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Influence of low-barrier hydrogen bonds on solid state ^{17}O NMR spectra of labelled phthalate species

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The first ^{17}O solid state NMR study of a low barrier hydrogen bond (LBHB) is reported which shows that very strong hydrogen bonds strongly affect both the quadrupole interaction and the isotropic chemical shift reducing both.

Hydrogen bonding plays a vital role in both chemical and biological systems. Non-covalent forces are important in determining the secondary, tertiary and quaternary structures of proteins. Changes in hydrogen bonding interactions between ground and transition states can also make an important contribution to enzyme catalysis.[1] The proposal that short strong hydrogen bonds (SSHBs) can contribute up to 20 kcal mol^{-1} stabilisation energy to transition states[1–3] has provoked a vigorous debate in which the validity of this concept has been challenged.[4–6] SSHBs have been taken as synonymous with low barrier hydrogen bonds (LBHBs).[7] In such bonds, the potential energy barrier between the two possible states of a hydrogen bond, in which the hydrogen atom is associated with either one or other of the donor or acceptor atoms, is lowered so that a single well potential energy system results. The monoanions of carboxylic acids have been the focus of most studies of LBHBs with examples reported of both centred and non-centred hydrogen atoms.[8] In these systems the O–O bond is short (~ 2.4 Å) but the concept that such short bonds should be associated with exceptional hydrogen bond strength has been disputed.[4,6,9]

Solid state ^{17}O NMR can be used, in principle, to study hydrogen bonding since oxygen is directly involved in the bonds of interest. The ^{17}O isotropic chemical shift (δ_{iso}), the quadrupole coupling constant (C_Q)[10] and the asymmetry parameter (η) are very sensitive to the bonding state.[11] Despite the low natural abundance (0.037%) and consequent necessity for enrichment in ^{17}O the number of solid state NMR studies in recent years has increased rapidly because of the high sensitivity of the ^{17}O NMR parameters to local structural details and its ability to probe directly structurally significant environments.[12,13] Most work to date concerning application of ^{17}O NMR to study hydrogen bonding has been in solution. In recent solution work the relaxation times of the ^{17}O have been used to determine the quadrupole interaction which has subsequently been related, *via ab initio* calculations, to the bonding state.[11] There have recently been some preliminary solid state ^{17}O measurements in a hydrogen bonded environment,[14] however the current study is the first report of ^{17}O in a SSHB. Solid state NMR spectra are presented from ^{17}O-labelled phthalic acid[15] and three alkali metal mono- and di-anion phthalates.[16–18]

^{17}O solid state NMR spectra were accumulated at a resonance frequency of 81.35 MHz on a Varian-Chemagnetics Infinity 600 spectrometer. Fast magic angle spinning (MAS) of ~ 20 kHz was used in a Chemagnetics 3.2 mm probe. Short excitation pulses were applied of 0.6 μs (corresponding to a tip angle of π/6) and 1.2 μs in a spin-echo sequence. The echo spacing was approximately an integral number of rotation periods. Typically 100–500k acquisitions were co-added using a recycle delay of ~ 1 s. Spectra were referenced to H_2O at 0 ppm. The MAS NMR spectra together with simulations are shown in Fig. 1.

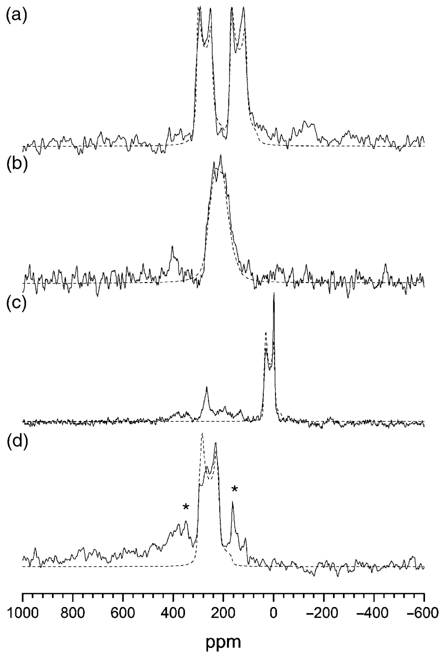

Fig. 1 ^{17}O 14.1 T MAS NMR spectra of (a) phthalic acid, (b) dilithium phthalate hemihydrate, (c) lithium hydrogen phthalate dihydrate and (d) potassium hydrogen phthalate dihydrate. [Note that the spinning speed in (d) was lower so that the spinning sidebands (*) are more prominent.]

Phthalic acid shows two completely resolved well defined second-order quadrupolar lineshapes[10] [Fig. 1(a)] with similar C_Q values but with δ_{iso} values that differ by ~ 130 ppm (Table 1). The dilithium salt gives a broader line intermediate in position to the two resonances of phthalic acid [Fig. 1(b)]. A single set of parameters provides a good simulation of both the MAS and static spectra (latter not shown) and this was confirmed by repeating the experiment at a different applied magnetic field. The monolithium salt has a well defined second-order quadrupolar lineshape with a large decrease in the isotropic chemical shift [Fig. 1(c), Table 1]. (The very sharp feature on this line at ~ 0 ppm is due to a small amount of fluid-like water in the sample.) There is also some weak intensity in the region 200–300 ppm. The monopotassium salt shows a

Table 1 ^{17}O NMR parameters from simulation of the MAS NMR spectra

Sample	δ_{iso}(ppm) ± 5	C_Q/MHz ± 0.1	η ± 0.05
Phthalic acid			
Site 1	312	7.2	0
Site 2	180	7.4	0
Lithium hydrogen phthalate dihydrate	46	5.9	0.21
Dilithium phthalate hemihydrate	272	7.6	0.44
Potassium hydrogen phthalate dihydrate	305	8.4	0.2

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quadrupolar lineshape [Fig. 1(d)] with NMR parameters that are similar (Table 1) to the dilithium salt and phthalic acid, but are very different from the monolithium salt.

The ^{17}O NMR parameters observed in these four compounds show a very wide variation compared to previous studies, covering a chemical shift range $\geqslant$250 ppm with C_Q differences of ~40%. Recently there have been the first reports of high resolution ^{17}O NMR studies of solid organic materials. In poly(L-alanine) the α-helix and β-sheet show a difference in δ_{iso} for ^{17}O of 33 ppm, which is related to the different hydrogen bonding of these different units.[19] In potassium hydrogen benzoate the distinct oxygen sites show a difference in parameters of C_Q = 8.5 MHz, δ_{iso} = 290 ppm for the carbonyl group oxygen atom, and C_Q = 6.3 MHz and δ_{iso} = 230 ppm for the hydroxy group oxygen atom.[20] The limited data that currently exist for such materials indicate that as the hydrogen bond strength increases the shielding increases, so that both the chemical shift and C_Q decrease. Phthalic acid has two oxygen sites in the ratio 1 : 1. From comparison with solution ^{17}O NMR studies, the peak with a shift of 312 ppm can be assigned to the carbonyl group oxygen atom. The shift difference between the two observed peaks results from the different chemical nature of these species. However the similarity of C_Q indicates that the degree of hydrogen bonding is similar and this is confirmed by the similar O–O distance[21] of these sites. The equality of the signal intensity indicates that the two sites were equally enriched, as expected. The dilithium salt showed a chemical shift of ~280 ppm, comparable with phthalic acid. A single set of parameters simulates the line well, hence either the notionally different sites are in fact very similar, or on the NMR timescale there is some averaging of the environments. Neutron diffraction studies of lithium hydrogen phthalate monohydrate[17] have revealed that it exhibits a very short hydrogen bond with the structural properties associated with LBHBs (O–O distances of 2.4 Å). The oxygen resonance observed in the spectrum of lithium hydrogen phthalate hemihydrate in the present study provides strong evidence for a LBHB since it has a low isotropic chemical shift (the *lowest* yet reported for such a compound) and a much smaller C_Q than the other salts. The NMR spectrum reveals only one site with some additional minor intensity. Observation of a single site could indicate that locally the sites are structurally the same or alternatively there is some averaging for the NMR that is not seen by diffraction, highlighting the caution needed when the term equivalence is invoked since it depends on the timescale. This is likely to be especially true when small, mobile atoms such as hydrogen and lithium are present. The single line implies that in lithium hydrogen phthalate hemihydrate all the oxygen sites are equivalent on the NMR timescale, a result that may be attributable to electronic equivalence. Alternatively, it may be attributed to dynamic proton disorder, as has been proposed to explain an analogous equivalence in the ^{17}O solid state NMR spectrum of the benzoic acid dimer.[20] The monopotassium salt of phthalic acid contains an intermolecular hydrogen bond according to an X-ray determination and not a strong symmetric intramolecular hydrogen bond.[22] A single site simulation consistent with the MAS data is shown (and is also consistent with static and multiple field data). The ^{17}O NMR interaction parameters are similar to the dilithium salt with an isotropic chemical shift of ~305 ppm and C_Q = 8.4 MHz. There is *no* evidence of a second environment with a smaller quadrupole interaction and there is certainly no intensity at the shift seen in the monolithium salt. Hence as expected from the crystal structure there is no ^{17}O resonance characteristic of an SSHB environment. The contrast between the ^{17}O NMR spectra of these monoanionic salts is striking since the resonance of the lithium with the SSHB salt is shifted by a large amount compared to the potassium salt where the hydrogen bonding is weaker. As more data is collected it will become important to establish the exact nature of the correlation between the NMR parameters and the hydrogen bond strength.

This communication shows that ^{17}O NMR is a direct and sensitive probe of the hydrogen bonding state in solid organic compounds, easily identifying low barrier hydrogen bonds. The data indicates that the quadrupole interaction and in particular the chemical shift are strongly affected by hydrogen bonding. ^{17}O NMR should find widespread application as a probe of hydrogen bonding state, identifying other SSHBs, and determining the protonation states of proteins.

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