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Isotopomeric Polymorphism

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Isotopic substitution is generally regarded as nonperturbing. Changing one isotope for another can certainly affect the molecular spectroscopy and to a lesser extent the structure (via the so-called geometric isotope effect[1]); it changes kinetics[2] and equilibrium constants[3] and can alter the temperature of spontaneous phase transitions,[4] sometimes by as much as 25 K.[5] However, when isotopically labeled substances are being used, the usually well-justified assumption is made that they do not alter the fundamental nature of the material under study. We shall show that in at least one instance—the complex of pentachlorophenol with 4-methylpyridine (4MPPCP)—this assumption is unjustified; substitution of a single deuterium for a normal hydrogen leads to the thermodynamic stability of an entirely different crystal polymorph.

Compounds of pentachlorophenol with nitrogen bases range from hydrogen-bonded complexes, in which the phenolic O−H remains intact, to *bona fide* salts, where the phenolic proton is fully transferred to the nitrogen.[6] The extent of the proton transfer obviously depends on the relative pK_a of phenol and conjugate acid. The most interesting behavior is found in the critical region, where the proton is partially transferred. This is encountered in the compound of PCP with 4-methylpyridine (4MP); 4MPPCP has a very short O−H···N hydrogen bond[7] (r_{NO} = 255 pm at 300 K), which further shortens[8] at low temperature; neutron diffraction shows the proton migrates to a near centered position at low temperature.[9] Most remarkable, however, is the report that a different crystal structure is obtained when the compound is singly deuterated on the hydrogen bond proton (giving 4MPPCP-d_1). 4MPPCP has a triclinic structure, while the structure obtained for 4MPPCP-d_1 is monoclinic and disordered.[10] The hydrogen bond in the monoclinic form is considerably weaker (r_{NO} = 263 pm); the relative orientation of the two rings is quite different, and there is no obvious relationship between the two structures.

This phenomenon could, of course, have been ordinary polymorphism; the two isotopomers were originally prepared differently and crystallized from different solvents. Nonetheless, the intriguing possibility that the relative thermodynamic stability of two polymorphs might hinge on a single isotope substitution led us to prepare the two isotopomers and investigate them by solid-state NMR.

Figure 1 compares the centerband region of the proton magic angle spinning NMR[11] spectra of 4MPPCP,[12] with 0, 55, and 90% deuterium on the hydrogen-bonded position. Only the rotational centerband is shown. The four lines in the 0% structure correspond, reading from left to right, to the OH, pyridine 3,5 and 2,6 protons, and the methyl groups. Their intensities (when centerbands and rotational sidebands are summed) are close to the expected 1:2:2:3 ratio. The low shielding of the OH proton (δ_i = 17.9 ppm at 298 K) is consistent with the strong hydrogen bond in the triclinic form.

The more shielded region of the spectrum of the 90% deuterated sample is similar but not identical to that of the 0% sample; however, the OH resonance in the less shielded region of the spectrum is replaced by two weak peaks at 12 and 14 ppm. These clearly belong to residual OH protons. The splitting of these peaks is presumably a result of the reported crystallographic disorder; their comparatively lower chemical shifts bespeak a much weaker hydrogen bond. These results immediately confirm that the protonated and 90% deuterated materials have different structures and that neither sample contains the other polymorph.

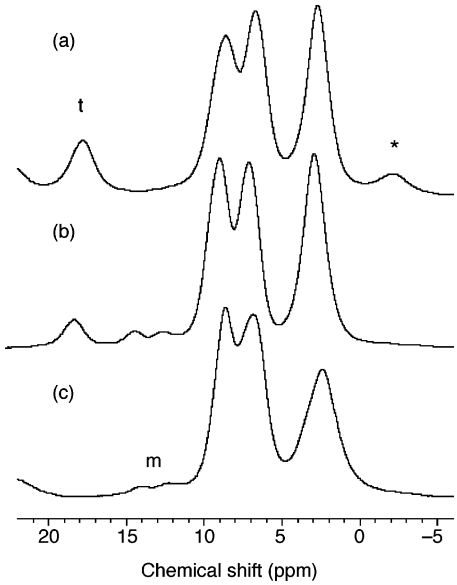

Figure 1. ^{1}H MAS NMR spectra of (a) 4MPPCP, (b) 4MPPCP-$d_{0.9}$, (c) 4MPPCP-$d_{0.55}$. Monoclinic and triclinic OH signals are indicated by "m" and "t"; a rotational sideband is marked with an asterisk.

Both polymorphs of 4MPPCP melt at around 70 °C without decomposition; repeated cycles of melting and freezing do not induce any signal from the other polymorph. Seeding the molten deuterated form with a few crystals of the triclinic polymorph gives no detectable quantity of that form; seeding the protonated form with the monoclinic polymorph results in only a very small proportion of the latter form. Protonated crystals all correspond crystallographically to the reported triclinic unit cell; conversely, crystals of the 90% deuterated form all give the monoclinic cell. Finally, the spectrum of 55% deuterated material (Figure 1b) shows resonances from both polymorphs; the relative intensities of these resonances do not change on repeated cycles of melting and refreezing in a MAS sample rotor within the NMR spectrometer.

Further evidence is provided by ^{2}H NMR. At low levels of deuteration we encounter (Figure 2a) a MAS spectrum with few sidebands, indicating a small electric quadrupole coupling constant. At 90% deuteration (Figure 2c) a much more extensive series of sidebands is obtained; with the 55% deuterated sample, interleaved sets of chemical-shift resolved sidebands are observed. While the deuterium quadrupole coupling constant of both forms varies somewhat with isotope composition, there are clearly two distinct crystalline forms present at intermediate isotope compositions.

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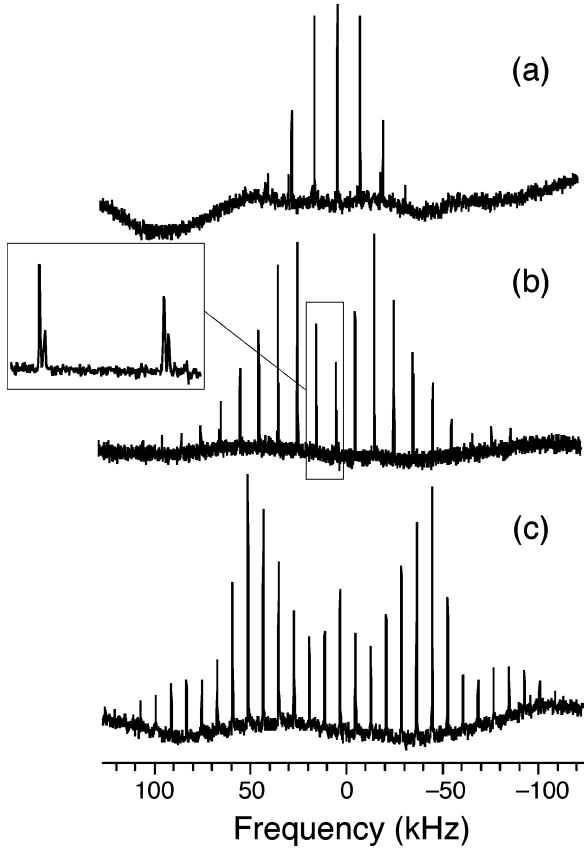

Figure 2. ^{2}H MAS NMR spectra of (a) 4MPPCP-$d_{0.1}$, (b) 4MPPCP-$d_{0.55}$, (c) 4MPPCP-$d_{0.9}$. (Inset) Centerband and the +1 sideband at higher resolution.

Table 1. NMR Parameters of the Two Polymorphs of 4MPPCP; Deuterium Data for the Triclinic Form Were Extracted from the 10% Deuterated Sample

	e^2qQ/h (kHz)	η_Q	σ_{iso} (ppm)	$\Delta\sigma$ (ppm)	η_s
triclinic	88	0.27	17.9	37	0.3
monoclinic	137	0.10	13.0	8	−

Table 1 gives the limiting chemical shift and quadrupolar couplings; in every instance, the data are consistent with a strong hydrogen bond in the triclinic polymorph and a much weaker hydrogen bond in the monoclinic form.

Over a concentration range of 20−80% of deuterium, both polymorphs are present; in this concentration range, the two isotopomers of 4MPPCP are immiscible in the solid state! Significant isotope fractionation is observed between the two polymorphs with protons, as expected, favoring the triclinic form.

What is the physical origin of the differential stability of the isotopomer polymorphs? One clue to this comes from the temperature dependence of the proton chemical shift. Over the range 190−322 K, the triclinic OH proton chemical shift decreases from 19.0 to 17.7 ppm. Such large temperature coefficients are characteristic of low-barrier hydrogen bonds,[13] since they demand a thermally accessible vibrational excited state with significantly different properties from those of the ground state. A LBHB potential, however, also entails a comparatively small vibrational zero-point energy for this mode and a correspondingly small energy difference between hydrogen and deuterium zero-point energies. In contrast, a more normal hydrogen-bonded OH would be expected to have zero-point energies which differ by 400−500 cm^{-1} from hydrogen to deuterium. If, therefore, the hydrogen and deuterium zero-point energies of the triclinic form are straddled by the zero-point energies of the monoclinic form, then the deuterated monoclinic and protonated triclinic forms will be thermodynamically stable. Hydrogen bonding is known to drive other varieties of polymorphism;[14] we note parenthetically that 4MPPCP-d_7 (deuterated everywhere except the hydrogen bond) crystallizes 100% in the triclinic structure, emphasizing that the polymorphism is mediated only by the atom in the hydrogen bond. Thermotropic solid−solid-phase transitions have not been observed in these compounds.

We dub this phenomenon "isotopomeric polymorphism". While its occurrence is likely a serendipitous concurrence of strongly and weakly hydrogen-bonded polymorphs with closely matched lattice energies, it demonstrates that the nonperturbing nature of a given isotope substitution is something that needs to be demonstrated, not assumed.

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(11) ^{1}H and ^{2}H NMR spectra were obtained using a Bruker Avance NMR spectrometer operating at a field of 14 T, using a simple one-pulse sequence with magic angle spinning. The respective 90° pulses were 4.0 and 3.0 μs; both isotopes were referenced to the respective isotropic frequencies of solid dimethyl sulfone-d_6, which was assumed to lie 2.4 ppm downfield from TMS.
(12) 4MPPCP was obtained by dissolving pentachlorophenol (Aldrich; recrystallized from acetone) in dry acetonitrile, adding an equimolar amount for freshly distilled 4-methyl pyridine, and allowing to crystallize. It was deuterated by solution in and evaporation from CH_3OD and recrystallized from dry ethanol. Intermediate isotope compositions were obtained by mixing weighed amounts of the dry isotopomers in a sealed flask in a dry environment, followed by melting at ~70 °C in a water bath.
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