Crystallization and disorder of the polytypic α1 and α2 polymorphs of piroxicam
Crystallization and disorder of the polytypic $\alpha_1$ and $\alpha_2$ polymorphs of piroxicam

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Polymorphism of the active pharmaceutical ingredient piroxicam, C13H13N2O2S, is investigated with an aim to clarify the identity and crystallization conditions of the $\alpha_1$ and $\alpha_2$ polymorphs. The structures are polytypic, containing identical 2-dimensional layers, with different symmetry relationships between the layers. The $\alpha_1$ structure is orthorhombic and non-centrosymmetric (space group type Pca2_1), while the $\alpha_2$ structure is monoclinic and centrosymmetric (space group type P2_1/c). $\alpha_2$ can be crystallized by evaporation from ethanol at 25°C, while $\alpha_1$ is obtained by crystallization from the same solvent at 4°C. The polytypic relationship provides a suitable condition for order-disorder phenomena to be observed in single crystals. Intermolecular interaction energies calculated using the PIXEL method suggest that the centrosymmetric interlayer regions in $\alpha_2$ involving the pyridyl groups are more stabilizing than the corresponding non-centrosymmetric interlayer regions in $\alpha_1$. This is consistent with observations of inversion twinning in non-centrosymmetric $\alpha_1$ crystals. The interlayer regions involving the benzothiazine groups have very similar interaction energies in the two structures.

Introduction

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) belonging to the class of oxicam.$^1$ Crystalline piroxicam is known to show polymorphism, which has been studied quite extensively since its discovery. The compound is established to crystallize in several anhydrous forms,$^{2–5}$ and one monohydrate form.$^6$ For the anhydrous compound, there are currently eight entries in the Cambridge Structural Database (CSD; Nov. 2013 release plus updates), which fall into four structural groups (Table 1). As is often the case for well-studied compounds, the nomenclature of the polymorphs in the primary literature is inconsistent. The situation up to 2004 was summarised in a helpful article by Sheth$^{6}$ who noted that the $\alpha_1$ and $\alpha_2$ structures frequently appear in varying ratios in bulk samples. A single-crystal structure for $\alpha_2$ was later determined by Vrečer$^7$ and it crystallizes commonly by slow cooling from various solvents. Form III was observed by Reck$^8$ et al. in 1990, and has been obtained by rapid pouring of hot saturated solutions onto dry ice$^9$ or by spray drying.$^5$ The crystal structure of form III was determined from powder X-ray diffraction (PXRD) data in 2012 (BIYSEH07).$^5$

The subject of this paper is the polymorph originally labelled as the $\alpha$ form, and later (ambiguously) re-labelled as form II.$^8$ An orthorhombic crystal structure was first reported from single-crystal data in 1988 by Reck$^9$ et al. (BIYSEH02).$^9$ In that paper, the authors noted that Weissenberg photographs contained diffuse strips and a few weak additional reflections, which led them to propose an order-disorder (OD) model, with the orthorhombic form being one maximum-degree-of-order (MDO) structure. On the basis of the OD model, a monoclinic structure corresponding to a second MDO structure was deduced.$^10$ The orthorhombic and monoclinic structures were labelled $\alpha_1$ and $\alpha_2$, respectively, and they are polytypes.$^{11}$ Reck$^9$ et al. initially showed the existence of $\alpha_1$ and $\alpha_2$ by comparing to measured PXRD patterns, and they noted that the $\alpha_1$ and $\alpha_2$ structures frequently appear in varying ratios in bulk samples. A single-crystal structure for $\alpha_2$ was later determined by Vrečer$^7$ et al. (BIYSEH06),$^7$ where the authors refer to it as form II.

Although the polytypic relationship and probable disordered nature of $\alpha_1$ and $\alpha_2$ was described by Reck$^9$ et al. in 1990,$^{10}$ the identity of the polymorphs does not seem to be clear in the subsequent literature. This is possibly because of the close structural relationship between the polytypes or perhaps because of the introduction of the ambiguous form II label by Vrečer$^7$ et al.$^7$ The summary article by Sheth$^6$ et al. is unclear on this point: it states that "...form II has also been named $\alpha_1$, $\alpha_2$, $\alpha_3$...",$^6$ which indicates that all three $\alpha$ labels refer to the same “form II”. In this article, we aim to clarify the existence and identity of the piroxicam polymorphs $\alpha_1$ and $\alpha_2$, by describing their polytypic relationship and by identifying reproducible crystallization conditions for both. The structural situation is comparable to that described for aspirin, which exhibits intergrowth polymorphism.

Scheme 1 Molecular structure of piroxicam

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on account of the polytypic relationship between forms I and II.\textsuperscript{12,13} A similar situation has also been shown for felodipine, where crystals reported to be form II comprise domains of two polytypes.\textsuperscript{14} In this paper, we retain the original piroxicam $\alpha_1/\alpha_2$ notation of Reck et al. for consistency with the original work.

### Table 1 CSD entries for anhydrous piroxicam

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>CSD Refcode</th>
<th>Symmetry and approximate unit-cell parameters (Å, °)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form I (= β form)</td>
<td>BIYSEH01, BIYSEH04</td>
<td>Monoclinic, $P2_1/c$</td>
<td>[2]</td>
</tr>
<tr>
<td>Form II</td>
<td>BIYSEH02</td>
<td>Orthorhombic, $Pca_2_1$</td>
<td>[3]</td>
</tr>
<tr>
<td>Form III</td>
<td>BIYSEH07</td>
<td>Triclinic, $P$–1</td>
<td>[5]</td>
</tr>
</tbody>
</table>

\[ \begin{align*}
\alpha_1 & = 8.0, b = 10.1, c = 10.5 \\
\alpha_2 & = 81.2, \beta = 69.3, \gamma = 69.8
\end{align*} \]

**Fig. 1** Simulated powder X-ray diffraction patterns (CuKα radiation, $\lambda = 1.5406 \text{ Å}$) for piroxicam structures in the CSD. All patterns are based on crystal structures determined at room temperature.

### Materials and Methods

Piroxicam (USP32) was purchased from Chr. Olesen Pharmaceuticals A/S (Gentofte, Denmark) and was found to be Form I by PXRD. All solvents used were of HPLC grade with purity $\geq 99.8\%$.

#### Crystallization experiments

Crystallization experiments were set up at concentrations 2.0, 5.0, 10.0 and 15.0 mg/mL in various solvents as listed in Table 2. The samples at 2.0 mg/mL were sonicated for 10 mins in order to obtain a clear solution. At 5.0 mg/mL in methanol, ethanol, acetonitrile and $n$-propanol, a suspension was formed upon sonication, which was further heated to 50°C to obtain a clear solution. At 10.0 and 15.0 mg/mL, all samples except for acetone, dichloromethane, dimethylsulfoxide and dimethylacetamide formed a suspension and were heated to obtain a clear solution. All hot solutions were cooled slowly to room temperature (preventing rapid crashing) and left to evaporate at either 25 or 4°C.

### X-Ray Diffraction

Single-crystal X-ray diffraction data were collected on a Bruker D8-QUEST instrument, equipped with a PHOTON-100 detector and an Incoatec IgS microsource (CuKα radiation; $\lambda = 1.5418 \text{ Å}$) at 298 K. Data collection and reconstruction of precession images were carried out using the APEX2 package.\textsuperscript{16} Powder X-ray diffraction data were collected on a Panalytical X’Pert Pro instrument, equipped with a PIXcel detector using non-monochromated CuKα radiation ($\lambda = 1.5418 \text{ Å}$). The sample was placed in a zero-background Si holder and measured in reflection geometry with sample spinning. Samples were ground thoroughly before mounting in an effort to minimise preferred orientation. The PXRD patterns were fitted by Pawley refinement using TOPAS Academic,\textsuperscript{17} starting from the unit-cell parameters of BIYSEH02 ($\alpha_1$) and BIYSEH05 ($\alpha_2$).

### Computational Methods

Energy minimisation of the crystal structures was carried out using the CASTEP module\textsuperscript{18} in Materials Studio.\textsuperscript{19} The starting structures were BIYSEH05 ($\alpha_2$) and a transformed version of BIYSEH02 ($\alpha_1$) as described in the Results and Discussion section. The PBE functional was applied\textsuperscript{20} with a plane-wave cut-off energy of 520 eV and a dispersion correction according to Grimme.\textsuperscript{21} All other parameters were set to the “fine” defaults within Materials Studio; full details are included in the ESI\textsuperscript{†}. All atomic coordinates and unit-cell parameters were optimized.

### Results and Discussion

#### Crystallization studies

We have crystallized piroxicam under various conditions and solvents, as summarized in Table 2, with an emphasis on targeting the $\alpha_1$ and $\alpha_2$ forms. Numerous other authors have reported piroxicam crystallization results, so the following discussion compares to the published results where relevant.

Michalić et al. were first to describe the crystallization behaviour in ethanol in 1982.\textsuperscript{1} They stated that fast cooling of saturated ethanolic solutions leads to the “needle form” whereas slow cooling produces the “cubic form”. The “cubic form” is identifiable as form I, but it is difficult to identify the “needle form” conclusively as either $\alpha_1$ or $\alpha_2$. The published PXRD pattern matches most closely with $\alpha_1$, but the stated melting point (196–198°C) matches with $\alpha_2$ (according to our DSC results). In 1999, Csóka et al. also obtained “white needle crystals” from ethanol, with a melting point that indicates $\alpha_2$.\textsuperscript{22} We find that slow evaporation from ethanol gives initially $\alpha_2$ as needles, but that these needles convert to form I over 1–2 weeks on standing in the same solution. The $\alpha_2$–I conversion appeared to take place more rapidly for the lower solution concentrations (ca 5 mg/mL) than at the higher concentrations.
Table 2 Summary of crystallization results for piroxicam in selected solvents and conditions. Polymorph identity is established by unit-cell determination on selected single crystals and by PXRD of the bulk.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Slow evap. at 25°C</th>
<th>Slow evap. at 4°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>(\alpha_2)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Acetone</td>
<td>(I + \alpha_2)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Methanol</td>
<td>(I + \alpha_1)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Isopropyl acetate</td>
<td>(I + \alpha_2)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>(I + \alpha_2)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>(n)-Propanol</td>
<td>(\alpha_2)</td>
<td></td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Dimethylacetamide</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Isopropyl acetate</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>(n)-Propanol</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>(I)</td>
<td></td>
</tr>
<tr>
<td>Dimethylacetamide</td>
<td>(I)</td>
<td></td>
</tr>
</tbody>
</table>

Note: All solvents are anhydrous. The presence of water leads readily to crystallization of piroxicam monohydrate.

In 1991, Janik et al. studied the influence of various solvents on the crystallization behaviour, and reported that the “\(\alpha\) structure” crystallized from ethanol, isopropanol, THF, acetonitrile and chloroform. We find some conflicting results: we observe that form I crystallizes as large rods from acetonitrile or chloroform under slow evaporation at 25°C. However, the conclusions of Janik et al. were made solely on the basis of IR spectra, without measurement of PXRD patterns, so the effectiveness of their polymorph identification may be in doubt.

Also in 1991, Vreec et al. produced \(\alpha_1\) by crash cooling of methanol, ethanol, acetone, \(n\)-propanol or chloroform solutions. The identity of \(\alpha_1\) is clear from the published DSC traces (compared to our DSC traces reported herein), but accompanying PXRD data were not reported and the authors did not make any distinction between \(\alpha_1\) and \(\alpha_2\). Indeed, they refer to “form II” in their 1991 paper for obtained \(\alpha_1\) samples, but in 2003 refer again to “form II” for samples that are clearly \(\alpha_2\). We observe that \(\alpha_1\) is obtained exclusively and reproducibly by slow evaporation of piroxicam solutions in ethanol, methanol, acetone or isopropyl acetate at reduced temperature (around 4°C). As seen in SEM images (Fig. 2), \(\alpha_1\) crystallizes as fine needles. The PXRD patterns of the bulk crystallized materials (Fig. 3) match well with the pattern simulated from BIYSEH02.

In summary: we find that \(\alpha_1\) can be crystallized reproducibly from ethanol, methanol, acetone or isopropylacetate at 4°C, while \(\alpha_2\) crystallizes from ethanol at 25°C, but undergoes solvent-mediated transformation to form I if left in contact with the crystallization solution.

Crystal structures of \(\alpha_1\) and \(\alpha_2\)

To enable a direct comparison between the crystal structures of \(\alpha_1\) and \(\alpha_2\), we transform the published structure of BIYSEH02 (\(\alpha_1\)) using the matrix \([1 0 0 / 0 1 0 / -1 0 0]\) to give unit-cell parameters \(a = 17.4, b = 11.8, c = 7.0\) Å in the non-standard space group setting \(Pbc\). H atoms are not included in BIYSEH02, but can be unambiguously added in geometrical positions. This transformed structure of BIYSEH02 is compared below to the CSD entry BIYSEH05 (\(\alpha_2\)).

The two structures contain identical layers in the \(bc\) planes, but the \(a\) axis (the long axis) is aligned differently. The orthorhombic unit cell of \(\alpha_1\) can be transformed to the monoclinic unit cell of \(\alpha_2\) by application of the transformation matrix \([1 0 0 / 0 1 0 / 0 0 1]\), which corresponds to shearing of the unit cell parallel to the \(c\) axis, i.e. \(a(\alpha_2) = a(\alpha_1) + \frac{1}{2}c(\alpha_1)\). In projection along the \(c\) axis, the structures appear identical (Fig. 4). The difference is seen in projection along the \(b\) axis (Fig. 4). The layers in \(\alpha_1\) are related by \(2\) \(\alpha\) screw axes parallel to \(c\), and by \(b\)- and \(c\)-glides perpendicular to the \(a\) and \(b\) axes, respectively. The structure is non-centrosymmetric and polar, with all \(N\)–\(CH_3\) vectors pointing in the same direction along the \(c\) axis. In the \(\alpha_2\) structure, inversion centres exist between the layers. The two alternative orientations for a given layer are related to each other by a mirror operation perpendicular to the \(c\) axis (Fig. 5).
There are two different interlayer regions: one where the pyridyl rings meet (at the upper and lower edges of the unit cell drawn in Fig. 4), and one where the benzothiazine ends of the molecules meet (at the middle of the unit cell in Fig. 4). In both regions, the local intermolecular relationships are mirrored, but the contacts remain similar. The principal interactions are C—H···O from the pyridyl and benzothiazine rings to the O atoms of the S=O, C=O and C—OH groups. The intermolecular interactions and their energies are discussed in more detail subsequently.

**Fig. 4** Unit cells of the $\alpha_1$ and $\alpha_2$ structures. The structures look identical in projection along the c axis (left), but different in projection along the b axis (right). The consistent layers are in the bc planes (horizontal). $\alpha_1$ is non-centrosymmetric and polar (all N–CH$_3$ groups point in the same direction along c), while $\alpha_2$ is centrosymmetric. H atoms are not shown.

**Fig. 5** Overlay of $\alpha_1$ (blue) and $\alpha_2$ (red) showing the mirror relationship between the alternative layer orientations.

**Fig. 6** Schematic illustration of the idealized geometry for the diffraction patterns of $\alpha_1$ and $\alpha_2$ in the a*c* planes. Blue spots correspond to orthorhombic $\alpha_1$. Red and green spots correspond to two orientations of monoclinic $\alpha_2$, related to each other by 2-fold rotation around the real c axis (horizontal). The black spots are coincident in all three lattices.

**Relationship between the diffraction patterns**

One of our principal interests with the $\alpha_1$ and $\alpha_2$ piroxicam structures is their polytypic relationship and the potential for stacking faults and/or intergrowth polymorphism, similar to aspirin.$^{12,13}$ By considering the relationship between the single-crystal diffraction patterns of the two forms, we consider here how such phenomena would be observed. With the consistent layers in both structures lying in the bc planes, $\alpha_1$ and $\alpha_2$ have their a* and b* axes aligned, but not their c* axes. The idealized geometry in the plane containing a* and c* is shown in Fig. 6. $\alpha_1$ has an orthorhombic lattice with c* perpendicular to a*, and parallel to the c axis in real space (horizontal in Fig. 6). In $\alpha_2$, c* makes an angle of $\sim 7^\circ$ to this direction. The geometry is such that the diffraction spots along a* for $\alpha_2$ are offset by one third of the lattice spacing for $\alpha_1$. This offset could occur in either direction, giving three sets of evenly-spaced diffraction spots along a* (Fig. 6). Since the (idealized) offset between the spots is $\frac{1}{3}$a*, the lattices come back into coincidence in every third row along c* (i.e. $l = 0, 3, 6,$ etc.). This is also expressed by the transformation matrix relating the two unit cells: $[1 \ 0 \ \frac{1}{3} / 0 \ 1 \ 0 / 0 \ 0 \ 1]$. The observation of three sets of discrete Bragg spots, as indicated in Fig. 6, would refer to a situation where the domain sizes of the three cases ($\alpha_1 + \alpha_2$ in two different orientations related by 180° rotation around the c axis) were suitably large. Smaller domain sizes, corresponding to more frequent turnover between domains, would generate diffuse streaks along a* for $l \neq 0, 3, 6,$ etc.

**Single-crystal X-ray diffraction**

Crystals of $\alpha_1$ obtained from ethanol at 4°C were studied by single-crystal X-ray diffraction. A representative reconstructed precession image for the h1l plane is shown in Fig. 7. In the image shown, faint diffuse streaks are visible along a*, which give some indication of layer stacking disorder, but we have not observed any crystals with additional Bragg peaks that might indicate significant $\alpha_2$ domains. Since the structure is non-centrosymmetric, the presence of one stacking fault corresponding to the inversion-related interlayer arrangement in $\alpha_2$ would manifest itself as inversion twinning. We have found...
some crystals where the Flack parameter refines to zero (indicating no inversion twinning) and others where it refines to a non-zero value (with suitably small uncertainty) due to inversion twinning. Thus, twinning of the α₁ structure by incorporation of the α₂ interlayer arrangement is found to occur, but to date we have not observed any clear indications of sizeable α₂ domains within α₁ single crystals. A representative structure from our α₁ crystal has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1050926).

Fig. 7 Reconstructed h1l/ precession image for a representative crystal of α₁, aligned as in Fig. 6. Faint streaks are visible in the vertical direction.

Numerous crystals of α₂ were studied, and these were frequently found to be twinned. Using the unit cell established for α₂ in space group P2₁/c (a ≈ 17.6 Å, b ≈ 11.9 Å, c ≈ 7.0 Å, β ≈ 97°), the relationship between the twin domains was established to be a 180° rotation around the c axis, as indicated in Fig. 6. A typical reconstructed precession image for the h1l plane is shown in Fig. 8. The Bragg reflections of the two twin components are clearly separated, and diffuse streaks indicate less ordered regions. The coincidence of the two lattices for l = 3 is apparent. The twin operation corresponds to introduction of the α₁ interlayer arrangement, but again we have not observed any clear indications of Bragg reflections corresponding to sizeable α₁ domains within α₂ single crystals. A representative α₁ structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1050927).

Finally, it is interesting to note that twinned α₂ crystals indexed in a standard way commonly indicate a ≈ 52.3 Å (≈ 3 × 17.6 Å). The reason for this is clear from Figs. 6 and 8. A similar long axis was reported by Reck et al. in their first determination of the α₁ structure, i.e. the orthorhombic form. This could indicate that their α₁ crystals contained sizeable domains of the α₂ structure (i.e. their diffraction pattern resembled the situation in Fig. 6). This would amount to intergrowth polymorphism, similar to the situation reported for aspirin and felodipine form II. We have not reproduced any such result to date, but it is clear from the polytypic relationship that there is potential for such a situation to exist.

Thermal analysis

Thermal analysis of bulk α₁ and α₂ was carried out by differential scanning calorimetry (DSC), with form I also measured for comparison (Fig. 9). Form I shows a single sharp melting endotherm with onset 201.2°C. α₂ also shows a single sharp melting endotherm with onset 198.8°C, which matches well with the α₂ melting point reported by Michalić et al. (196–198°C). For α₁, a first endotherm is seen at 194.8°C, corresponding to melting, followed by an exotherm that corresponds to crystallization of form I then a subsequent melting endotherm for form I.

Fig. 9 DSC thermograms for bulk samples of form I, α₁ and α₂.

Intermolecular interaction energies

To obtain an indication of the relative stabilities of α₁ and α₂, the structures of BIYSEH02 (α₁) and BIYSEH05 (α₂) were energy-minimized using dispersion-corrected density functional theory calculations (DFT-D). Details and minimized structures are provided in the ESI. The resulting energies (at 0 K) suggest that α₂ is moderately more stable than α₁, which is nominally consistent with the observed melting points. Pairwise intermolecular interaction energies were then calculated from the minimized structures using the PIXEL method (Table 3). The total potential energy for a molecule in each structure is indistinguishable within the expected precision of these calculations. However, the distribution of the interactions is different. The results are visualised in Fig. 10 using energy-vector diagrams of the type developed by Shishkin and co-workers, generated using the processPIXEL program. Table 3 shows sums of the principal stabilising interactions partitioned into intra- and interlayer regions. The most striking result is that the
pyridyl interlayer region in the $\alpha_2$ structure is calculated to be more stabilising than any of the other interlayer regions. This is mainly due to a particularly stabilising pairwise interaction between inversion-related molecules, with a substantial coulombic component originating from C—H···O interactions involving both SO$_2$ groups (Fig. 11). The corresponding non-centrosymmetric interaction in the $\alpha_1$ structure involves only one such contact and is substantially less stabilising. If the twinning in both structures were to be controlled by the intermolecular interaction energies, Table 3 implies the following observations: (i) inversion twinning in the non-centrosymmetric $\alpha_1$ structure is most likely to occur at the pyridyl interlayer region; (ii) twinning in the $\alpha_2$ structure is most likely to occur at the benzothiazine interlayer region.

Table 3 Interaction energies (kJ·mol$^{-1}$ per molecule) calculated for $\alpha_1$ and $\alpha_2$ using the PIXEL method, applied to DFT-D minimized structures. Full details are available in the ESI.$^\dagger$

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>Total</th>
<th>Intralayer</th>
<th>Interlayer</th>
<th>Interlayer</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>$-153.8$</td>
<td>$-53.7$</td>
<td>$-53.4$</td>
<td>$-38.9$</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>$-153.9$</td>
<td>$-52.7$</td>
<td>$-57.1$</td>
<td>$-39.9$</td>
</tr>
</tbody>
</table>

Fig. 11 The most stabilising pairwise intermolecular interaction in the $\alpha_2$ structure: centrosymmetric, with C—H···O interactions (light blue lines) between the pyridyl rings and SO$_2$ groups.

Conclusions

With this clarification of the structures of piroxicam forms $\alpha_1$ and $\alpha_2$, and a specific report of crystallization conditions for both, piroxicam has four well-established polymorphs. We have chosen to retain the $\alpha_1/\alpha_2$ notation of Reck et al. in order to maintain consistency with the original work. Where the “form II” label introduced by Vrečer et al. is seen in the literature, it should be considered carefully whether the information in the paper is sufficient to distinguish $\alpha_1$ from $\alpha_2$. We have obtained single-crystal data that show that orthorhombic $\alpha_1$ can exist with only minimal twinning/disorder, but single crystals that we have obtained for monoclinic $\alpha_2$ have frequently been twinned. So far, we have not obtained any single crystals that show clear domains of both the $\alpha_1$ and $\alpha_2$ polymorphs simultaneously, as would be the case for intergrowth polymorphism.

This article certainly does not represent the end of the story for piroxicam polymorphism. We are currently aware of two additional crystal structures, one of which we have obtained during our solution crystallization experiments, and one of which has its unit-cell parameters and simulated PXRD pattern reported.$^{27}$ The latter is a high $Z$ form. There has also been a recent report of a further new form obtained from chloroform solution by electrospray methods,$^{28}$ and we have produced similar PXRD patterns in the course of our work. Thus, at least two more anhydrous piroxicam crystal structures are already known, and there appears to exist one other solid form whose structure is yet to be established. This will bring the known total (so far) up to seven polymorphs, making piroxicam one of the more prolific polymorphic pharmaceutical compounds.

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Notes and references

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† Electronic Supplementary Information (ESI) available: details of the DFT and PIXEL calculations for $\alpha_1$ and $\alpha_2$. See DOI: 10.1039/b000000x/.


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The polytypic \( \alpha_1 \) and \( \alpha_2 \) polymorphs of piroxicam are described and it is shown that they can be crystallized controllably.