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Pressure-induced formation of a solvate of paracetamol

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Recrystallisation of paracetamol from a solution in methanol at a pressure of 0.62 GPa gives a new 1 : 1 solvate that has been characterised by single crystal X-ray diffraction.

The phenomenon of solvate formation during the crystallisation of organic compounds is not only of fundamental interest to experimental and theoretical structural chemists, but is also of crucial importance to the pharmaceutical industry.[1] The conditions under which solvates are formed or undergo desolvation are also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling and compression. Paracetamol (acetaminophen) is an analgesic drug that is used widely throughout the world. Despite extensive studies on the crystallisation of the compound from a wide range of solvents, it is only very recently that the first of its solvates or adducts have been isolated and structurally characterised. These include a monohydrate[2] and a trihydrate,[3] five hemiadducts of paracetamol with 1,4-dioxane, *N*-methylmorpholine, morpholine, *N*,*N*-dimethylpiperazine and piperazine, and a related 1 : 1 adduct of paracetamol with 4,4′-bipyridine.[4,5]

Whilst the thermal stabilities of the paracetamol adducts containing amines and dioxane are generally relatively high, this is not the case for the two hydrates and both compounds dehydrate within minutes at temperatures greater than 0 °C to give the monoclinic polymorph of paracetamol.[2,3] All previous attempts to obtain solvates of paracetamol with simple alcohols have been unsuccessful.[6]

The application of high pressures has been shown to be particularly effective at modifying intermolecular interactions and frequently leads to new polymorphs of simple organic compounds, particularly when crystal growth occurs from liquids under pressure.[7] Boldyreva *et al*. have also demonstrated that the application of pressures in excess of 4 GPa to solid paracetamol results in conversion of the monoclinic polymorph to the orthorhombic form, but for kinetic reasons the conversion is incomplete.[8] In order to overcome these kinetic factors, we are currently investigating the effects of high-pressure recrystallisation from *solution*, with particular emphasis on the preparation of new solvates (and polymorphs) of pharmaceutical compounds. Thus recrystallisation of paracetamol from a methanol solution contained in a Merrill-Bassett diamond-anvil cell at a pressure of 0.62 GPa resulted in the growth of a single crystal (Fig. 1), subsequently identified as a 1 : 1 paracetamol–methanol solvate.† On returning to ambient pressure the crystal redissolved and so all measurements were performed *in situ* at 0.62 GPa.

The Raman spectra‡ of both known polymorphs of paracetamol have been shown to be almost identical, and feature a characteristic pattern of bands in the region 1450–1800 cm^{-1} associated with the stretching modes of C=O and aryl C–C bonds, and the deformation mode of the N–H bond.[9] Our Raman studies on the monoclinic polymorph of paracetamol in the absence of methanol show that this pattern persists at high pressures, although the bands are shifted to higher energy. Infrared studies on the monoclinic polymorph at pressures up to 5.0 GPa also show this to be the case.[10] In contrast, the Raman spectrum of the crystal recrystallised from methanol at 0.62 GPa and contained within the diamond-anvil cell showed a substantially different pattern of bands in this region, thereby indicating the formation of either a new polymorph of paracetamol or a solvate.

Indexing of the reflections obtained from a single crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from either of the two known polymorphs of paracetamol.[11] Solution and refinement of the structure was not straightforward using direct methods owing to the limited amount of data that can be collected using the diamond-anvil cell on account of shading by the body of the pressure cell. Hence the incomplete data set was input into the global optimisation program, DASH, that has recently been modified to solve structures from high-pressure single crystal data-sets collected on a range of small molecule structures.[12] This program rapidly identified a global minimum by simulated annealing thereby allowing subsequent refinement of the structure.§ Whilst not ideal, the *R*-factor of 13.4% is typical for refinement of high-pressure data sets and is sufficient to identify the main structural features of the solvate.

The crystal packing of this solvate is dominated by hydrogen bonding giving rise to layered two-dimensional networks (Fig. 2). One of the two layers is also found in the monoclinic and orthorhombic polymorphs of paracetamol – the NH···OH hydrogen bond forms C(7) motifs at the unitary level of graph set analysis.[18] However, it should be noted that the conformation of the paracetamol molecules in the solvate is different from that of the monoclinic and orthorhombic forms, *i.e*. the H–N···O–H dihedral angle is close to 180° for the solvate, but is close to 0° for the monoclinic and orthorhombic forms. These chains are linked *via* methanol molecules giving an overall layered structure that closely resembles that of the paracetamol monohydrate, although in the monohydrate the additional O–H bonds of water molecules link layers together to form a three dimensional network.[2] One striking feature of the structure of the methanol solvate is the presence of large hydrophobic cavities.

Given the paucity of the data, it is not possible to discuss the detailed aspects of the hydrogen bonding in the structure. Nevertheless, it is possible to rationalise the pattern of donor–acceptor interactions found in the structure by examining the

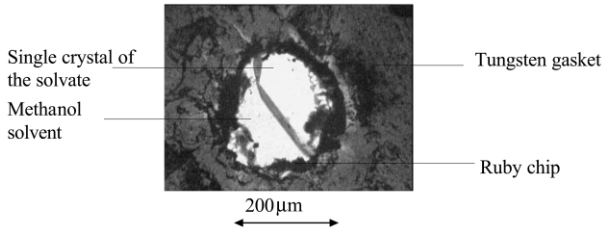

Fig. 1 Optical image of single crystal of the paracetamol–methanol 1 : 1 solvate in a diamond-anvil cell at 0.62 GPa.

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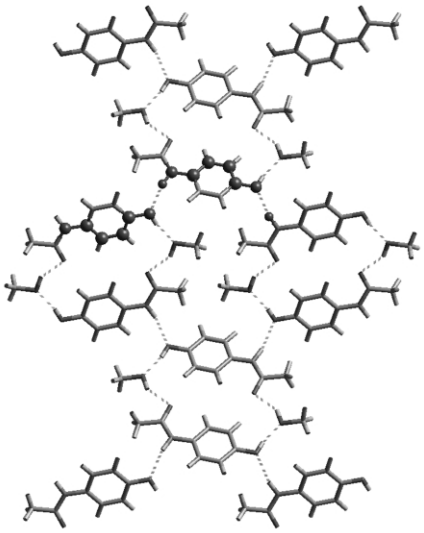

Fig. 2 Two dimensional hydrogen bonded network of paracetamol–methanol solvate at 0.62 GPa [C(7) chains referred to in the text are shown as balls and sticks].

relative strengths of H-bonding interactions using the assumption that hydrogen-bond strength is related to the average donor-hydrogen–acceptor distance. A search of the Cambridge Structural Database (version 5.24) for ArOH···O(H)R, ArOH···O=C(amide) and ROH···O=C(amide) mean hydrogen bond lengths is summarised in Table 1.

For both the monoclinic and orthorhombic polymorphs of paracetamol, the two interactions are NH···O(H)Ar and ArOH···O=C(amide), and on the basis of Table 1 the latter is the stronger of the two. Rather surprisingly then, in the methanol solvate the former interaction persists whilst the latter interaction is not present, but is replaced by two new interactions ROH···O=C(amide) and ArOH···O(H)R. One way of rationalising this observation is to identify from the Table the strongest ROH···O interaction, which is ROH···O=C(amide). Given this, it is then a competition between either the combination NH···O(H)Ar and ArOH···O(H)R or the combination NH···O(H)R or ArOH···O(H)Ar. At 1.78 Å the strongest interaction is ArOH···O(H)R thereby favouring the former combination.

The angle between the mean planes of the amide and phenyl group is known to be very susceptible to the degree of protonation/deprotonation of the OH and NH groups[19] and at 11.2° is close to that found in the monohydrate (10.3°), but significantly different from the corresponding angles in the monoclinic and orthorhombic polymorphs of paracetamol (20.5° and 17.7°, respectively).

This work demonstrates the potential of high-pressure recrystallisation as a method for the preparation of new solvates of pharmaceutical compounds. Investigations are underway to discover whether slow release of pressure at low temperature will allow isolation of such solvates at ambient pressure.

Table 1 Mean hydrogen bond lengths obtained from searches of the CSD for typical distances in hydrogen bonded systems containing specified functional groups. Distances to hydrogen atoms were normalised to typical neutron distances (N–H 1.009 and O–H 0.983 Å)

	Acceptor (O)		
Donor (O–H or N–H)		O(H)Ar	O(H)R
ArO–**H**	1.78	1.87	1.78
	1.92	1.99	1.92
RO–**H**	1.84	1.89	1.85

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Notes and references

† *Crystallisation procedure*. A solution of paracetamol in methanol (*ca*. 1 M) was loaded at 20 °C into a Merrill-Bassett diamond-anvil cell[13] equipped with 800 μm culet diamonds and a tungsten gasket. By varying the pressure in the range 0.1–1.0 GPa, a pressure of 0.62 GPa was found to be the optimum. At this pressure and at ambient temperature, precipitation of polycrystalline material occurred. The temperature was then cycled near *ca.* 60 °C in order to dissolve all but one of the crystallites and on slow cooling to 20 °C a single crystal grew from solution.

‡ Raman spectra were recorded using a Jobin-Yvon LabRam 300 instrument with excitation by a Hg–Cd laser operating at 441.4 nm.

§ *Crystal data*. Diffraction data were collected on a Bruker APEX CCD diffractometer at 293(2) K using Mo–Kα radiation (λ = 0.71073 Å) and the SMART program for control of data collection.[14] The program GEMINI[14] was used to obtain an orientation matrix. Data reduction was performed using SAINT.[14] The program SHADE[15] was used to reject reflections for which either the incident or the diffracted beam was completely absorbed by the cell resulting in the shading of the detector, and also performs an analytical correction for cell absorption. Reflections with very poorly fitting profiles between their measured and calculated profiles were also rejected. An absorption correction was applied using the program SADABS.[16] Structure solution was performed using the program DASH.[12] Full matrix structure refinement was performed using CRYSTALS.[17] The positional coordinates of methanol and paracetamol atoms were refined as two separate rigid groups. All non-hydrogen atoms were refined isotropically and hydrogens were placed in calculated positions.

$C_9H_{13}NO_3$, M = 183.21, colourless block, monoclinic, $P2_1/c$, a = 7.630(2), b = 17.209(3), c = 7.3708(11) Å, β = 115.52(3)°, V = 873.4(4) Å^3, ρ (calc.) = 1.393 g cm^{-3}, T = 293 K, μ = 0.105 mm^{-1}, 801 reflections measured of which 223 were independent (R_{int} = 0.05), θ_{max} = 20.84°, 14 parameters and 4 restraints, a 2θ cut off of 36.3° was used giving 172 unique reflections, R = 0.1342 [based on F^2 and 118 data with $F^2 > 2\sigma(F^2)$], R_w = 0.2161 (based on F^2 and all 172 reflections), the final difference maps extremes were +0.33 and −0.43 e Å^{-3}. CCDC 218910. See http://www.rsc.org/suppdata/cc/b3/b310394c/ for crystallographic data in .cif or other electronic format.

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