

On the Polymorphism of Aspirin**

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A second polymorph of aspirin, *o*-acetylsalicylic acid, (form II), was recently reported by Peterson, Zaworotko, and co-workers (hereafter referred to as PZ).^[1] This new form was obtained by crystallization of pure aspirin in the presence of either levetiracetam or acetamide from MeCN, and it was characterized by single-crystal X-ray diffraction. Form II was “also characterized by melting point, IR, DSC, and HPLC”. It was stated that “there are clear differences between the unit-cell parameters” of form I and form II, and also that “the molecular geometry of aspirin molecules in form II is slightly different in terms of the torsion angle defined by the carboxylic acid and acetyl groups, although the centrosymmetric carboxylic acid dimer remains intact”. The crystal packing of the new polymorph proposed by PZ is different from that of form I. Notably, “methyl groups form catemeric C–H...O hydrogen bonds with the carbonyl oxygen of the acetyl group versus centrosymmetric dimers in form I”.

While new polymorphs of older compounds are constantly being discovered^[2] and there is much interest in this phenomenon in the pharmaceutical industry because of the legal implications of finding new polymorphs and pseudopolymorphs of active pharmaceutical ingredients (APIs),^[3] we wish to clarify in this communication that the form II of aspirin as reported by PZ may just as easily be derived, to the accuracy and precision reported by these workers, from experimental diffraction data collected from what is undoubtedly a single crystal of the well-known form I. While the

reasons for this unusual occurrence are still being explored by us, we have deemed our initial result to be of sufficient importance to warrant a preliminary communication, not least because of the peculiar chemico-legal significance of polymorphism in the pharmaceutical industry today, and the ubiquitous nature of the molecule in question.

The first crystal structure determination of aspirin (form I) was performed by Wheatley,^[4] who stated in his 1964 paper that “a number of attempts” had been made prior to his work. The space group is $P2_1/c$, and the conventional R -factor was 0.108. Somewhat high R -factors such as these were not uncommon in those times. In 1984, Kim et al. reported the same structure with an R -factor of 0.046.^[5] In 2002, Wilson redetermined the same crystal structure from neutron diffraction data collected at seven temperatures between 20 K and 300 K,^[6] and the R -factors (on F) in these determinations are in the range 0.080 to 0.090. We felt these R -factors to be definitely high and accordingly redetermined the crystal structure. For this purpose we selected a well-formed crystal from a commercial sample (Merck Art. 85, DAB 7). The unit cell [$a = 11.2776(2)$, $b = 6.5517(1)$, $c = 11.2741(2)$ Å, $\beta = 95.837(1)^\circ$, $V = 828.70(2)$ Å³] corresponds to that reported by Wheatley,^[4] Kim,^[5] and Wilson.^[6] The refinement on data to $2\theta = 56^\circ$ (MoK α radiation) is acceptable ($R1[I > 2\sigma(I)] = 0.033$); indeed, this is the best structure determination on aspirin form I to date,^[7] and we use it as a benchmark in this paper.

At the outset, we noted several anomalous indicators in the PZ structure: 1) The data are truncated to $2\theta = 40^\circ$ (MoK α); 2) The R -factors are unacceptably large ($R1[I > 2\sigma(I)] = 0.162$, $wR2(\text{all data}) = 0.308$); 3) All atoms are refined isotropically, implying that anisotropic refinement was not possible; 4) Several of the refined U_{iso} values are zero or disturbingly close to zero. Most revealingly, we noted that the unit cell reported by PZ [$a = 12.095(7)$, $b = 6.491(4)$, $c = 11.323(6)$ Å, $\beta = 111.509(9)^\circ$, $V = 827.1(8)$ Å³] can be transformed to the cell obtained by us for form I with the metric transformation $[1 \ 0 \ 1/2 \ 0 \ -1 \ 0 \ 0 \ 0 \ -1]$. Likewise, our experimental form I cell can be transformed to a cell having $a = 12.084$, $b = 6.552$, $c = 11.274$ Å, $\beta = 111.81^\circ$, $V = 828.7$ Å³. This is depicted schematically in Figure 1.

We next returned to our experimental diffraction data and applied this relationship so that our data were indexed on the basis of the PZ unit cell.^[8] Subsequent integration and data reduction was followed by a straightforward structure solution with direct methods,^[9] using default settings in the space group $P2_1/c$ obtained automatically by the software. The result (Figure 1) was completely superimposable on the PZ structure! Isotropic refinement on data to $2\theta = 50^\circ$ proceeded to $R1 = 0.081$ with reasonable molecular and intermolecular geometries and U_{iso} values in the range 0.019(1)–0.027(1) Å². However, anisotropic refinement failed completely. In short,

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author. These include: a detailed comparison of the form I and form II structures, a description of the transformation between the two structures/lattices in real and reciprocal space, full details of the procedure for producing the form II structure from simulated data and from our experimental data, and electronic files (CIF, HKL, RES) to accompany the discussion.

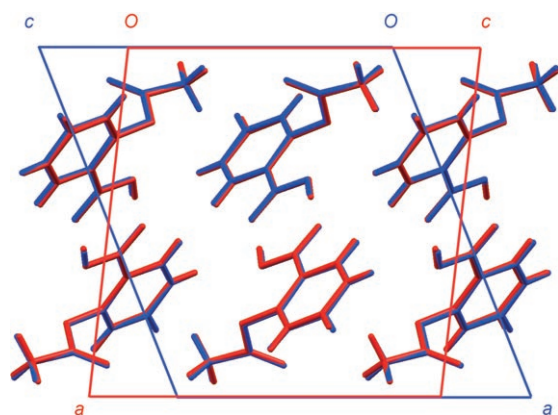


Figure 1. Superposition of the form I structure (red) and the PZ structure (blue), showing the metric relationship between the unit cells. For the form I cell, the b direction points into the page. For the PZ cell, the b direction points out of the page.

the same single-crystal data set may be reduced on the basis of two different unit cells, and both can be solved to obtain crystal structures that are ostensibly different yet chemically reasonable. However, while one of the structures (form I) refines satisfactorily, the other structure (form II) resists complete refinement. It is obvious that the first structure is correct. Is the second structure incorrect?

It is instructive to consider how and why this situation could have arisen. Since our refinement has an R -factor of 0.033, we clearly examined a crystal of form I. It is not evident at the present time and with the data given by PZ in their paper^[1] whether 1) they examined a crystal of form II and could not proceed with the refinement beyond a reasonable point because of reasons not yet known or 2) they examined a crystal of form I, from the data of which the form II structure emerged, as we have shown is possible. In any case, it is difficult for us now to be sure of the indexing procedure employed by PZ and to understand how they obtained their particular unit cell. Incorrect unit cells usually get eliminated either because they do not lead to a sensible space group, the structure does not solve, or if it does solve, the refinement leads to absurd molecular and/or intermolecular geometries. None of these situations occurred for the PZ crystal.

Inspection of Figure 1 shows that the consequences of proceeding with the PZ unit cell on a form crystal are subtle.^[10] The principal distinction between the form I and form II structures is the positioning of the symmetry elements with respect to the molecules. In each unit cell, two distinct sets of inversion centers can be envisaged, one set lying in the (100) planes, and one set lying in the (200) planes (Figure 2). If the origin is chosen in both structures so that the carboxylic acid dimers are formed about the (200) inversion centers, the (100) inversion centers in the form I structure are consistent with C–H...O dimers. For the form II structure, however, the unit cell is skewed along the [001] direction, shifting the (100) inversion centers with respect to the molecules. Now, 2_1 screw axes that lie half-way between the inversion centers in space group $P2_1/c$ generate C–H...O catemers in the b direction. Ordinarily, such a situation would produce physically unreasonable intermolecular contacts. In this case, however, the

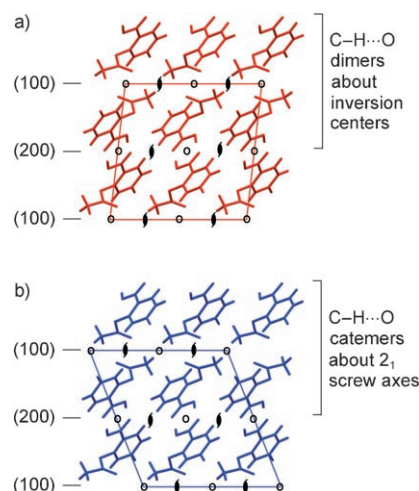


Figure 2. Positions of the symmetry elements in the form I (a, red) and form II (b, blue) crystal structures of aspirin. In both cases, centrosymmetric O–H...O dimers are formed about inversion centers in the (200) plane of the unit cell. In form I (a), centrosymmetric C–H...O dimers are formed about inversion centers in the (100) planes. In form II (b), the symmetry elements in the (100) planes are translated by $\frac{1}{4}c$, such that C–H...O catemers are formed about 2_1 screw axes running along b .

metric features have conspired to ensure that the new positions for the symmetry elements are suitable to generate seemingly normal catemers. In summary, we have here an apparently bizarre occurrence,^[11] wherein an “incorrect” crystal structure does not suffer from unacceptable intermolecular contacts. Indeed, PZ have described the packing of form II in terms of perfectly acceptable current paradigms of weak hydrogen bonding,^[12] and the lattice energies of the two forms, one certainly real and the other not identified satisfactorily, are within 0.45 kJ mol^{-1} of each other; according to Dreiding force field calculations form II is the more stable form.

Numerous sources of potential error exist in crystal structure determinations. These can arise, for example, from poor crystallinity, solvent loss, presence of impurities, disorder, and subtle twinning. Our principal point is that there can be no substitute for a fully acceptable and properly rigorous X-ray structural analysis accompanied by a correct modeling of the structure in difficult and ambiguous cases. This is painfully true in the present situation where so much store is set by the discovery of a new polymorph of an API. The present example sounds a cautionary note, and we wish to make the plea that structural chemists apply proper evaluation to the crystallographic results that are obtained with increasingly automated methods.^[13] Too often, the crystallographic analyses that underpin structural studies are taken lightly and deemed to be a more or less routine exercise. At the present time, what is sure is that data collected on an authentic sample of form I of aspirin can be treated to produce the form II structure reported by PZ to their level of accuracy and precision. Since the main experimental evidence that they provided for the existence of form II of aspirin was their single-crystal X-ray structure determination, all of their claims must be re-evaluated with appropriate and additional

experimental evidence before one is able to conclude that a new polymorph of aspirin has indeed been discovered. In the end, it is not clear if their form II structure is an artifact of improper handling of data or a poor crystallographic result on a suboptimal crystal. Nothing in their paper^[1] helps one to select between these possibilities.

We are aware of two possible caveats in the argument in this paper: 1) We have chosen to measure and analyze data collected from a commercial sample rather than from one crystallized in the presence of levetiracetam or acetamide and acetonitrile, that is, under the conditions chosen by PZ. Whether this is an important issue can only be revealed by experimentation. 2) Our calculations do not simulate entirely the data interpretation of PZ in that our simulation is based on 437 reflections, all with l even, none with l odd. PZ used 748 reflections, with the same maximal 2θ value of 40° ; among their 648 reflections with $l > 2\sigma(I)$, there must be some with l odd.^[10] We are currently investigating both these issues.

In conclusion, we wish to state that at the present time, and with the information given by PZ in their paper,^[1] it is not possible to determine if there is a second form of aspirin in the samples obtained by PZ, or whether levetiracetam or acetamide would be needed to produce any such form. We would not like to express any opinion as to whether cocrystallization of a compound with another compound is likely to increase the chances of obtaining polymorphs. These are matters that need to be resolved with further experimentation and/or modeling. We are currently examining these issues with the aim of obtaining a larger and more complete “structural landscape” of the aspirin system.

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- [7] Crystal data on form I of aspirin: $C_9H_8O_4$, $M_r = 180.15$, monoclinic, space group $P2_1/c$, $a = 11.2776(2)$, $b = 6.5517(1)$, $c = 11.2741(2)$ Å, $\beta = 95.837(1)^\circ$, $V = 828.70(2)$ Å³, $T = 123(2)$ K, μ -($Mo_{K\alpha}$) = 0.115 mm^{-1} , 24 706 reflections measured, 2043 unique reflections ($R_{int} = 0.0255$), 1756 observed reflections, $R1$ - $[I > 2\sigma(I)] = 0.0330$, $wR2(\text{all data}) = 0.0925$, $S = 1.08$. CCDC 610952 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [8] Full details of our experimental procedures are available in the Supporting Information. To put aside any question of experimental issues, crystal quality, etc. we note that the PZ result can be obtained purely by manipulation of data simulated from the form I structure. If the simulated single-crystal data set is subjected to the transformation $[1\ 0\ \frac{1}{2}\ 0\ -1\ 0\ 0\ 0\ -1]$, the form II structure can be refined against the transformed data to emulate the PZ result.
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- [10] Comprehensive details of the relationship between the structures are available in the Supporting Information. The appearance of the form II structure from the form I data set is not a case of a false solution from direct methods. It is the wrong choice of unit cell (and indeed the wrong crystal lattice) that results in a false arrangement of symmetry elements. We further add that since the transformation $[1\ 0\ \frac{1}{2}\ 0\ -1\ 0\ 0\ 0\ -1]$ is not a genuine crystallographic one, the resulting form II unit cell does not account for all reflections in the form I diffraction pattern. Specifically, all reflections hkl with odd l are omitted and therefore the simulated transformed data set is only 50% complete. For the experimental data, all reflections with odd l appear unobserved. Remarkably, even this does not prohibit stable (isotropic) refinement of the form II structure: standard F^2 refinement against all data produces a model with reasonable geometry and U_{iso} values. Of course, the R -factors are high. Acceptable R -factors can be obtained by application of a $2\sigma(I)$ cut-off. The fact that PZ did not report this issue suggests that some of their odd l reflections were non-zero at the $2\sigma(I)$ level.
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- [13] The problems in the PZ structure are manifested in the high R -factors, the erratic U_{iso} values, and the (supposed) necessity for an unacceptable 2θ cutoff. All these indicators are flagged as suspicious within an automated checking system such as checkCIF/PLATON.