Interesting proton behaviour in molecular structures. Variable temperature neutron diffraction and *ab initio* study of acetylsalicylic acid: characterising librational motions and comparing protons in different hydrogen bonding potentials†

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Received (in London, UK) 18th April 2002, Accepted 9th October 2002
First published as an Advance Article on the web 11th November 2002

Variable temperature single crystal neutron diffraction has been used to examine the behaviour of protons in the structure of acetylsalicylic acid (Aspirin). The neutron diffraction study, at seven temperatures between 20 and 300 K, has allowed a full description of the molecular structure and the intermolecular interactions in the material and their variation with temperature. In particular the variable temperature studies have allowed the full description of the apparent torsional motions of the terminal methyl group, which exhibit characteristic substantial zero-point motion. The extracted values for the barrier height for the cosine potential governing this motion are found to be in good agreement with that found from *ab initio* calculations and are compared with those found in a range of other materials. Our previously postulated empirical method for correcting bond lengths in such a case is once again found to have some validity. The data also yield a full description of the various hydrogen bonds present, notably the direct observation of likely anharmonicity in the potential governing the hydrogen bond in the carboxylic acid dimer motif. The availability of data at various temperatures is found to be important in identifying this effect, and in discriminating between alternative explanations of the observed structural parameters. The direct images of protons in various hydrogen bonding potentials, calculated from the neutron data, are also found to be valuable in this context.

1. Introduction

As part of an ongoing programme examining hydrogen bonding, detailed hydrogen atom parameters and possible hydrogen atom disorder, particularly in pharmaceutical and bioactive molecules, we have determined the crystal and molecular structure of acetylsalicylic acid by variable temperature single crystal neutron diffraction. The compound under study is a widely used proprietary painkiller and analgesic, commonly marketed as Aspirin (brand-name registered by Bayer) which also finds wide use as an anti-coagulant and in the treatment of heart conditions.

The structure of the title compound has previously been determined by X-ray diffraction,[1] and an improved determination by Kim *et al.*[2] The compound ($C_9H_8O_4$; $M = 180.16$) crystallises in space group $P2_1/c$ with four molecules in the unit cell. The structure consists of centrosymmetric dimers, with two molecules linked through the familiar carboxylic acid dimerisation unit comprising two hydrogen bonds. This dimeric linkage takes place across the centre of symmetry in the crystal structure.

Since our interest is in the detailed arrangement and behaviour of hydrogen atoms, our method of choice is neutron single crystal diffraction, which allows accurate and reliable determination and refinement of hydrogen atom parameters, including their anisotropic atomic displacement parameters (ADPs).

Recent work in this area has shown there to be much untapped information in the hydrogen atom behaviour in a range of molecules, not only by adding the extra information obviously available from a neutron determination, but also in particular by extracting additional information from determining the neutron structure at a series of temperatures. Determination of a structure at a series of temperatures can allow important information regarding hydrogen atom "dynamics" to be obtained, for example methyl group librations and vibrations,[3–6] proton migration[7–9] and proton disorder.[10,11]

A detailed account of the basic structure and crystal packing in Aspirin is available in the account of the X-ray study,[2] and a preliminary account of the variable temperature neutron study has been published.[12] We concentrate here on more detailed aspects of the variable temperature neutron diffraction findings, particularly with reference to the physics underlying some of these. Part of this work has also been used to benchmark *ab initio* isolated molecule quantum chemical calculations.

2. Experimental

The single crystal used in this experiment was grown by slow evaporation from a water–ethanol solution, and was of dimension $4 \times 3 \times 2$ mm^3. The large sample volume allowed the variable temperature data sets to be collected in a rather short data collection time.

The crystal was mounted inside a Displex closed cycle refrigerator on a (φ, χ) orienter, yielding temperature control of better than ± 1 K throughout the experiment. Data were collected on the SXD instrument at the ISIS spallation neutron source,[13] using the time-of-flight Laue diffraction method.[13,14] This

† Electronic supplementary information (ESI) available: bond lengths and angles from the refinements, refined atomic coordinates and ADPs. See http://www.rsc.org/suppdata/nj/b2/b203775k/

Table 1 Summary of data collection and refinement parameters

Diffractometer	SXD neutron time-of-flight Laue diffractometer
Detectors	Two, 64×64 element 3×3 mm pixel, scintillator PSDs
Detector position	Low angle: $2\theta_c = 55°$, $L_2 = 190$ mm; High angle $2\theta_c = 125°$, $L_2 = 150$ mm
Wavelength range	0.5–5.0 Å
Compound	2-(acetoyloxy)benzoic acid (Aspirin), $C_9H_8O_4$
Molecular weight	180.2
Recrystallising solvent	water/ethanol
Crystal size	$2 \times 2 \times 1.5$ mm^3

Unit cell	Space group $P2_1/c$, $Z = 4$						
***T*/K**	**20**	**60**	**100**	**140**	**180**	**220**	**300**
***a*/Å**	11.186(3)	11.204(3)	11.233(3)	11.273(3)	11.305(3)	11.340(3)	11.416(5)
***b*/Å**	6.5400(10)	6.5440(10)	6.5440(10)	6.5550(10)	6.5630(10)	6.5740(10)	6.598(2)
***c*/Å**	11.217(3)	11.223(3)	11.231(3)	11.271(3)	11.305(3)	11.318(3)	11.483(5)
***β*/°**	96.07(2)	95.95(2)	95.89(2)	95.82(2)	95.88(2)	95.87(2)	95.60(3)
***V*/Å^3**	816.0(3)	818.4(3)	821.2(3)	828.6(3)	834.4(3)	839.3(3)	860.8(6)
ρ_{calc}/g cm^{-3}	1.465	1.461	1.456	1.443	1.433	1.424	1.389

Data collection	20 data frames at each temperature						
***T*/K**	**20**	**60**	**100**	**140**	**180**	**220**	**300**
Observed refs	5399	4456	5560	3227	2570	2145	1864
Unique refs $I > 2\sigma(I)$	2720	2155	2644	1523	1189	973	748
R_{int}	0.061	0.059	0.058	0.064	0.065	0.059	0.064

Absorption coefficient	μ (cm^{-1}) $= 0.80 + 0.75\lambda$						
Refinement	Initially in GSAS,[15] final refinements in SHELXL-97,[16] refined on F^2						
Refined parameters	190, all atoms anisotropic, including hydrogen atoms						
***T*/K**	**20**	**60**	**100**	**140**	**180**	**220**	**300**
***R*(*F*)**	0.088	0.082	0.080	0.088	0.088	0.090	0.087
***wR*(F^2)**	0.195	0.195	0.196	0.208	0.201	0.211	0.194
Goof (S)	1.129	1.154	1.091	1.167	1.161	1.043	1.017

method uses a wavelength-sorted white neutron beam, along with large area position-sensitive detectors, to allow a large volume of reciprocal space to be measured in a single crystal setting (a "frame"). The full data collection comprises a series of such frames, each collected with a stationary crystal-detector arrangement.

The data collection parameters are summarised in Table 1. A total of 20 frames, each containing information from two detectors, were collected at each temperature, with exposure times for each frame varying from around 40–180 minutes. The intensities were extracted and reduced to structure factors using standard SXD procedures[14] as detailed in Table 1. The structure factor sets were used for structural refinement in GSAS[15] and SHELXL-97.[16]

CCDC reference numbers 195133–195139. See http://www.rsc.org/suppdata/nj/b2/b203775k/ for crystallographic data in CIF or other electronic format.

3. The crystal and molecular structure

Refinement was carried out, on F^2, using the X-ray coordinates[2] as a starting model for the 20 K data set. The refined parameters from each temperature were then used as starting parameters for the next refinement. These were carried out in the same order as the data were collected, *i.e.* 20, 60, 100, 140, 180, 220 and 300 K. In the final refinement at each temperature, positional and anisotropic thermal parameters were refined for all atoms, including the hydrogens. The refinements all converged satisfactorily using this model, the final refinement comprising 190 parameters, as detailed in Table 1. The resulting structures are shown in Fig. 1. Bond lengths and angles from the refinements, along with refined atomic coordinates and ADPs, are available as ESI.†

The molecular geometry is similar to that determined previously and is relatively unremarkable, apart from the variable temperature effects discussed below. As stated above, the molecules are held together as dimers by a pair of equivalent hydrogen bonds (HB) between the carboxylic groups, across the centre of symmetry (see below). The acetoxy group is oriented with its plane approximately perpendicular to that of the benzene ring/carboxylic groups (typical C_1–C_2–O_3–C_8 torsion angle of 81.8° at 100 K). Neither of the oxygen atoms in the acetoxy group are involved in hydrogen bonds. There are no other significant short intermolecular contacts.

4. The methyl group

The variable temperature neutron diffraction data in this study have been used in a detailed analysis of the thermal motion of the methyl group in the structure. Such terminal methyl groups frequently display enhanced librational motions, indicated by large ADPs in their crystal structures, the associated thermal ellipsoids also displaying characteristic elongation (Fig. 2). This elongation is indicative of apparent "torsional" motion of this group. Such intermolecular torsional motion in crystals has been widely studied, and the feasibility of using the mean square displacements from diffraction measurements in estimating force constants and barriers to internal rotation for a wide range of groups has been established.[19,20]

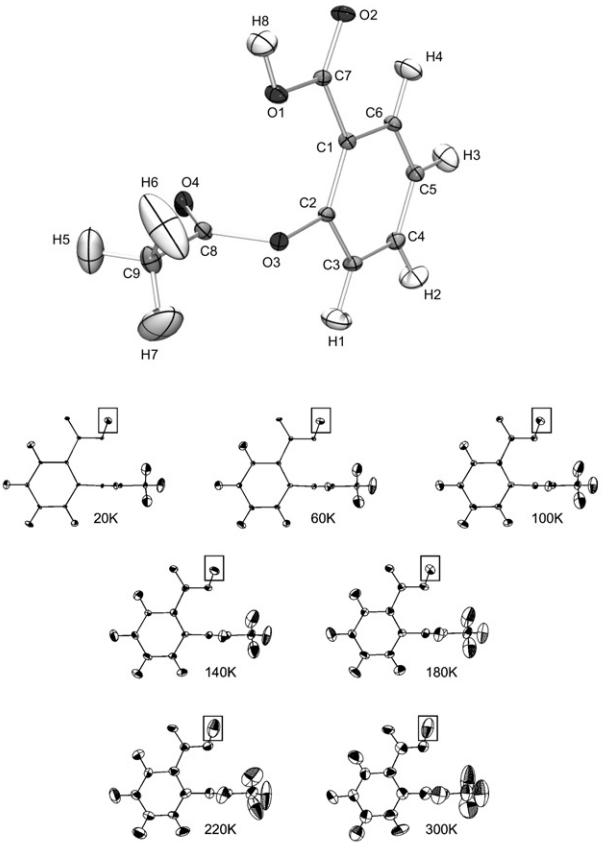

Fig. 1 (a) A view of the structure of acetylsalicylic acid (Aspirin) as determined from neutron diffraction at 100 K, showing the atomic numbering used. (b) The evolution of the molecular structure as determined by variable temperature single crystal neutron diffraction. Drawn using ORTEP.[17,18]

The model employed to analyse these excess torsional motions is based on the results of thermal motion analysis of the refined ADPs. Such analysis is normally carried out in the framework of the TLS formalism,[21] and we employed here the program THMA11[22] to undertake this analysis. While the quality of the fits to our rapidly-determined ADPs is not as good as for higher-precision data, the TLS-fits allow us

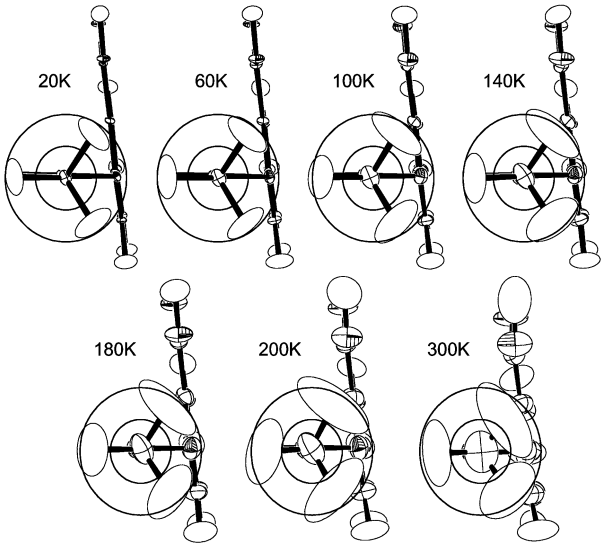

Fig. 2 The characteristic elongation of the thermal ellipsoids of the methyl group in Aspirin and its trend with temperature. This effect can be modelled as apparent excess torsional motion of the CH_3 group.

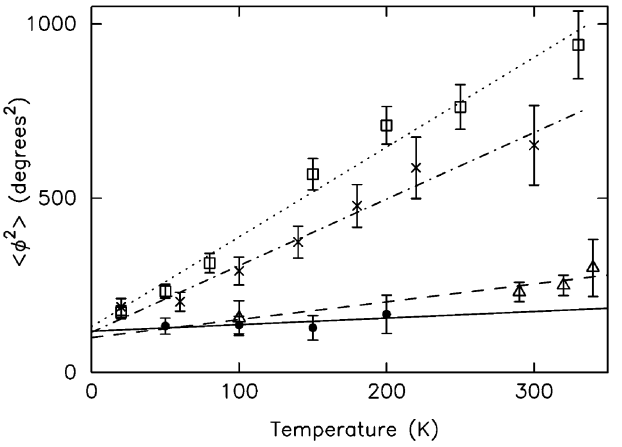

Fig. 3 The mean-square torsional motions $\langle\varphi^2\rangle$ in various molecular systems. The barrier heights in ascending order are: paracetamol[3,6] (□), 2.2 kJ mol^{-1}; Aspirin[12, and this work] (×), 4.0 kJ mol^{-1}; 1,5-dimethylnaphthalene[4] (△), 11.2 kJ mol^{-1}; 1,8-dimethylnaphthalene[5] (●), 32.5 kJ mol^{-1}. The constant zero-point torsional motion $\langle\varphi_o^2\rangle \sim 120$ deg.^{2} is also evident.

reliably to examine temperature-dependent trends, the main purpose of the analysis in the present case.

The excess torsional motion of the methyl group is modelled using the simple assumption of harmonic motion within a 3-fold cosine potential.[19] Although this assumption will almost certainly be breaking down at the higher temperatures measured in this study, we can use the simple model to gain useful physical insights. Analysing the ADPs leads to a determination of the mean square amplitude of libration $\langle\varphi^2\rangle$, which in the simple model is related to the force constant for a harmonic oscillator by the equation

$$\langle\varphi^2\rangle = \langle\varphi_o^2\rangle + RT/f \quad (1)$$

where R is the gas constant, T the temperature and f the force constant. $\langle\varphi_o^2\rangle$ can be termed the zero-point torsional motion. The results of this analysis for Aspirin have been reported previously,[12] and the expected linear trend is found (see Fig. 3). The values determined for the force constant and barrier height in Aspirin are 5.6 J mol^{-1} deg^{-2} and 4.0 kJ mol^{-1}, respectively. Comparing this (Fig. 3) with the findings for the methyl groups in three other systems studied by variable temperature neutron diffraction shows, as one might expect, that the excess torsional motions of methyl groups which are relatively free to rotate (Aspirin and paracetamol) are considerably larger than in systems where the methyl groups are sterically hindered (the dimethylnaphthalenes). In addition, it is clear that in each of these four cases, although there is a wide variation in the degree of torsional motion (and hence the force constant and barrier height), an almost constant value is found for the zero-point torsional motion. The value determined for $\langle\varphi_o^2\rangle$ is approximately 120 deg.^{2}

The question of the nature of this zero-point motion is beyond the scope of this work, but it is worth noting that its magnitude determined here is in reasonable agreement with predictions from tunnelling-rotation spectroscopy.[23]

4.1 Bond length corrections

In our previous study of paracetamol, the comprehensive variable temperature neutron diffraction data allowed us to propose a novel empirical method for using multiple temperature data to estimate bond length corrections.[6] That is, to estimate C–H bond lengths in the methyl group which are effectively free of the effects of thermal motion. These effects can result in substantial apparent shortening of crystallographically determined bond length values, particularly in groups

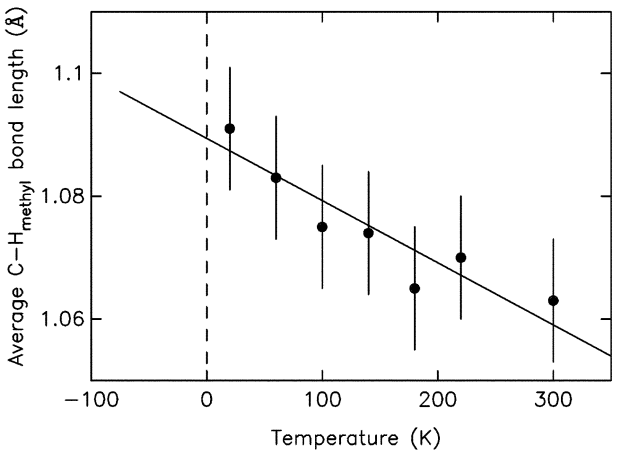

Fig. 4 Empirical correction for thermal motion effects in the average C–H_{methyl} bond length in Aspirin. Extrapolation to the temperature at which the effective thermal motion is zero results in a corrected C–H bond length of ~1.098 Å.

where the thermal motion is high. The empirical correction method uses the determination of excess torsional motions (Fig. 3), and relies on the extrapolation of the linear fit to the (virtual) temperature at which this excess motion would be completely eliminated. In the present case this temperature at which $\langle\varphi^2\rangle = 0$ is found to be $T_{eff} = -75$ K. Given the relatively low precision of the individual C–H_{methyl} bond lengths, particularly at the higher temperatures, here we apply the method to the average C–H_{methyl} bond length.

Extrapolating this average bond length to the temperature at which we assume the effects of thermal motion have been removed (T_{eff}), we obtain an estimate for the corrected C–H bond length of 1.098 Å (Fig. 4), in reasonable agreement with that previously estimated by this method for paracetamol (1.103 Å). These values also agree well with the typical estimates of the undistorted length of a C–H bond based on other diffraction and spectroscopic methods.

4.2 Quantum chemical calculations of the methyl group rotation

In order to try to obtain more insights into the nature of the methyl group motions, we have carried out Gaussian *ab initio* calculations of the Aspirin and paracetamol structures. In these isolated molecule calculations, we used the crystallographically determined equilibrium molecular structure as starting model, and optimised the geometry at the 6-31G** level of basis set (in the HyperChem package[24]). Using the optimised geometry, a full 360° rotation of the methyl group was carried out, at 10° steps, about the bond joining it to the rest of the molecule. The aims of these calculations is to explore the potential governing the rotation of this group by using the value of the calculated energy as the group follows this trajectory.

For this model to offer some insight into the true situation in the crystal structure, the methyl group in the latter should ideally be in a quasi-isolated molecule situation. That is, this group should primarily sit in a potential field governed by its intramolecular environment, with its intermolecular contacts minimised. This has already been concluded to be the case for paracetamol,[6] and an analysis of the intermolecular contacts in the Aspirin structure shows this to be the case here also.

It thus appears not unreasonable to treat this group within the isolated molecule framework of the Gaussian *ab initio* calculations employed. The results of these calculations for Aspirin and paracetamol yield barrier heights of 4.6 and 2.9 kJ mol^{-1}, respectively. From this it can be seen that the order of barrier heights obtained is in agreement with those determined experimentally, and that the absolute magnitudes calculated for these barriers are also in reasonable agreement with the experimental values (4.0 kJ mol^{-1} for Aspirin, 2.2 kJ mol^{-1} for paracetamol). A recent comparison of calculations for the dimethylnaphthalenes[25] has also shown the simple model adopted here to have some validity.

5. The dimeric hydrogen bond

The molecules in the Aspirin crystal structure are held together in dimers by the familiar carboxylic acid dimeric linkage, involving two symmetry-equivalent hydrogen bonds. These are of medium strength, with O···O separation of around 2.6 Å (Table 2).

In many cases, it has been observed that the proton in such moderately strong carboxylic acid dimeric HB appears to be disordered (Fig. 5).[26–34] This effect is very apparent in smaller molecule systems, and is probably so pronounced in these small dimeric systems because the local environment around the two possible hydrogen atom positions can appear very similar and hence result in a small energy difference between the two possible configurations.

In a neutron diffraction determination, this situation is initially manifest in elongated thermal ellipsoids (elongated in the direction of the HB). These have been observed in various benzoic acid derivatives,[10,11,35] where this anomalous ellipsoid has been successfully modelled as the type of disorder illustrated in Fig. 5.

If variable temperature neutron diffraction data are available, the distribution of the hydrogen atom over the two possible sites can be used to derive thermodynamic information. The energy difference ΔH° between the two configurations is related to the relative occupancies of the two sites by the Van't Hoff relationship

$$\ln K = (\Delta H^\circ/RT) + (\Delta S^\circ/R) \qquad (2)$$

where $K = P_A/P_B = P_A/(1 - P_A)$, P_A and P_B being the relative occupancies of the two H atom sites.

An examination of the thermal parameters of the hydrogen atom involved in the dimeric HB in Aspirin shows that while this atom appears to be well localised at and below 180 K, there is evidence of significant elongation of the ellipsoid above 200 K (see Fig. 1b). This anomalous behaviour of the thermal parameters is accompanied by an apparent lengthening of the O_1–H_8 covalent bond (Fig. 6), and we seek an explanation for these effects from amongst several possibilities.

5.1 Disorder model

Following the models successfully proposed for the benzoic acid derivatives (see Fig. 5), we can attempt to model the

Table 2 Hydrogen bond geometry (Å, °)

	20 K	60 K	100 K	140 K	180 K	220 K	300 K
O1···O2	2.641(4)	2.640(5)	2.635(4)	2.635(7)	2.648(8)	2.638(11)	2.627(15)
O1–H8	1.017(6)	1.015(7)	1.009(6)	1.006(10)	1.008(12)	1.04(2)	1.07(3)
H8···O2	1.624(6)	1.627(7)	1.627(6)	1.630(9)	1.641(12)	1.598(18)	1.56(3)
O1–H8···O2	177.0(6)	177.2(7)	177.7(6)	176.5(9)	176.9(12)	177.4(16)	175.3(18)

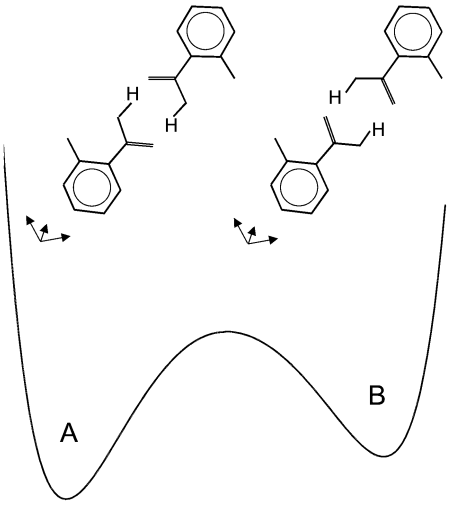

Fig. 5 Disorder in carboxylic acid dimeric hydrogen bonds. The two configurations A and B have slightly different energies in the crystal environment. In terms of the crystal structure, which is averaged over the whole crystal, this means that two possible sites for the hydrogen atom in this HB are potentially populated, one position close to each of the two oxygen atoms in the COOH group.

situation here as a split proton site. A second site was thus introduced at a covalently-bonded distance from the second oxygen atom, and the relative occupancies of the two sites refined (with the total occupancy constrained to eqn. 1). The results of these refinements are summarised in Fig. 7. Significant occupancy of the second site is indicated at both 300 K ($P_B = 0.19$ (4)) and 220 K ($P_B = 0.16(3)$), but with little evidence of site disorder at 180 K ($P_B = 0.01(3)$) or below. If we attempt to model this using our simple Van't Hoff model (eqn. (2)), the model clearly breaks down (Fig. 7) if we make the reasonable assumption that the two determinations for which we can apparently refine the occupancy of a second site should form the basis of our fit. Evidently we would expect a considerably higher occupancy of the second site at 180 K and below for the disorder model to make thermodynamic sense (see Fig. 7).

With the alternative for the onset of this apparent disorder being an unsubstantiated assumption of some sort of order–disorder phase transition, for which there appear to be no precedents in this type of system, we seek an alternative explanation in terms of the shape of the HB potential.

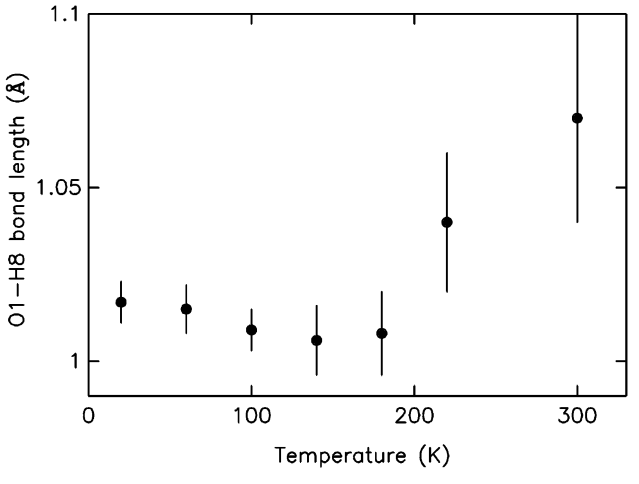

Fig. 6 Apparent elongation of the O–H covalent bond in the carboxylic acid HB dimer in Aspirin as a function of temperature (see section 5.3).

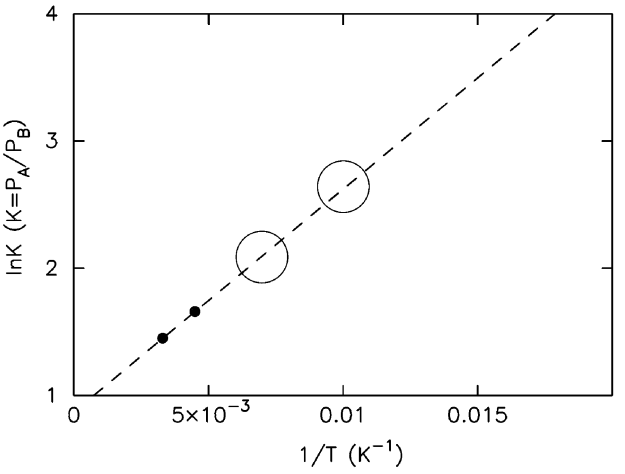

Fig. 7 Plot of ln K *vs.* $1/T$, showing the inadequacy of the site disorder model in fitting the whole range of variable temperature data. It is clear that for eqn. (2) to be satisfied, considerably higher occupancies of site B should be observed at temperatures below 200 K, as shown by the large open circles corresponding to B site occupancies of 0.11 at 140 K and 0.07 at 100 K. This is not the case - effectively full occupancy of site A is found below 200 K.

5.2 Probing the anharmonicity of the HB potential

This aspect of the Aspirin structure has been discussed in some detail previously.[12] Here we reprise the earlier discussion and augment with some additional comparisons.

In the previous work[12] it was shown that the elongation of the thermal ellipsoid for atom H8 could be interpreted in terms of anharmonicity in the HB potential. This information was obtained by removing the constraints of the harmonic model usually employed. This is most easily achieved by using Fourier syntheses to image directly the scattering density in the region of this hydrogen atom. These revealed clearly asymmetric density distributions above 200 K, indicating that we are observing the proton exploring the anharmonic regions of the HB potential. The ideal extension of this – from imaging the proton behaviour to modelling it in a structure refinement incorporating anharmonic thermal parameters[36,37] – has unfortunately not been possible. Since the main thrust of our experiment was to collect data rapidly in order to explore the temperature-dependent features, this necessarily limits the precision and extent of the available data. While routine structure refinement is enabled by our data,[12] reliable anharmonic refinements require very high precision data[38–40] which we do not have available in the present case. In spite of this limitation, however, our observations of the behaviour of the proton density as a function of temperature allow us to observe the anharmonicity directly in a qualitative way, and this observation is of interest in itself, particularly in the relatively long HB (~2.64 Å) we have here. In this context, we also note that the data/parameter ratios for our higher temperature data sets are rather lower than usually expected in single crystal diffraction, a consequence of our desire to collect many data sets rapidly as a function of temperature. However, the pertinent findings of our data reported here are retained in preliminary examination of data sets in which the "unobserved" reflections are assigned estimated values. In addition, the features found in our work are reproduced qualitatively in independent maximum entropy reconstructions of a different (more complete and higher resolution) 300 K data set on a partially deuterated form of the title material.[41]

The situation in Aspirin can be further contrasted with that in benzoic acid, for which the proton disorder model was so conspicuously successful.[10,11] The Fourier syntheses in the region of the dimeric HB in both materials is shown in Fig. 8a. The contrast is clear – in benzoic acid (175 K) we

see clear evidence of two density maxima corresponding to the disorder model positions for the partial H atoms, while in Aspirin we observe only a single peak, asymmetrically elongated in the direction of the HB and indicative of anharmonicity.

We note here also similar observations of an asymmetric proton density accompanying hydrogen bond formation in the O–H···O HB in 3-deazauracil[42] (O···O separation 2.563 Å) which interestingly is observed at 100 K (see also section 5.3 below).

5.3 Migrating and non-migrating protons

There has been much recent interest in the possibility of hydrogen atoms in hydrogen bonds changing position as a function of temperature. This "proton migration" has mostly been observed to date in short, strong HB, of homo-[7,9,43] and hetero-nuclear[8] type. In extreme cases the apparent motion of such protons can be as large as 0.2 Å, and can traverse the HB from being close to the "donor" to being close to the "acceptor".[8,43]

One of the most noticeable features of systems in which proton migration occurs is the elongation of the D–H "covalent" bond from its expected value of around 1 Å or so (in the case of O–H or N–H donor groups). Of course, in short, strong HB systems, this elongation is often observed even when there is no evidence of proton migration, but nonetheless it can be a signature of a broadening or shallowing of a potential, and possibly of incipient migration. In passing, we also note that such elongation can also be observed, for example, in zwitterionic systems such as L-alanine.[44]

As stated above, such elongation of the D–H covalent bond becomes apparent in the carboxylic dimer HB in Aspirin above 200 K (see Fig. 6). This elongation is rather dramatic, with the refined O–H distance increasing by no less than 0.06 Å.[12] Further, in the structure of 3-deazauracil mentioned above, the O–H bond to the hydrogen-bonded hydrogen atom is also elongated to 1.027(7) Å.[42] Is proton migration therefore another possible explanation for the anomalous behaviour of the HB proton in Aspirin?

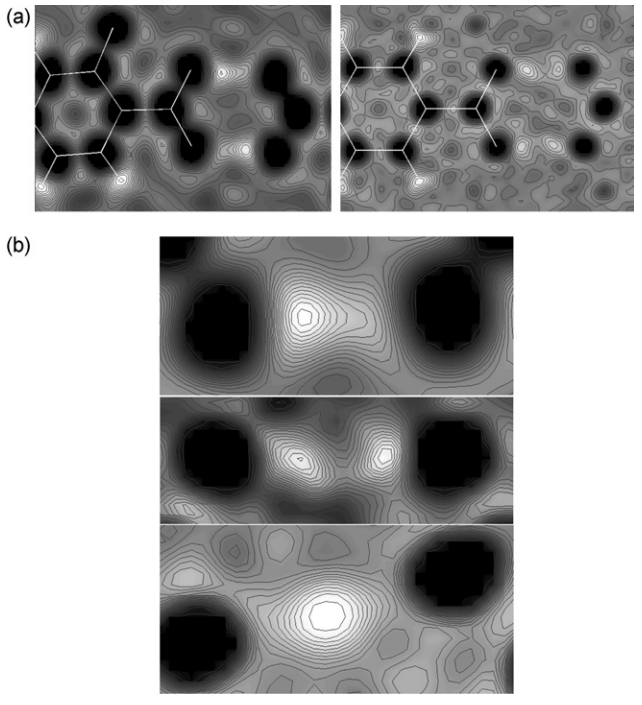

Fig. 8 (a) Fourier syntheses of the hydrogen atom density in the carboxylic dimer in benzoic acid (left) and Aspirin (right). The difference is clear, with a disorder model appropriate in the former but a single site exhibiting anharmonicity in the latter. (b) Detail of the scattering around the hydrogen-bonded hydrogen atom in Aspirin (top), benzoic acid (middle) and urea–phosphoric acid (bottom). The asymmetric nature of the density seen for this atom in Aspirin, contrasted with the split site in benzoic acid and the symmetric density in urea phosphoric acid, has profound implications for deductions about possible proton migration.

In order to investigate these possible cases of migration, it is necessary once again to examine both the thermal parameters and the actual scattering density at the proton position, as the nature of both of these can substantially affect the determined bond lengths.

In Aspirin, we have seen that the scattering density at the proton position is strongly asymmetric above 200 K (Fig. 8b) and in a normal (harmonic) crystal structure refinement this leads to an apparent elongation of the D–H bond length.[12] Indeed this elongated bond length value, together with evidence of asymmetric density from a Fourier syntheses, can be used as a measure of the degree of anharmonicity in the potential being experienced by the hydrogen atom. A similar situation is observed in 3-deazauracil, when a slight asymmetry in the proton scattering density is accompanied by the small elongation of the D–H bond.[42] In these cases there is no proton migration.

In contrast, in the urea–phosphoric acid[7,9] and 4-methylpyridine–pentachlorophenol[8] systems, any elongation of the thermal motion is considerably less pronounced, and Fourier syntheses show the scattering density distribution causing this to be rather symmetric (Fig. 8b). Hence in these cases the apparent change in the proton position is deduced to be real, rather than an artefact of the crystallographic modelling; these protons do indeed migrate.

It is thus clear that the phenomenon of proton migration is a rather subtle effect. Elongation of D–H (and shortening of H···A) distances, and the change in apparent hydrogen atom position from standard crystallographic refinements of even high quality neutron diffraction data, is only part of the story. To confirm or contradict the presence of this effect requires an examination of the ADPs (thermal parameters) often as a function of temperature, and also in many cases direct imaging of the proton scattering density in Fourier syntheses. In the case of Aspirin, it is only at the final, Fourier syntheses, stage (or alternatively in a full anharmonic refinement) that one can definitively eliminate the possibility of a migrating proton and instead attribute this behaviour to the effects of anharmonicity.

6. Conclusions

The crystal and molecular structure of Aspirin, as determined by variable temperature single crystal neutron diffraction, has proven to be rich in interest. In addition to the examination of the torsional motions of the methyl group, the carboxylic acid dimer has once again provided insight into the characterisation of proton disorder and migration, and the use of the thermal motion and observed scattering density of hydrogen atoms as a direct probe of hydrogen bond potentials.

7. Acknowledgements

This work was funded by EPSRC under grants GR/L71902, GR/M41773 and GR/R04690.

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