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Towards Designing Proton-Transfer Systems—Direct Imaging of Proton Disorder in a Hydrogen-Bonded Carboxylic Acid Dimer by Variable-Temperature X-ray Diffraction**

Chick C. Wilson and Andres E. Goeta*

Intermolecular hydrogen bonding plays an important role in the formation of anisotropic interactions in condensed systems. Hydrogen transfer through hydrogen bonds between molecules enables charge and energy transfer to occur in solid chemical and biological systems and has widespread implications for issues as diverse as ferroelectrics, electrochemical processes, and enzyme action.[1] The phenomenon has been extensively studied by a variety of spectroscopic methods, including IR,[2,3] nuclear quadrupole resonance (NQR),[4] NMR,[3,5,6] and neutron scattering methods.[7] Until recently,

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[*] Prof. C. C. Wilson
Department of Chemistry, University of Glasgow
Glasgow G12 8QQ (UK)
and
ISIS Facility, CCLRC Rutherford Appleton Laboratory
Chilton, Didcot, Oxon OX11 0QX (UK)
Fax: (+44) 141-330-4888
E-mail: C.C.Wilson@chem.gla.ac.uk

Dr. A. E. Goeta
Department of Chemistry, University of Durham
South Road, Durham DH1 3LE (UK)

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however, only limited structural studies of the underlying details of the process have been performed.[8,9] The key to extending structural investigations into this regime and to approaching the underlying chemical physics of the solid-state effect is the application of variable-temperature (VT) diffraction methods. Recent VT neutron diffraction work has begun to tackle issues such as proton disorder, transfer, and migration in hydrogen-bonded systems.[10–12] These systematic variable-temperature investigations offer much added value in terms of understanding the system, for example, its energetics, and giving clues as to its dynamics.

Many derivatives of benzoic acid crystallize as hydrogen-bonded dimers, and dynamic double proton transfer within the hydrogen bonds mediates the interconversion between two tautomeric forms.[13] This is manifest in the crystal structure as disorder of the hydrogen-bonded hydrogen atom over two sites. A direct crystallographic approach has been used to determine the relative abundance of the two forms in the crystal structure by refining the site occupancy factors (SOF) of the two proton sites in the course of a crystal-structure determination by using single-crystal neutron diffraction.[10,11] Complementary NMR relaxometry has also been extensively employed to examine this situation in these materials.[6,14] For example, the energy asymmetry between the two configurations in the parent benzoic acid crystal structure has been found to be 0.50(4) kJ mol^{-1} by VT single-crystal neutron diffraction,[10] which also showed that the asymmetry in *p*-chlorobenzoic acid was rather higher at 1.64(9) kJ mol^{-1}.[11] Both determinations are in good agreement with the NMR relaxometry results.

We have recently begun to re-explore the possibility that VT X-ray diffraction can offer significant input in the early stages of this work.[9] In particular, it is expected that this technique can both screen out systems in which there appear to be no anomalous features worthy of study by neutron diffraction, as well as indicate the temperature range of importance to any further investigations. Herein we demonstrate, through variable-temperature X-ray diffraction studies of the structure of 2,4,6-trimethylbenzoic acid, that this disorder can indeed be directly imaged from the X-ray diffraction data. We further show that the use of the variable-temperature approach allows this effect to be identified unambiguously and trends in the disorder to be followed. These data provide not only an initial characterization of the effect but also, with care, can yield a reasonable quantitative assessment of the energy difference.

Previous X-ray diffraction measurements on 2,4,6-trimethylbenzoic acid[15] had provided evidence for the presence of hydrogen atom disorder, both from the C−O/C=O bond lengths being "almost equal" in length and from Fourier syntheses which indicated a disordered electron-density distribution in the region of the hydrogen-bonded hydrogen atom. The aim of the present X-ray diffraction experiments was to provide a more quantitative determination of this disorder, and specifically its temperature dependence, and to gain further indications about the possibilities of X-ray diffraction in quantifying this important effect underlying solid-state proton transfer. The anticipated vehicle for this quantification was indirect—the use of the difference in C=O and C−O bond lengths in the dimeric motif as a fingerprint of possible hydrogen atom disorder.

The structure was determined by X-ray diffraction at four temperatures in the range 100–290 K.[16] The main features of the refined structure follow those of the original determination;[15] we focus here on the carboxylic acid dimer unit (Figure 1). In this respect, the results show this method to be much more effective than initially expected. Difference Fourier sections through the $(COOH)_2$ dimeric link show a dominant peak corresponding to a single hydrogen atom position at 100 K, but a much more equal split site at 290 K (Figure 2). The intermediate temperatures bear out this finding (Figure 2) and visually show an increasing trend for the occupation of the second site. Thus, the VT X-ray diffraction studies gives the clearest indication that this system has a proton-disorder situation in which the proton gradually orders onto one preferred site as the temperature is lowered. As expected, this finding is also borne out by the trend in C−O and C=O bond lengths in the carboxy group (Figure 3). In principle, bond-length trends can be used to extract the relative occupancies of the two configurations.[19] However, as has been pointed out previously,[9] the latter technique is an indirect method for quantifying the hydrogen atom disorder, and a major difficulty in this context is to decide what the "equilibrium" C−O/C=O bond-length distribution for a fully proton-ordered situation should be. This is nontrivial in the solid state, unless benchmarking neutron diffraction studies are available to indicate the relation of the C−O/C=O distribution to the relative proton occupancies in the two configurations present in the crystal.

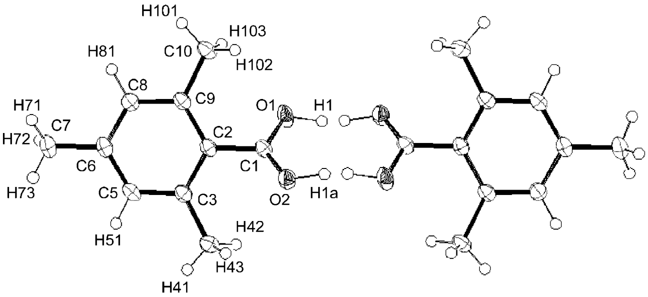

Figure 1. Crystal structure of the dimeric unit in 2,4,6-trimethylbenzoic acid at 100 K, with the two partially occupied sites shown together with the atomic numbering scheme.

A similar approach to that adopted here in quantifying more directly these disordered hydrogen atoms has previously been used[9] in studies of the *p*-quinonemethide and *o*-quinone forms of citrinin. Once again it was found here that imaging the disorder with X-ray diffraction data is feasible, as is the important aspect of exploiting the variable-temperature data to look for trends. This not only has the potential to begin to reveal the thermodynamics of the system, but also acts as a powerful check for verifying the reliability and reproducibility of the X-ray diffraction images. In the earlier study of citrinin,[9] reliable occupancies were obtained for the two higher temperatures—where the occupancy of the minor site is more significant—from direct refinements of a split hydro-

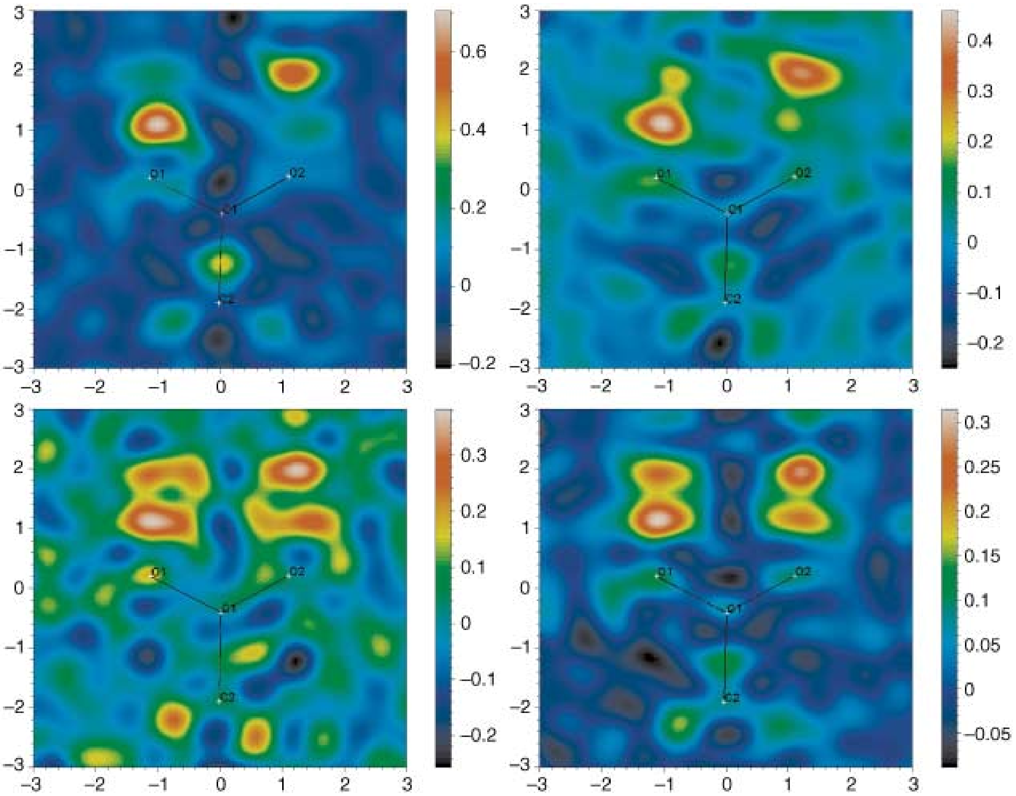

Figure 2. X-ray difference Fourier maps in the region of the COOH group in 2,4,6-trimethylbenzoic acid at 100 (top left), 170 (top right), 240 (bottom left), and 290 K (bottom right). Maps were calculated by using phases from a model containing all atoms apart from the carboxy group hydrogen atom. The density corresponding to the hydrogen-bonded hydrogen atom is clearly seen in these images, as is the increasing redistribution of this over two sites as the temperature is increased; this redistribution represents an increasing population of the minor (B) configuration in the crystal.

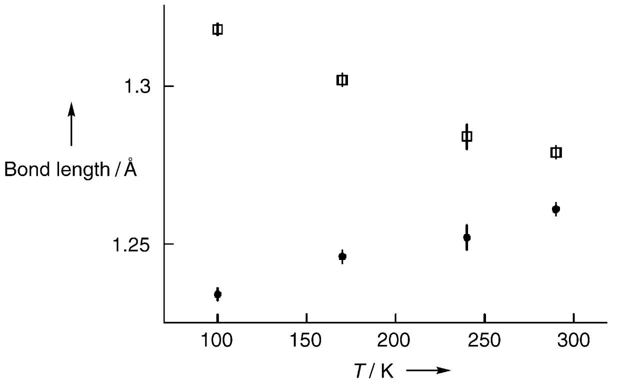

Figure 3. Trends in the C=O (●) and C−O (□) bond lengths for the COOH group in 2,4,6-trimethylbenzoic acid. Increasing population of the minor (B) configuration, represented by increasing the distribution of hydrogen atom density onto the "C−O" unit, is reflected in an equalization of the two C−O bond lengths in the carboxy group.

gen atom site. Attempts in the current work to quantify the hydrogen atom disorder in 2,4,6-trimethylbenzoic acid directly from the refinement of the hydrogen atom SOFs from the X-ray diffraction data are, as expected, somewhat problematic. This is a well-known difficulty, with bonding effects and correlation of SOFs with thermal parameters conspiring to make the obtained hydrogen atom occupancies less reliable. Through the use of the visual evidence of the electron-density distribution between these two sites that is available directly from the Fourier maps, and taking into account the fact that the indicated thermal parameters for the disordered hydrogen atom sites are approximately the same as for the other hydrogen atoms, a refinement strategy was adopted that fixed the isotropic thermal factors (ITFs) of the disordered hydrogen atom sites to be equal to the average of the other hydrogen atom ITFs. This model produced stable refinements and a clear trend in the SOFs (Table 1).

The clear evidence from the Fourier map views of the hydrogen atom density can be used directly to obtain a second estimate of the relative occupancies and so increase the reliability of these determinations. In an effort to improve the reliability of this method, the Fourier maps have been calculated for a range of data cut-offs (based on the ratio $F/\sigma(F)$) and consistency sought between the peak magnitudes for the hydrogen atom sites indicated in these maps. For three of the data sets (at 100 K, 170 K, and 290 K) clear images of the two possible distinct sites are obtained (albeit weakly indicated in the 100 K data). The images are less clear at 240 K, and the peak heights can only be estimated for the 2σ and 3σ cut-off data. The results obtained from these analyses are most promising and in good agreement with those found from the standard (constrained) refinement method (Table 1). To verify the reliability of our results, 290 K data

Table 1: Population $P^{[a]}$ of the major (A) configuration in the structure of 2,4,6-trimethylbenzoic acid as a function of temperature. These parameters provide semiquantitative support to the compelling evidence of Figure 2 regarding the redistribution of the hydrogen atom with temperature.

T [K]	P_A (Fourier)	P_A (SOF)	ITF_{fix}
$100^{(crystal\ 1)}$	0.90(9)	0.94(4)	0.048
$170^{(crystal\ 2)}$	0.79(8)	0.84(4)	0.068
$240^{(crystal\ 2)}$	0.66(8)	0.65(7)	0.090
$290^{(crystal\ 1)}$	0.65(6)	0.62(5)	0.125
$290^{(crystal\ 3)}$	0.58(6)	0.65(4)	
$290^{(crystal\ 4)}$	0.61(6)	0.68(4)	
$290^{(crystal\ 5)}$	0.60(6)	0.61(19)	

[a] Determined by constrained refinement of the relative SOFs of the two possible hydrogen atoms sites and from the magnitude of the Fourier map peaks at these two sites.

were collected from three further crystals, and the same imaging and refinement procedures were followed. In all cases the information from the Fourier images showed good agreement, and while the SOF refinements were less consistent (as expected), it is clear that the overall trends are reliably established.

After extraction of the relative occupancies of the disordered hydrogen atoms, this information can be used to estimate the energy difference between the two configurations in the crystal structure. We define K as shown in Equation (1), where P_A is the occupancy of the major

$$K = P_A/P_B = P_A/(1-P_A) \tag{1}$$

configuration and P_B is the occupancy of the minor configuration (the crystallography yields the average occurrence of each configuration throughout the whole sample) as given in Table 1. The variation in K with temperature is given by Equation (2), where R is the gas constant and ΔS^o is the

$$\ln K = -(\Delta H^o/RT) + (\Delta S^o/R) \tag{2}$$

entropy difference between the two configurations. A plot of $\ln K$ versus $1/T$ should therefore yield a straight line, from the slope of which the energy difference between the two configurations ΔH^o can be deduced.

In Figure 4 the two distinct sets of $\ln K$ versus $1/T$ from the experimental data are shown, together with the average fit, which gives an energy difference between the two configurations in the crystal structure of 2.5(3) kJ mol^{-1}. This value can be compared with the values of 0.50(4) kJ mol^{-1} for benzoic acid[10] and 1.64(9) kJ mol^{-1} for *p*-chlorobenzoic acid[11] obtained previously from neutron diffraction data. The value of this "asymmetry" governs the energetics of the proton transfer between the two configurations, and the ability to calculate this value will, in principle, allow the energy asymmetry to be tuned by varying the chemistry or crystallography of a chosen system.

To obtain fully quantitative results in this area it is still clear that more accurate and reliable hydrogen atom occupancies are highly desirable. Complementary neutron or NMR relaxometry measurements are required to provide at least one or (preferably) more representative snapshot data points to give accurate occupancies for a calibration of the X-ray diffraction determinations. However, it is clear that X-ray diffraction data can be used to establish the trends and, with care, can yield good estimates of the relative occupancies. The VT X-ray diffraction results can further provide information for subsequent neutron diffraction measurements as to choice of systems, temperatures, etc., and we aim to pursue this line of study if appropriate crystals can be obtained. We believe that combining these methods in this way will enhance the capability of rapid X-ray diffraction determinations of hydrogen atom ordering as a tool for further understanding and possible rational design of proton-transfer systems. This would also turn variable-temperature X-ray diffraction into a more quantitative method for the determination of proton-disorder/proton-transfer effects. It is clear that obtaining higher resolution X-ray diffraction data could also somewhat enhance this method, but this would involve more extended data collection times, and the thrust of our work is to stress the utility of variable-temperature X-ray diffraction as a reliable, rapid diagnostic for such systems.

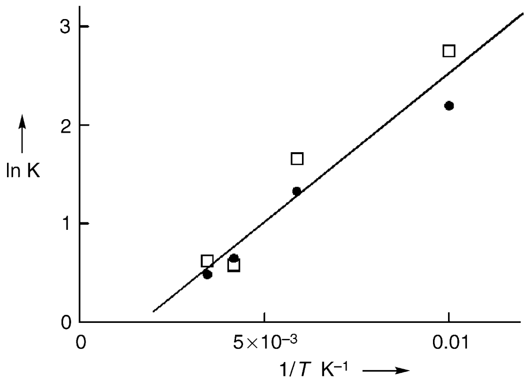

Figure 4. The energy difference between the two configurations (A and B) of 2,4,6-trimethylbenzoic acid in the solid-state crystal structure can be obtained from the slope of the plot of $\ln K$ versus $1/T$. The data represented here are from the magnitude of the Fourier peaks (●) and from the SOF refinements (□). The fit shown is the average best fit, from which the value of 2.5(3) kJ mol^{-1} for the energy difference is extracted.

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[16] Single crystals of 2,4,6-trimethylbenzoic acid were grown from isopropyl alcohol and data were collected on a Bruker SMART-1k CCD X-ray diffraction apparatus at four temperatures between 100 and 290 K. All datasets for **1** were collected by a series of ω scans at different φ values by using $\mathrm{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $C_{10}H_{12}O_2$ crystallizes in the monoclinic *C*2/*c* space group with $Z = 8$. No absorption corrections were carried out. The structure at 290 K was solved by direct methods with the SHELXS-97 program[17] and the model obtained was refined at all temperatures by using the SHELXL-97 program.[18] Refinement was on F^2 against all independent reflections by the full-matrix least-squares method. At all temperatures the hydrogen atoms were located from difference Fourier maps and their positions and isotropic atomic displacement parameters freely refined. Treatment of the hydrogen atom of the carboxy group is described in the text. Two different crystals were used in the data collection (and three others in subsequent verification of the reliability of the results at 290 K). Crystal data at $T = 290$ K: colorless plate of dimensions $0.46 \times 0.34 \times 0.10$ mm^3, $a = 15.152(6)$, $b = 7.029(3)$, $c = 17.473(7)$ Å, $\beta = 90.626(5)°$, $V = 1860.8(12)$ Å^3, $\rho_{\mathrm{calcd}} = 1.172$ g cm^{-3}, $\mu = 0.081$ mm^{-1}. 11931 reflections measured, $2\theta_{\max} = 56.80°$, 2294 independent reflections, $R_{\mathrm{int}} = 0.0301$, 161 parameters refined, $R_1 = 0.0504$ (for 1430 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1536$ (for all data). Crystal data at $T = 240$ K: colorless triangular plate of dimensions $0.40 \times 0.30 \times 0.08$ mm^3, $a = 15.037(2)$, $b = 7.035(1)$, $c = 17.356(2)$ Å, $\beta = 90.347(5)°$, $V = 1836.0(3)$ Å^3, $\rho_{\mathrm{calcd}} = 1.188$ g cm^{-3}, $\mu = 0.082$ mm^{-1}. 5877 reflections measured, $2\theta_{\max} = 56.58°$, 2263 independent reflections, $R_{\mathrm{int}} = 0.0461$, 161 parameters refined, $R_1 = 0.0761$ (for 1279 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1305$ (for all data). Crystal data at $T = 170$ K: colorless triangular plate of dimensions $0.40 \times 0.30 \times 0.08$ mm^3, $a = 14.884(2)$, $b = 7.043(1)$, $c = 17.272(3)$ Å, $\beta = 91.828(6)°$, $V = 1809.7(5)$ Å^3, $\rho_{\mathrm{calcd}} = 1.205$ g cm^{-3}, $\mu = 0.083$ mm^{-1}. 7225 reflections measured, $2\theta_{max} = 56.60°$, 2229 independent reflections, $R_{\mathrm{int}} = 0.0358$, 157 parameters refined, $R_1 = 0.0451$ (for 1500 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1236$ (for all data). Crystal data at $T = 100$ K: colorless plate of dimensions $0.46 \times 0.34 \times 0.10$ mm^3, $a = 14.752(4)$, $b = 7.036(2)$, $c = 17.212(4)$ Å, $\beta = 93.216(5)°$, $V = 1783.6(8)$ Å^3, $\rho_{\mathrm{calcd}} = 1.223$ g cm^{-3}, $\mu = 0.084$ mm^{-1}. 5583 reflections measured, $2\theta_{\max} = 56.58°$, 2207 independent reflections, $R_{\mathrm{int}} = 0.0277$, 157 parameters refined, $R_1 = 0.0475$ (for 1727 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1315$ (for all data). CCDC-216279 (290 K), CCDC-216278 (240 K), CCDC-216277 (170 K), and CCDC-216276 (100 K) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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