3] in which the positions of hydrogen atoms are obtained in unknown cases by using plots of chemical shifts *vs.* bond lengths for a series of related compounds. However, clearly such procedures require prior knowledge of many structures. Moreover, considerable scatter is generally found in the plots, resulting in substantial error-bars in the results. Here we present a method of obtaining more accurate information from a single NMR measurement on an organic compound of interest, followed by computations of shielding (and hence chemical shift) as a function of the hydrogen position.

The system chosen for study is methylnitroacetanilide (MNA). This exists in at least two polymorphic forms, isolated[4] as long ago as 1885, designated white and yellow, both of which have had their structures determined by single-crystal X-ray diffraction analysis.[5] The white form has a single molecule in the asymmetric unit and exhibits intermolecular hydrogen bonding between the amide nitrogen and amide carbonyl oxygen, forming a chain of molecules. The yellow form has two molecules in the asymmetric unit and shows intramolecular hydrogen bonding between the amide nitrogen and one of the oxygens of the nitro group. The ^{13}C MAS NMR spectra of the two forms have been reported.[6] Fig. 1 illustrates the high-speed ^{1}H MAS spectra, which clearly reveal the high-frequency shifts caused by hydrogen bonding. Evidently such bonds are marginally stronger in the white form (δ_H = 10.6 ppm) compared to the yellow form (δ_H = 10.1 ppm, average for the two molecules in the asymmetric unit).

The published structure of the white form[5] has hydrogens placed at (unrefined) chemically reasonable positions. We have used Gaussian 98 density functional theory (DFT)[7] computations based on the diffraction-determined structures of the H-bonded "dimer" in the cluster-model approach to NMR shielding in molecular solids to simulate the chemical shifts. We believe it is appropriate to use the heavy-atom positions as obtained from X-ray studies rather than fully optimised geometry since the former is a well-defined experimental situation. Many shielding computations use this approach and, moreover, there is generally little difference in results between the two cases.[8,9] When the published hydrogen atom position is used, the shielding difference between the computed average shift for the methyl protons and that of the H-bonded proton is 2.04 ppm, whereas the observed value is 7.80 ppm – a substantial discrepancy.

Therefore we computed this parameter as a function of the N–H bond length while retaining all other atoms at their known crystallographic positions. Fig. 2 shows a plot of the isotropic shielding constant against N–H distance. Use of this plot suggests the N–H bond length is 1.03 Å, with an estimated accuracy of ±0.02 Å. Obviously this is different from the

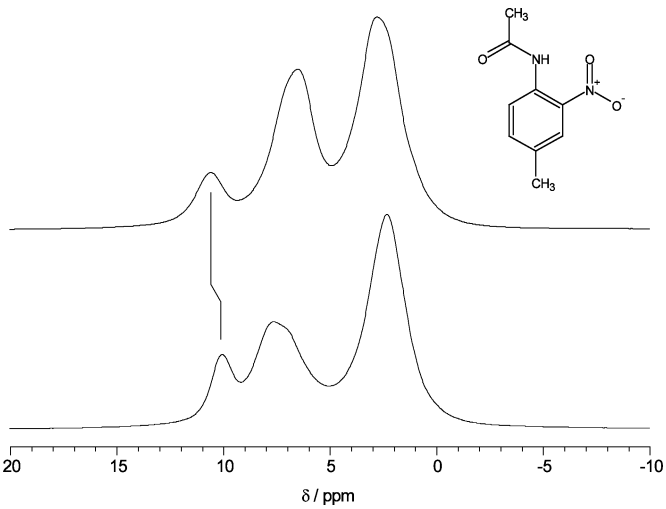

Fig. 1 Proton fast MAS NMR spectra of MNA. Top: white form. Bottom: yellow form. Upper right: molecular structure.

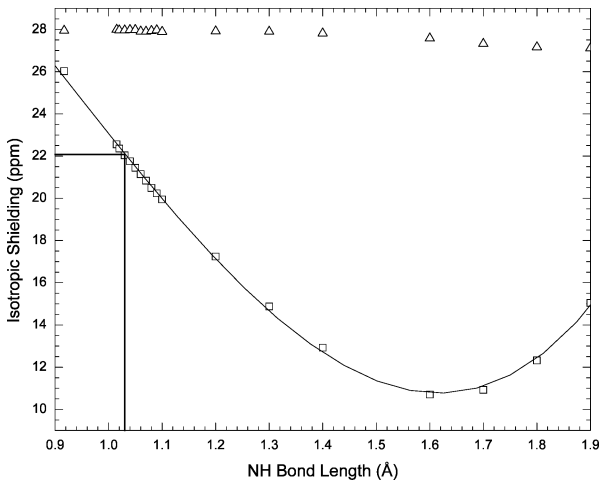

Fig. 2 DFT computed isotropic shielding constant (on an absolute scale) of the hydrogen-bonded proton in the white form of MNA, plotted (squares) as a function of the N–H distance for the dimer, with all other atoms fixed at the positions given in the literature.[5] The curve represents an empirical fit to a cubic equation. The triangles are for the hydroxyl proton of the dimer which is not hydrogen bonded. The horizontal and vertical lines show the derivation of the N–H distance from the observed shielding.

DOI: 10.1039/b309302f

published[5] value (0.92 Å). Variation of the N–H···O bond angle produces only a relatively small change in shielding. The minimum in Fig. 2 corresponds approximately to a central position for the hydrogen atom in the H-bond. The measured shielding clearly corresponds to a double-minimum energy situation. The points given by triangles show that the shielding of the hydroxyl proton in the dimer which is not involved in an H-bond does not vary significantly with the N–H bond distance in the dimer, as expected. Computations for the central molecule in a trimeric cluster showed a similar variation to Fig. 2.

Similar computations were carried out for the asymmetric unit of the yellow form, in this case for isolated molecules with the geometries appropriate to the crystallographic asymmetric unit. The results suggest a N–H bond length of 0.99 Å (average for the two molecules in the asymmetric unit) compared to the published value[5] of 0.92 Å. This value reflects the weaker hydrogen bonding in this polymorph.

Our methodology has been validated by applying it to L-histidine hydrochloride hydrate, where there are two N–H···O hydrogen bonds, involving nitrogen atoms designated as δ_1 and ε_2. The crystal structure has been solved by both X-ray[10] and neutron[11] diffraction. Moreover, the N–H distances have also been derived[12,13] from NMR dipolar coupling constants. Table 1 gives the relevant data.

X-ray diffraction responds to electrons rather than nuclei whilst dipolar coupling constants (and hence derived internuclear distances) are strongly influenced by local motions.[14] Neutron diffraction is expected to give the most accurate distances between nuclei (but the technique is not readily available). The data show that our method gives better results than either X-ray diffraction or dipolar coupling for L-histidine hydrochloride monohydrate.

Therefore we believe our approach, which does not require measurements for a range of related compounds, is a useful additional tool in the armoury for characterising hydrogen bonds in crystalline organic molecular solids. It is likely to be widely applicable.

The ^{1}H spectra were obtained on a Varian Infinity Plus 500 spectrometer, operating at 499.75 MHz for ^{1}H. A 2.5 mm od rotor was used with a spin rate of 27 kHz. A $\pi/2$ pulse of duration 3 μs was employed, with a recycle delay of 100 s, required because the spin-lattice relaxation time of the H-bonded proton is long. A total of 32 transients were collected, each transient containing 1024 data points. The FIDs were zero-filled to 8192 data points and Fourier-transformed with 6 points of back-linear prediction.

Table 1 N–H distances for L-histidine hydrochloride monohydrate

Method	N(δ_1)–H/Å	N(ε_2)–H/Å
X-ray diffraction[10]	0.883	0.956
Neutron diffraction[11]	1.070	1.026
NMR dipolar coupling[12]	1.090	1.050
NMR dipolar coupling[13]	1.11–1.14	1.07–1.09
NMR shielding (this work)	1.080	1.015

Computations were carried out on a Sun work station, using Gaussian 98 Rev A.9.[7] DFT calculations used the B3LYP functional which has been shown[15] to satisfactorily model hydrogen bonds. Convergence was achieved with the basis set 6-311+G**.

We thank EPSRC for funding this project under grants GR/N06670 and GR/N05635. We are grateful to AstraZeneca UK Ltd., GlaxoSmithKline plc, Pfizer Ltd. and Sanofi Winthrop Ltd. for additional financial support.

Notes and references

1 B. Berglund and R. W. Vaughan, *J. Chem. Phys.*, 1980, **73**, 2037.
2 R. K. Harris, *J. Chem. Soc., Faraday Trans. 1*, 1988, **84**, 3649.
3 K. Yamauchi, S. Kuroki and I. Ando, *J. Mol. Struct.*, 2002, **602–603**, 9.
4 L. Gutterman, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 1483.
5 J. C. Moore, A. Yeadon and R. A. Palmer, *J. Crystallogr. Spectrosc. Res.*, 1983, **13**, 279.
6 R. A. Fletton, R. W. Lancaster, R. K. Harris, A. M. Kenwright, K. J. Packer, D. N. Waters and A. Yeadon, *J. Chem. Soc., Perkin Trans. 2*, 1986.
7 Gaussian 98, Revision A.9, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
8 J. C. Facelli, *J. Phys. Chem.*, 1998, **102**, 2111.
9 G. R. Goward, D. Sebastiani, I. Schnell, H. W. Spiess, H.-D. Kim and H. Ishida, *J. Am. Chem. Soc.*, 2003, **125**, 5792.
10 K. Oda and H. Koyama, *Acta Crystallogr., Sect. B*, 1972, **28**, 639.
11 H. Fuerst, D. Hohlwein and S. F. Mason, *Acta Crystallogr., Sect. B*, 1977, **33**, 654.
12 X. Zhao, J. I. Sudmeier, W. W. Bachovchin and M. H. Levitt, *J. Am. Chem. Soc.*, 2001, **123**, 11097.
13 I. Schnell and K. Saalwächter, *J. Am. Chem. Soc.*, 2002, **124**, 10938.
14 Y. Ishii, T. Terao and S. Hayashi, *J. Chem. Phys.*, 1997, **107**, 2760.
15 G. A. Kumar, Y. P. Pan, C. J. Smallwood and M. A. McAllister, *J. Comput. Chem.*, 1998, **19**, 1345.