

Crystal morphology of ibuprofen predicted from single-crystal pulsed neutron diffraction data

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Low-temperature single-crystal pulsed neutron diffraction is used to determine accurate positions and thermal parameters for all 33 atoms of the ibuprofen molecule, and the data used to predict the crystal morphology.

Ibuprofen [2-(4-isobutylphenyl)propionic acid] is a cyclooxygenase enzyme inhibitor widely prescribed in tablet form to treat rheumatoid arthritis. The shape of ibuprofen crystals is important in the industrial tableting process, and is solvent dependent in the sense that the relative areas of the crystal faces vary significantly with choice of solvent.¹ Here we report on a potential-energy model which describes the essential features of the morphology, starting from an accurate neutron refinement of the published X-ray crystal structure.²

Racemic ibuprofen (supplied by Boots Pharmaceuticals), when recrystallised from acetonitrile, gave rectangular (001) plates extended along the *b* direction. Diffraction data† were collected from a single crystal at 100 K on the time-of-flight Laue diffractometer SXD at the ISIS spallation neutron source.³

The data were used in a refinement of atomic coordinates and anisotropic thermal (vibration) parameters by full-matrix least-squares methods on *F* with GSAS,⁴ using 1449 reflections with $I > 3\sigma(I)$. This gave a final $wR(F)$ of 0.053 on 33 atoms (298 parameters) (Fig. 1).

The racemic ibuprofen crystal has four molecules in a monoclinic cell, with $a = 14.397(8)$, $b = 7.818(4)$, $c =$

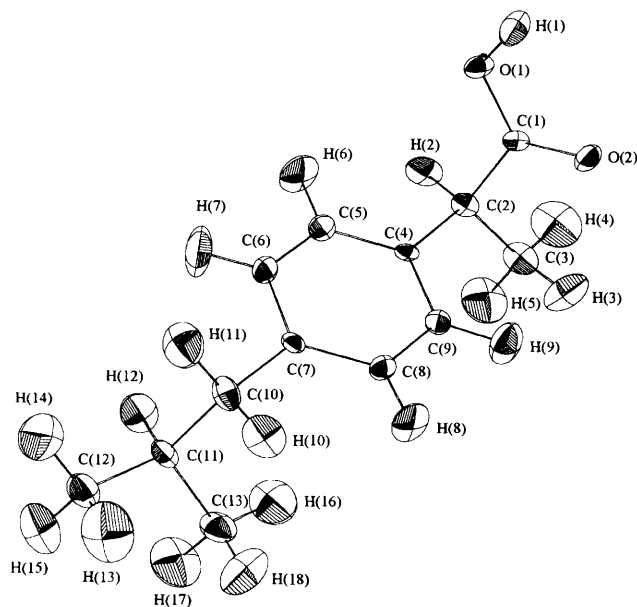


Fig. 1 An ORTEP⁵ plot of the ibuprofen molecule, with anisotropic thermal ellipsoids at 40% probability

10.506(6) Å and $\beta = 99.70(3)^\circ$. These four molecules form two dimers, each comprising a chiral molecule hydrogen bonded to its mirror image across a centre of inversion within the space group $P2_1/c$ (Fig. 2).

The positions of the carbon and oxygen atoms in this study show good agreement with the X-ray analysis. However, the mean C–H bond length observed with neutrons (1.077 Å) is a very significant improvement on the X-ray mean value of 0.984 Å. This is because neutrons locate atomic nuclei, whereas an X-ray structure is defined by maxima in the electron density distribution. Since electron density in C–H is displaced towards carbon, X-ray analysis underestimates the bond length. Hydrogen atoms participate in 95 of the 100 closest intermolecular contacts in the crystal, and neutron data therefore improves crystal potential-energy calculations. This was confirmed by lattice-energy minimisation.⁶ Minimisation resulted in major distortion of the X-ray crystal structure, while insignificant changes in the neutron structure confirmed a satisfactory potential-energy model, with well described atom–atom interactions. Note also that hydrogen bonding affects the ibuprofen crystal shape by favouring growth in the *b* direction.

The refined neutron structure was input into the program HABIT,⁷ which calculates an attachment energy (E_{att}) for selected faces (Table 1). The E_{att} values were then used to

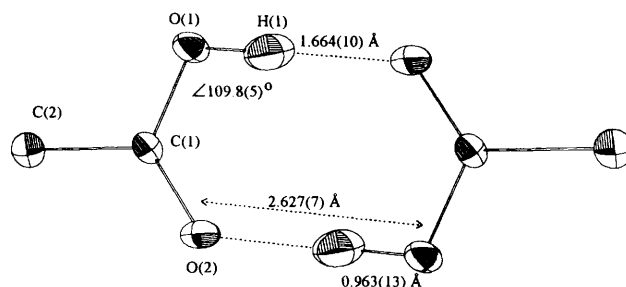


Fig. 2 The dimer motif. Unmarked atoms are in the molecule at $(1-x, 1-y, 1-z)$, and the O–H...O angle is $179.5(7)^\circ$. Atomic displacements from the mean plane through the six H and O atoms are H(1) -0.003 , O(1) 0.002 , O(2) -0.001 , C(1) -0.029 , C(2) -0.143 Å.

Table 1 Attachment energy (kcal mol⁻¹, cal = 4.184 J) of faces using neutron data (with X-ray values for comparison). The faces were identified according to interplanar spacing, and space-group symmetry

Face	Neutron	X-Ray
(100)	-4.20	-5.47
(002)	-16.17	-14.78
{110}	-17.07	-16.54
{111}	-17.71	-16.15
{ $\bar{1}$ 11}	-18.16	-16.51
{011}	-19.22	-17.85

generate the theoretical morphology (Fig. 3). The calculations show that attachment at the (100) face is least energetically favourable. Since E_{att} is assumed to be directly proportional to the relative growth rate, (100) is predicted to be the slowest growing face, and therefore dominates the theoretical morphology [Fig. 3(a)]. This feature of the model is indeed

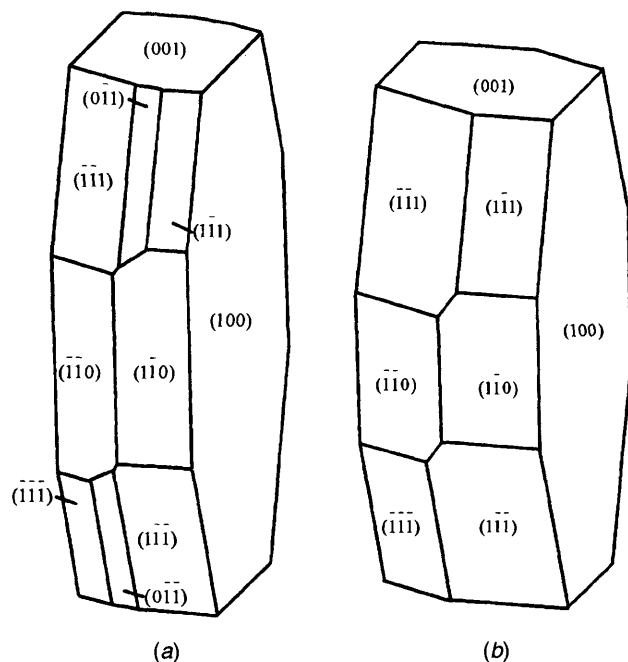


Fig. 3 SHAPE⁸ plots of the attachment energy model; (a) neutron data, (b) X-ray data

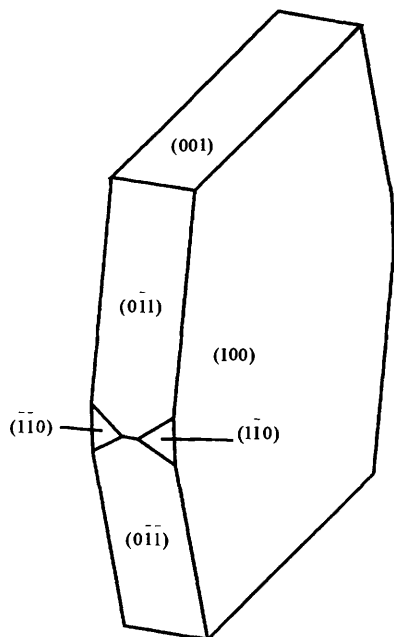


Fig. 4 A SHAPE⁸ plot of the crystal grown by sublimation

observed with crystals grown by sublimation (Fig. 4). Furthermore, racemic crystals cleave parallel to (100), a fact consistent with the weak interplanar bonding predicted in the theoretical model. Theory and experiment agree that (001) ranks next in morphological importance. The remaining two faces in the sublimation crystals are also predicted, albeit with differing morphological importance. Of the two predicted faces not appearing in Fig. 4, {111} is observed in crystals grown from acetonitrile, where presumably solvent interactions play a major role in slowing the growth rate sufficiently for it to be observed.

Repeating the morphology calculation with the X-ray structure as input (Table 1) resulted in {011} faces disappearing from the predicted form [Fig. 3(b)]. Otherwise, agreement between Figs. 3(a) and (b) is better than might be expected. This is because the theoretical morphology is determined by *relative* differences in E_{att} , so that although we are less confident in the *absolute* X-ray E_{att} values, the morphology prediction is still reasonable. X-Ray data can, of course, be improved by adjusting hydrogen-atom positions to assumed positions based on neutron diffraction values.⁹

The need for accurate hydrogen-atom positions therefore depends on the level of detail required from the model. This was also apparent in our recent work with another carboxylic dimer structure, benzoic acid.¹⁰ The two hydrogen atoms which link the dimer are disordered, and single-crystal neutron diffraction enabled their positions, and the energy difference between the two possible configurations, to be determined. This level of sophistication is not necessary for morphology calculations, and the crystal morphology of benzoic acid can be predicted quite successfully using X-ray data, without taking account of the disorder.

Footnote

† Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/9.

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