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Ab initio structure determination of phase II of racemic ibuprofen by X-ray powder diffraction

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Annealing of the quenched ibuprofen at 258 K yielded a new crystalline form, called phase II. Powder X-ray diffraction patterns of this phase II were recorded with a laboratory diffractometer equipped with an INEL G3000 goniometer and a curved position-sensitive detector CPS120. The starting structural model was found by a Monte-Carlo simulated annealing method. The final structure was obtained through Rietveld refinements with rigid-body constraints for the phenyl group and soft restraints on the other interatomic bond lengths and bond angles. The cell volume is 5% larger than that of the conventional phase I at 258 K. It is also shown that the orientation of the propanoic acid group is drastically changed with respect to phase I, leading to strong modifications of the orientation of the O—H···O hydrogen bonds with respect to the chains of dimers. These structural considerations could explain the metastable character of this phase II.

1. Introduction

Ibuprofen [2(4-isobutylphenyl)propanoic acid, $C_{13}H_{18}O_2$] is a widely used non-steroidal anti-inflammatory drug. It is currently available as a racemic mixture of *S*(+)-ibuprofen and *R*(−)-ibuprofen. The only known crystallographic form (phase I) for racemic ibuprofen has a monoclinic $P2_1/c$ space group (Shankland *et al.*, 1997; McConnell, 1974). Recently, a new crystalline phase, called phase II, was found by differential scanning calorimetry (DSC) and X-ray diffraction experiments (Dudognon *et al.*, 2008).

The enantiomer *S*(+)-ibuprofen crystallizes in the monoclinic space group $P2_1$ with two molecules per asymmetric unit to form a cyclic hydrogen-bonded dimer (Freer *et al.*, 1993).

In this paper we report the *ab initio* structure determination of phase II of racemic ibuprofen from X-ray powder diffraction experiments. We show that the directions of the O—H···O hydrogen bonds are different from those observed in phase I.

2. Experimental

2.1. Thermal treatment

Racemic ibuprofen (purity 99.8%) was purchased from Sigma. Samples were analysed without further purification. The kinetic conditions of the appearance of phase II were studied in detail and will be the subject of another publication. These conditions reveal the existence of a competition between phases I and II. As phase II is metastable, it was necessary to find the optimal conditions for the recording of the diffractogram of phase II that avoid the risk of pollution by phase I. Phase II was thus obtained by imposing the

following thermal history on the sample. The crystalline powder was melted (heating to 373 K), then cooled at 6 K min^{-1} until 143 K where it was annealed for 1 h. The sample was then heated (heating rate 6 K min^{-1}) to 258 K and kept at this temperature for 15 h. It should be noted that the quality of other recordings at different temperatures was lower.

2.2. Data collection

The X-ray powder diffraction patterns were measured on a laboratory diffactometer equipped with an INEL curved, position-sensitive detector (CPS120). The calibration of the detector was performed by the direct beam method. A bent quartz monochromator selected the $K\alpha_1$ wavelength of a Cu X-ray tube (λ = 1.54056 Å). The powder was enclosed in a Lindemann glass capillary (diameter 0.7 mm) mounted on the axis of a G3000 goniometer. The sample was rotated during the experiments in order to reduce the effect of possible preferential orientations. A Cryostream Plus controller from Oxford Cryosystems was used to regulate the temperature. Data were collected at 258 K in the 2θ range 0.2–113.8° ($2\theta_{step}$ = 0.015°). A diffraction pattern was recorded every hour from 2 through 15 h after the start of the annealing.[1]

3. Qualitative results

The evolution of the diffraction patterns, between 4 and 30° 2θ, for an annealing at 258 K is shown in Fig. 1. On the first pattern, a halo characteristic of an amorphous phase, with no Bragg peaks, is observed. This indicates that the ibuprofen sample is still amorphous after the quenching of the liquid to 143 K and the subsequent reheating to 258 K. On the second pattern Bragg peaks begin to appear, but the amorphous halo is still present. The magnitude of the Bragg peaks increases progressively during annealing. After 5 h, intense and thin peaks are observed and, at first sight, no significant evolution is seen for the following 10 h. These diffraction patterns are assigned to the new crystalline form, the so-called 'phase II'.

4. Structure solution and refinement

To improve the statistics, the last ten diffraction patterns measured at 258 K were summed up. For the determination of the lattice parameters, the profiles of 24 reflections with a 2θ angle lower than 30° were refined individually with the program *WinPlotr* (Roisnel & Rodriguez-Carvajal, 2002) in order to obtain their 2θ positions. The 2θ values of these reflections were input to the program *TREOR* (Werner *et al.*, 1985) and these reflections were indexed completely in a unique solution. The cell is monoclinic with the following parameters: a = 12.409, b = 5.890, c = 17.614 Å, β = 94.73° and V = 1283.1 Å^3. The calculated figures of merit are $M(24)$ = 18 and $F(24)$ = 38 (0.010,65) (de Wolff, 1968; Smith & Snyder,

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: WS5072). Services for accessing these data are described at the back of the journal.

Table 1
Crystallographic data, profile and structural parameters for phase II of racemic ibuprofen obtained after Rietveld refinements.

Crystal data	
Chemical formula	$C_{13}H_{18}O_2$
M_r	206.28
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	258
a, b, c (Å)	12.3794 (9), 5.8723 (5), 17.5615 (15)
β (°)	94.873 (4)
V (Å^3)	1272.03 (18)
Z	4
D_x (g cm^{-3})	1.077
Radiation type	X-ray, λ = 1.540560 Å
$F(000)$	448
μ (mm^{-1})	0.56
Specimen shape, size (mm)	Cylinder, 0.7
2θ range (°)	5–90
Data collection	
Diffractometer	Inel CPS120
Specimen mounting	0.7 mm diameter Lindemann capillary
Data collection mode	Transmission
Scan method	Stationary detector
Step size (° 2θ)	0.015
2θ values (°)	$2\theta_{fixed}$ = 0.2–113.8
Refinement	
R factors and goodness-of-fit	R_p = 0.040, R_{wp} = 0.056, R_{exp} = 0.126, R_{Bragg} = 0.058, χ^2 = 20.1
No. of profile data steps	7579
No. of contributing reflections	1037
No. of refined parameters	59
U	0.864 (45)
V	−0.230 (12)
W	0.034 (1)
η_0	0.522 (20)
X	0.0116 (11)
$Asym_1$	0.0362 (24)
$Asym_2$	0.0151 (4)
B_{ov} (Å^2)	4.7

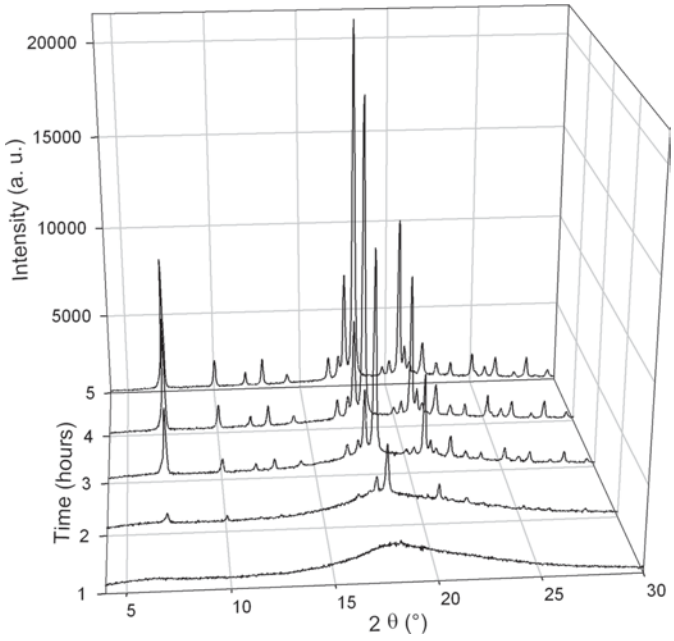

Figure 1
Three-dimensional plot of powder patterns during annealing at 258 K.

1979). Therefore, the number of molecules in the cell is $Z = 4$. The volume of the cell of phase II at 258 K is 5% larger than the volume $V = 1210.7$ Å^3 of phase I at the same temperature (the refinement of the X-ray diffraction pattern recorded in the same conditions for phase I gives $a = 14.610$, $b = 7.876$, $c = 10.669$ Å, $\beta = 99.51°$ and $V = 1210.7$ Å^3). The input of the 2θ positions in the program *DICVOL* (Boultif & Louër, 2004) gives two solutions, but the best figures of merit $M(24) = 30$ and $F(24) = 64$ (0.006,63) are obtained with the same monoclinic cell.

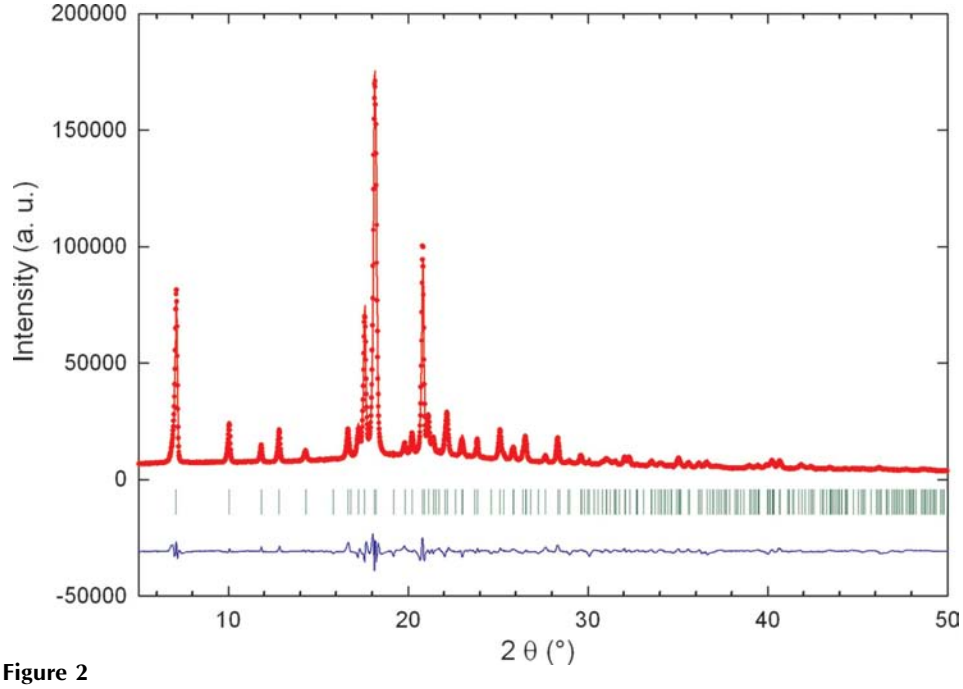

Figure 2
Final Rietveld plot of phase II of ibuprofen at 258 K, between 5 and 50° 2θ for clarity. Observed intensities are indicated by dots, the best-fit profile (upper trace) and the difference pattern (lower trace) are solid lines. The vertical bars correspond to the positions of the Bragg peaks.

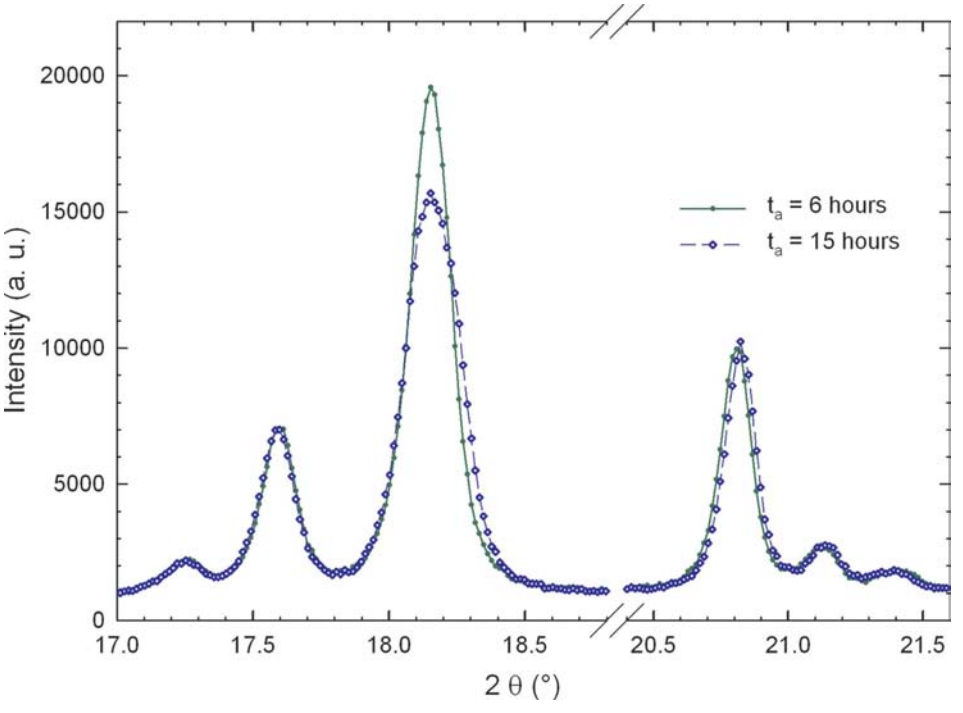

Figure 3
Selected diffraction patterns after an annealing of 6 and 15 h at 258 K.

The X-ray diffraction pattern from 5 to 90° 2θ was refined using Le Bail's method (Le Bail *et al.*, 1988) of the program *FULLPROF* (Rodriguez-Carvajal, 2001; Roisnel & Rodriguez-Carvajal, 2002). A pseudo-Voigt function, a linear combination of a Lorentzian and a Gaussian of the same FWHM, was used to fit the Bragg peaks. This FWHM has a θ dependence according to Caglioti's law (Caglioti *et al.*, 1958). The asymmetry of the reflections was taken into account according to the Berar and Baldinozzi function (Bérar & Baldinozzi, 1993). The background was determined with a linear interpolation between 22 points regularly distributed from 5 to 90°. The 34 refined parameters are as follows: the lattice parameters a, b, c and β, the zero-shift, the Caglioti profile parameters U, V, W, the mixing parameter η_0 of the pseudo-Voigt function and its 2θ dependence X, 2 parameters for the asymmetry of the Bragg peaks and 22 points to define the background.

The systematic absence of $h0l$ reflections with l odd, $0k0$ with k odd, $00l$ with l odd, leads to the space group $P2_1/c$. Therefore, the asymmetric unit contains one molecule. At the end of the Le Bail refinements, the profile reliability factors are: $R_p = 0.0843$, $R_{wp} = 0.0804$, $R_{exp} = 0.0307$ and $\chi^2 = 6.89$; the lattice parameters are $a = 12.3805$ (5), $b = 5.8726$ (3), $c = 17.5624$ (7) Å, $\beta = 94.877$ (2)° and $V = 1272.26$ (9) Å^3. The widths of the Bragg peaks, which are close to the experimental resolution given by the standard compound $Na_2Ca_3Al_2F_{14}$ (NAC; Evain *et al.*, 1993), do not allow a microstructural analysis (size of crystallites and micro-strain effects). In order to obtain a

Table 2
Values of the bond lengths (Å) and angles (°).

C1—C2	1.506 (43)	C6—C7	1.381 (33)
C1—O1	1.277 (38)	C7—C8	1.383 (34)
C1—O2	1.212 (37)	C7—C10	1.512 (38)
C2—C3	1.491 (46)	C8—C9	1.384 (40)
C2—C4	1.481 (42)	C10—C11	1.512 (37)
C4—C5	1.383 (39)	C11—C12	1.523 (40)
C4—C9	1.382 (40)	C11—C13	1.535 (40)
C5—C6	1.383 (43)		
C2—C1—O1	107.6 (2.2)	C5—C6—C7	120.0 (2.0)
C2—C1—O2	126.1 (2.1)	C6—C7—C8	120.0 (2.3)
O1—C1—O2	109.5 (2.5)	C6—C7—C10	120.9 (1.9)
C1—C2—C3	107.8 (2.3)	C8—C7—C10	117.0 (2.5)
C1—C2—C4	99.7 (2.2)	C7—C8—C9	120.0 (2.4)
C3—C2—C4	102.6 (2.0)	C4—C9—C8	120.0 (2.4)
C2—C4—C5	118.0 (2.2)	C7—C10—C11	97.7 (2.2)
C2—C4—C9	121.9 (2.3)	C10—C11—C12	89.9 (2.2)
C5—C4—C9	119.9 (2.1)	C10—C11—C13	108.9 (1.8)
C4—C5—C6	120.0 (2.4)	C12—C11—C13	90.6 (1.7)

Table 3
Values of selected dihedral angles (°).

	Phase I (this work)	Phase II (Shankland *et al.*, 1997)
C1—C2—C4—C5	−76.5 (3.0)	95.5
O1—C1—C2—C4	114.6 (2.5)	−88.7
O2—C1—C2—C4	−113.8 (2.2)	89.6

starting stuctural model, the 'parallel tempering' algorithm of the program *FOX* (Favre-Nicolin & Černý, 2002) was used. The molecule of ibuprofen was built with bond lenghs, bond angles and torsion angles calculated from the atomic coordinates of Shankland *et al.* (1997) obtained from the structure determination of phase I. This molecule was introduced randomly in the cell. The relaxed restraints option used for the calculations modified the bond lenghs, bond angles and torsion angles. Atomic coordinates found by *FOX* were introduced in the program *FullProf* (Rodriguez-Carvajal, 2001) in order to perform Rietveld refinements. Soft restraints on the bond lengths and bond angles were applied. With these conditions, the phenyl ring became non-planar. To avoid this deformation, it was kept rigid. Some H atoms can be placed with geometrical arguments. For example, this was the case for the CH and CH_2 groups. Each C atom was at the centre of a tetrahedron and the H atoms completed these tetrahedra with a C—H bond length equal to 1.00 Å. Attempts to refine the overall Debye–Waller factor B_{ov} led to abnormally high values. So it was kept fixed at the value given by *FOX*. Therefore, for the Rietveld refinements, there were 59 ajustable parameters:

(i) 12 profile parameters: the lattice parameters a, b, c and β, the zero-point, U, V, W, η_0 and X defined above, and two asymmetry parameters.

(ii) 25 structural parameters: the scale factor and 24 atomic coordinates.

(iii) 22 points to define the background.

The final conventional Rietveld factors are: $R_p = 0.138$, $R_{wp} = 0.136$, $R_{exp} = 0.0303$ and $\chi^2 = 20.1$. The experimental and calculated diffraction patterns are shown in Fig. 2. The Rietveld factors appear to be rather high. This is probably due to the metastability of phase II of ibuprofen. Fig. 3 shows

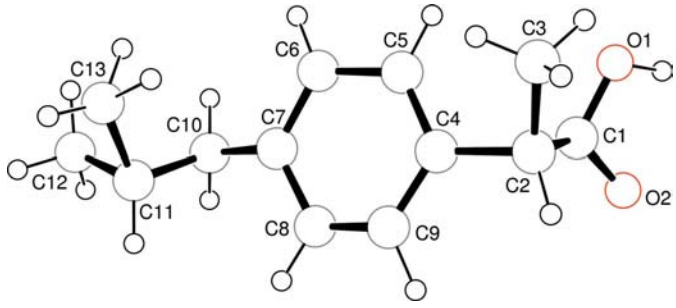

Figure 4
Atomic numbering and molecular structure of ibuprofen.

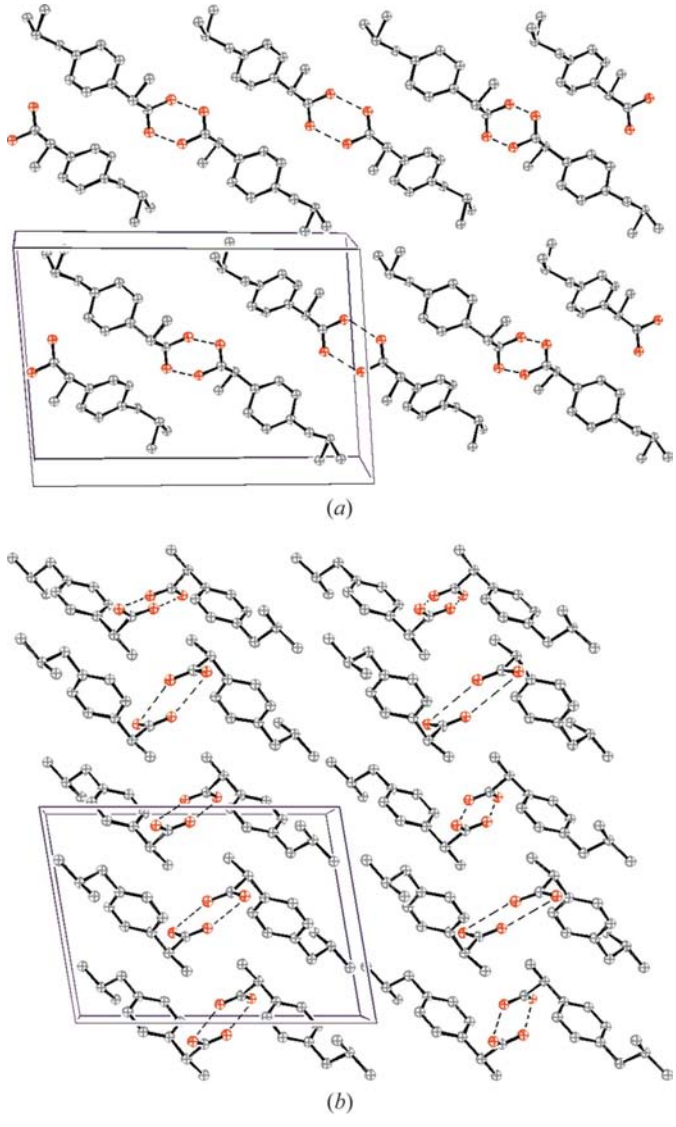

Figure 5
Perspective drawing of the unit cell along the twofold screw axis. Only one plane of dimers is drawn: (*a*) this work and (*b*) from Shankland *et al.* (1997). The dashed lines symbolize the hydrogen bonds.

selected diffraction patterns after an annealing of 6 and 15 h at 258 K and we can observe slight modifications, both on the angular positions and the intensities of some Bragg peaks. A representation of the molecule drawn with *ORTEP*3 (Farrugia, 1997) and the numbering of the atoms is shown in Fig. 4. Crystallographic data, profile and structural parameters are given in Table 1 and reduced coordinates for non-H atoms in the supplementary material. Bond lengths and bond angles calculated with *SHELX*97 (Sheldrick, 2008) and *PARST* (Nardelli, 1995) are given in Table 2.

5. Conclusions

Molecules form hydrogen-bonded dimers across centres of inversion within the space group $P2_1/c$, as is the case in phase I of ibuprofen (Shankland *et al.*, 1997). The O···O distance which characterizes the hydrogen bond is 2.70 Å. However, we observe in Fig. 5 different arrangements in the structure of phase I and II. In phase I (Fig. 5*b*) the direction of the hydrogen bond is practically perpendicular to the chains of dimers. The hydrogen bonds link the molecules belonging to two different chains and this has the effect of strengthening the cohesion of the lattice. On the other hand, in phase II (Fig. 5*a*) the hydrogen bond connects two molecules within the same chain, leading to a lower stability. This is associated with a change in the molecular conformation of the propanoic acid part of the molecule. The corresponding dihedral angles are shown in Table 3. As already mentioned, the volume of the cell, larger in phase II, also contributes to the metastability of this phase.

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