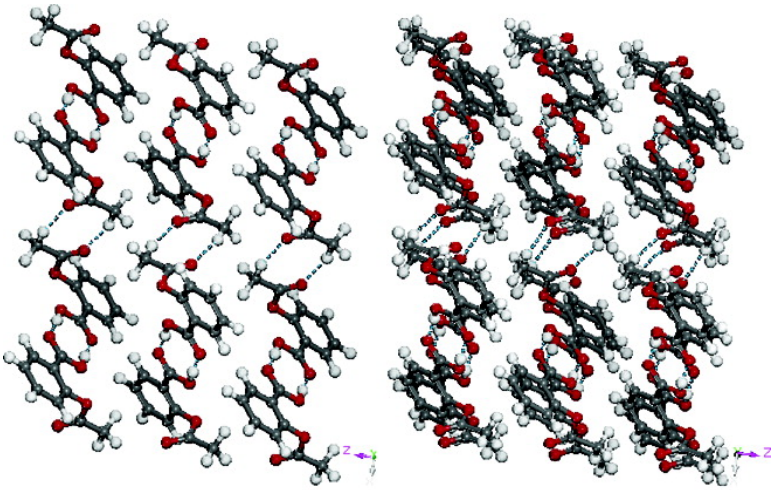
Communication

The Predictably Elusive Form II of Aspirin

Peddy Vishweshwar, Jennifer A. McMahon, Mark Oliveira, Matthew L. Peterson, and Michael J. Zaworotko

J. Am. Chem. Soc., **2005**, 127 (48), 16802-16803• DOI: 10.1021/ja056455b • Publication Date (Web): 09 November 2005



Form I Form II

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 46 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/09/2005

The Predictably Elusive Form II of Aspirin

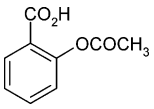
Peddy Vishweshwar,[†] Jennifer A. McMahon,[†] Mark Oliveira,[‡] Matthew L. Peterson,[‡] and Michael J. Zaworotko*,[†]

Department of Chemistry, University of South Florida, CHE205, 4202 East Fowler Avenue, Tampa, Florida 33620, and TransForm Pharmaceuticals, Inc., 29 Hartwell Avenue, Lexington, Massachusetts 02421

Received September 20, 2005; E-mail: xtal@usf.edu

Polymorphism, the existence of more than one crystalline form of a compound, is an intensely studied phenomenon, yet it remains poorly understood and controlled.[1] Polymorphism in active pharmaceutical ingredients, API's, is critical from both regulatory and intellectual property perspectives[1a] since polymorphs can exhibit different physical and/or chemical properties. However, the very nature of API's, which typically exhibit exterior hydrogen bonding sites and/or conformational flexibility, makes them ideal candidates for polymorphism control using additives or templates.[2] Furthermore, whereas API's have traditionally been limited to polymorphs, solvates, and salts,[3] in recent years, an alternative form, pharmaceutical co-crystals, has been targeted.[4] In this context, aspirin is somewhat of an enigma. Aspirin was first synthesized in 1853[5] and had by the turn of the 19th century become the world's best-selling drug.[6] In the 1960s and 1970s, aspirin was subjected to a series of studies[7] to determine whether it exhibits polymorphism, and there were indications that there could be a metastable form.[7d] However, these studies were inconclusive. In the end, differences in physical properties were attributed to salicylic acid impurities.[8] Most recently, computational studies have addressed polymorphism in aspirin.[9]

In this contribution, we report the results of a series of studies concerning pharmaceutical co-crystals of aspirin, resulting in isolation and structural characterization of the elusive form II of aspirin as well as a pharmaceutical co-crystal involving aspirin and another API, carbamazepine.



Aspirin

The crystal structure of aspirin form I has been studied by both X-ray[10] and neutron diffraction.[11] Herein we shall use as a reference point Wilson's 100 K structure[11] (CSD refcode: ACSALA02) to compare with form II since our data were also collected at 100 K. Form I consists of centrosymmetric carboxylic acid dimer moieties (O···O: 2.635 Å, 177.7°) that are, in turn, linked via centrosymmetric methyl C−H···O (C···O: 3.553 Å, 164.0°)[12] contacts of acetyl groups, thereby forming 1D chains (Figure 1a).

Aspirin form II was repeatedly obtained during attempted 1:1 co-crystallization of aspirin and levetiracetam from hot acetonitrile and was subsequently also observed in the presence of a molar equivalent of acetamide. Small plate-like crystals form in approximately 3 days, and one was mounted on a diffractometer directly from the viscous mother liquor to avoid conversion into form I. In addition to single crystal structure determination, form II was also characterized by melting point, IR, DSC, and HPLC

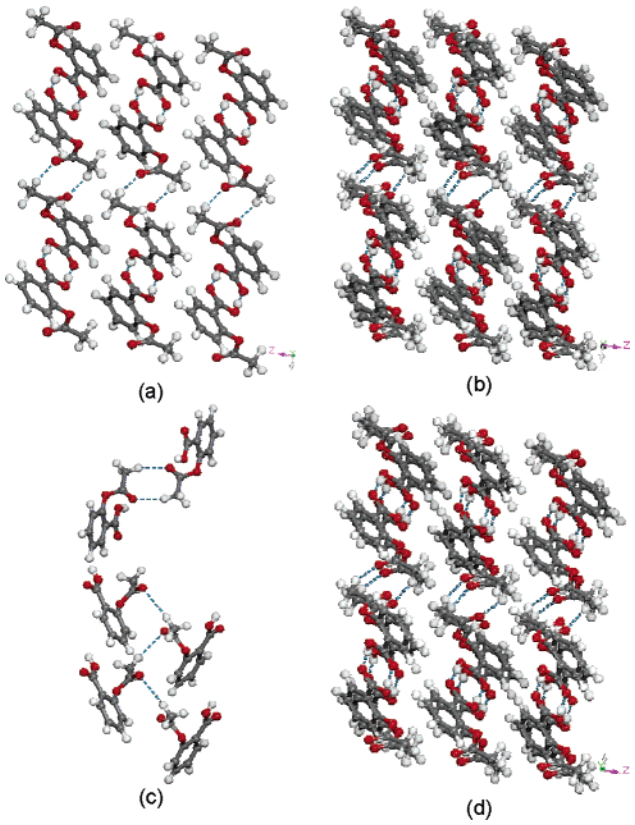


Figure 1. Crystal packing of aspirin forms I, II, and S. L. Price predicted form II. (a) Form I: 1D chains sustained by alternating carboxylic acid and acetyl group centrosymmetric dimers. (b) Form II: acid dimers are connected via catemeric methyl C−H···O and phenyl C−H···O (not shown) hydrogen bonds. (c) Acetyl group C−H···O dimers in form I and catemers in form II. (d) S. L. Price predicted form II. Note the similarity with the crystal packing of form II (b).

(see Supporting Information). Crystals of form II convert to form I under ambient conditions; however, they are relatively stable at 100 K. DSC thermograms reveal an endothermic peak at 135.5 °C for form II versus a melting transition at 143.9 °C for form I. The chemical composition of bulk samples of form II aspirin was determined by HPLC to be consistent with those of form I, salicylic acid content of 0.5−3.0% in form I versus 1.7% in a form II sample.

There are clear differences between the unit cell parameters: form I ($P2_1/c$): $a = 11.233(3)$ Å, $b = 6.544(1)$ Å, $c = 11.231(3)$ Å, $\beta = 95.89(2)°$, $V = 821.218$ Å^3; form II ($P2_1/c$):[13] $a = 12.095(7)$ Å, $b = 6.491(4)$ Å, $c = 11.323(6)$ Å, $\beta = 111.509(9)°$, $V = 827.1(8)$ Å^3. 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 [O···O: 2.632(14) Å, 173.1°].

[†] University of South Florida.
[‡] TransForm Pharmaceuticals, Inc.

10.1021/ja056455b CCC: $30.25

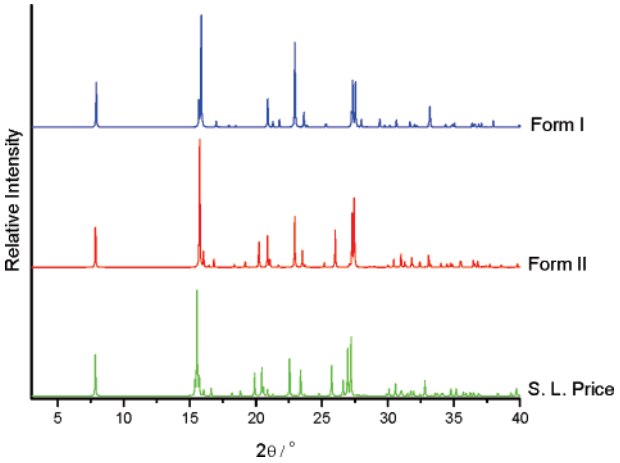


Figure 2. Simulated powder X-ray diffraction (PXRD) patterns of aspirin form I, II, and S. L. Price predicted form II crystal structures. See the noticeable additional peaks in form II and S. L. Price predicted form II compared to form I near 2θ: 20 and 26°.

However, the crystal packing of adjacent dimers is different; methyl groups form catemeric C−H···O [C···O: 3.85(2) Å, 164.0°] hydrogen bonds with the carbonyl oxygen (graph set C(4)) of the acetyl group versus centrosymmetric dimers (graph set $R^2_2(8)$) in form I (Figure 1). The existence of competing catemer/dimer motifs is well documented in polymorphs of carboxylic acids and primary amides.[1a,4,14] Simulated powder X-ray diffraction patterns also exhibit significant differences (Figure 2). It is interesting to note that a computational study concerning polymorphism in aspirin predicted a low energy polymorph with a low shear elastic constant, implying a low barrier to transformation. This calculated structure is consistent with that of form II.[9a]

The discovery of a new form of aspirin through attempted co-crystallization of amides and acids is perhaps unexpected when one considers that acids and amides are known to form reliable supramolecular heterosynthons.[15] Indeed, attempted co-crystallization of carbamazepine and aspirin resulted in the expected[4b] 1:1 co-crystal, the structure of which is illustrated in Supporting Information (Figure S3). This crystal structure[16] reveals that aspirin molecules form acid−amide supramolecular heterosynthons to carbamazepine molecules through O−H···O [O···O: 2.564(2) Å, 167.5°] and N−H_s···O [N···O: 2.914(3) Å, 168.4°] hydrogen bonds.

The salient feature of this study is not just the identification of aspirin form II, it is also the manner in which it was prepared. That crystallization of aspirin form II can occur in the presence of certain amides, whereas a co-crystal with carbamazepine can also occur and might appear to be counterintuitive. However, these observations are consistent with studies that have demonstrated how tailor-made additives can disrupt nucleation and induce polymorphism.[2] Supramolecular heterosynthons, therefore, seem to have implications for control of polymorphism.

To summarize, we have obtained and characterized a new polymorph and a new co-crystal of aspirin. In our opinion, the most salient features of the results reported herein are the method by which the once elusive form II of aspirin was isolated and the fact that it had been hitherto predicted.

Supporting Information Available: X-ray crystallographic information in CIF format, IR, DSC, HPLC, aspirin and carbamazepine 1:1 co-crystal packing diagram, torsional angle, and hydrogen bond tables. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon: Oxford, 2002. (b) Davey, R. J. *Chem. Commun.* **2003**, 1463. (c) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193.

(2) (a) Kuhnert-Brandstätter, M.; Aepkers, M. *Mikroskopie* **1961**, *16*, 189. (b) Davey, R. J.; Blagden, N.; Potts, G. D.; Docherty, R. *J. Am. Chem. Soc.* **1997**, *119*, 1767. (c) He, X.; Stowell, J. G.; Morris, K. R.; Pfeiffer, R. R.; Li, H.; Stahly, G. P.; Byrn, S. R. *Cryst. Growth Des.* **2001**, *1*, 305. (d) Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Cryst. Growth Des.* **2003**, *3*, 125. (e) Rubin-Preminger, J. M.; Bernstein, J. *Cryst. Growth Des.* **2005**, *5*, 1343.

(3) Haleblian, J. K. *J. Pharm. Sci.* **1975**, *64*, 1269.

(4) (a) Almarsson, Ö.; Zaworotko, M. J. *Chem. Commun.* **2004**, 1889. (b) Fleischman, S. G.; Kuduva, S. S.; McMahon, J. A.; Moulton, B.; Walsh, R. D. B.; Rodriguez-Hornedo, N.; Zaworotko, M. J. *Cryst. Growth Des.* **2003**, *3*, 909. (c) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, G. P. *J. Am. Chem. Soc.* **2004**, *126*, 13335. (d) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2005**, *5*, 1013.

(5) LaFont, O. *Rev. d'histoire de la pharmacie* **1996**, *43*, 269.

(6) (a) *Aspirin and Other Salicylates*; Vane, J. R., Bottling, R. M., Eds.; Chapman and Hall: London, 1992. (b) Moore, N.; Van Ganse, E.; Le Parc, J. M.; Wall, R.; Schneid, H.; Farhan, M.; Verrière, F.; Pelen, F. The PAIN Study: Paracetamol, Aspirin and Ibuprofen. *Clin. Drug Invest.* **1999**, *18*, 89. (c) Mehta, A. *Chem. Eng. News* **2005**, June, 46−47. (d) More information on aspirin can be found in Bayer's aspirin web site at URL http://www.aspirin.de.

(7) (a) Mitchell, A. G.; Saville, D. J. *J. Pharm. Pharmacol.* **1967**, *19*, 729. (b) Tawashi, R. *Science* **1968**, *160*, 76. (c) Tawashi, R. *J. Pharm. Pharmacol. Lett.* **1969**, *21*, 701. (d) Mitchell, A. G.; Saville, D. J. *J. Pharmacol.* **1969**, *21*, 28. (e) de Bisschop, M. *J. Pharm. Belg.* **1970**, *25*, 330. (f) Summers, M. P.; Carless, J. E.; Enever, R. P. *J. Pharm. Pharmacol. Lett.* **1970**, *22*, 615. (g) Kildsig, D. O.; Denbo, R.; Peck, G. E. *J. Pharm. Pharmacol.* **1971**, *23*, 374. (h) Bauer, K.; Voege, H. *Pharm. Ind.* **1972**, *34*, 960. (i) Summers, M. P.; Enever, R. P.; Carless, J. E. In *Particle Growth in Suspensions*; Smith, A. L., Ed.; Academic Press: London, 1973. (j) Bettinetti, G. P.; Giordano, F.; Giuseppetti, G. *Farmaco, Ed. Pratica* **1975**, *30*, 244. (k) Agafonov, V. N.; Leonidov, N. B. *Khimiko-Farmat. Zhurnal* **1978**, *12*, 127. (l) Jerslev, B.; Lund, U. *R. Dan. Sch. Pharm.* **1981**, *9*, 61. (m) Chang, C. J.; Diaz, L. E.; Morin, F.; Grant, D. M. *R. Dan. Sch. Pharm.* **1986**, *24*, 768.

(8) (a) Pfeiffer, R. R. *J. Pharm. Pharmacol. Lett.* **1971**, *23*, 75. (b) Mitchell, A. G.; Milaire, B. L.; Saville, D. J.; Griffiths, R. V. *J. Pharm. Pharmacol* **1971**, *23*, 534. (c) Mulley, B. A.; Rye, R. M.; Shaw, P. *J. Pharm. Pharmacol.* **1971**, *23*, 902. (d) Schwartzman, G. *J. Pharm. Pharmacol. Lett.* **1972**, *24*, 169.

(9) (a) Ouvrard, C.; Price, S. L. *Cryst. Growth Des.* **2004**, *4*, 1119. (b) Glaser, R. *J. Org. Chem.* **2001**, *66*, 771. (c) Payne, R. S.; Rowe, R. C.; Roberts, R. J.; Charlton, M. H.; Docherty, R. *J. Comput. Chem.* **1999**, *20*, 262.

(10) (a) Wheatley, P. J. *J. Chem. Soc.* **1964**, 6036. (b) Kim, Y.; Machida, K.; Taga, T.; Osaki, K. *Chem. Pharm. Bull.* **1985**, *33*, 2641.

(11) Wilson, C. C. *New J. Chem.* **2002**, *26*, 1733.

(12) Desiraju G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999.

(13) Crystal data of form II: chemical formula $C_9H_8O_4$, formula weight 180.15, monoclinic, space group $P2_1/c$, a = 12.095(7) Å, b = 6.491(4) Å, c = 11.323(6) Å, β = 111.509(9)°, V = 827.1(8) Å^3, Z = 4, ρ_{calc} = 1.447 Mg m^{-3}, T = 100 K, μ = 0.115 mm^{-1}, 1780 reflections measured, 748 unique reflections, 648 observed reflections [$I > 2\sigma(I)$], $R1_{obs}$ = 0.162, $wR2_{obs}$ = 0.308. Crystal size: 0.25 × 0.15 × 0.005 mm. All atoms were refined isotropically because of the relatively weak data.

(14) (a) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629. (b) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311. (c) Frankenbach, G. M.; Etter, M. C. *Chem. Mater.* **1992**, *4*, 272.

(15) Leiserowitz, L.; Nader, F. *Acta Crystallogr.* **1977**, *B33*, 2719.

(16) Single crystals of the 1:1 co-crystal of aspirin and carbamazepine were obtained by dissolving equimolar amounts of aspirin and carbamazepine in ethyl acetate and standing for 3 days. Crystal data: chemical formula $C_{24}H_{20}N_2O_5$, formula weight 416.42, triclinic, space group $P\bar{1}$, a = 9.0317(18) Å, b = 11.364(2) Å, c = 11.424(2) Å, α = 60.350(4)°, β = 85.599(4)°, γ = 84.724(4)°, V = 1014.0(3) Å^3, Z = 2, ρ_{calc} = 1.364 Mg m^{-3}, T = 100 K, μ = 0.097 mm^{-1}, 5971 reflections measured, 4052 unique reflections, 2931 observed reflections [$I > 2\sigma(I)$], $R1_{obs}$ = 0.057, $wR2_{obs}$ = 0.119. The co-crystal can also be obtained by solvent-drop grinding of equimolar amounts of aspirin and carbamazepine (20 μL of ethyl acetate per 100 mg of solid, 2−4 min of grinding).

JA056455B