Headache because of Aspirin!

Roland Boese
Headache because of Aspirin!
What is so special about Aspirin so that it seems to be monomorphemic in spite of millions of crystallization batches until today?

About 80% of all APIs exhibit polymorphism!
What is a Polymorph?

“A solid crystalline phase of given compound resulting from the possibility of at least two crystalline arrangements of that compound in the solid state”

What is a Polymorph?

A Cartoon:

Cell dimensions can be taken to characterize the form (amongst others)

For patent claims they are generally not suited because other settings may be selected!
Possible polymorphs of Aspirin

Specific Surface Energies and Dissolution Behavior

„Polymorphism in aspirin has been announced and then discarded in favor of morphology differences between crystals of the same phase.“

„Aspirin is only found experimentally in one crystal structure“

Predicted Form II of Aspirin is energetically very close to Form I.
Toward Crystal Structure Prediction for Conformationally Flexible Molecules: The Headaches Illustrated by Aspirin

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Table 3. Low Energy Crystal Structures Found in the Search with Ab Initio Optimized Molecular Structuresa

<table>
<thead>
<tr>
<th>structure</th>
<th>space group</th>
<th>$U_{latt}$ (kJ mol$^{-1}$)</th>
<th>$E_{tot}$ (kJ mol$^{-1}$)</th>
<th>density (g cm$^{-3}$)</th>
<th>$a$ (Å)</th>
<th>$b$ (Å)</th>
<th>$c$ (Å)</th>
<th>$\alpha$ (°)</th>
<th>$\beta$ (°)</th>
<th>$\gamma$ (°)</th>
<th>lowest Cij (GPa)</th>
<th>hydrogen bonds d(O···O) (Å) and (O···HO) (°)</th>
<th>motif</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>AK22</td>
<td>$P_{21}/c$</td>
<td>$-106.3$</td>
<td>$-102.9$</td>
<td>1.381</td>
<td>12.124</td>
<td>6.696</td>
<td>11.475</td>
<td>90.0</td>
<td>68.4</td>
<td>90.0</td>
<td>0.15</td>
<td>2.852 (170)</td>
</tr>
<tr>
<td>1a</td>
<td>AM6</td>
<td>$P_{21}/c$</td>
<td>$-102.7$</td>
<td>$-102.7$</td>
<td>1.428</td>
<td>9.800</td>
<td>9.152</td>
<td>9.434</td>
<td>90.0</td>
<td>82.0</td>
<td>90.0</td>
<td>4.72</td>
<td>2.886 (153)</td>
</tr>
<tr>
<td>2a</td>
<td>AI11</td>
<td>$P_{21}/c$</td>
<td>$-106.1$</td>
<td>$-102.7$</td>
<td>1.377</td>
<td>11.388</td>
<td>6.758</td>
<td>11.350</td>
<td>90.0</td>
<td>95.9</td>
<td>90.0</td>
<td>4.52</td>
<td>2.857 (169)</td>
</tr>
<tr>
<td>1a</td>
<td>FC2</td>
<td>$P_{21}/c$</td>
<td>$-100.8$</td>
<td>$-100.8$</td>
<td>1.405</td>
<td>9.828</td>
<td>6.993</td>
<td>13.375</td>
<td>90.0</td>
<td>67.9</td>
<td>90.0</td>
<td>5.40</td>
<td>2.679 (155)</td>
</tr>
<tr>
<td>1a</td>
<td>AK15</td>
<td>$P_{21}/c$</td>
<td>$-100.7$</td>
<td>$-100.7$</td>
<td>1.329</td>
<td>7.169</td>
<td>7.172</td>
<td>17.538</td>
<td>90.0</td>
<td>93.2</td>
<td>90.0</td>
<td>2.25</td>
<td>2.837 (170)</td>
</tr>
<tr>
<td>2a</td>
<td>DC46</td>
<td>$C_{2}/c$</td>
<td>$-104.0$</td>
<td>$-100.5$</td>
<td>1.418</td>
<td>17.649</td>
<td>8.953</td>
<td>15.199</td>
<td>90.0</td>
<td>44.7</td>
<td>90.0</td>
<td>2.55</td>
<td>2.877 (132)</td>
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<tr>
<td>1a</td>
<td>AB25</td>
<td>$P_{1}$</td>
<td>$-100.3$</td>
<td>$-100.3$</td>
<td>1.349</td>
<td>6.094</td>
<td>6.982</td>
<td>10.850</td>
<td>79.6</td>
<td>78.6</td>
<td>83.3</td>
<td>1.86</td>
<td>2.817 (172)</td>
</tr>
<tr>
<td>1a</td>
<td>AK7</td>
<td>$P_{21}/c$</td>
<td>$-100.1$</td>
<td>$-100.1$</td>
<td>1.350</td>
<td>11.052</td>
<td>6.829</td>
<td>11.835</td>
<td>90.0</td>
<td>84.1</td>
<td>90.0</td>
<td>3.02</td>
<td>2.848 (167)</td>
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</tbody>
</table>

a The structure in bold (2a AI11) corresponds to the experimental crystal structure (ExpMinOpt, Table 2), and the structure in italics seems unlikely to be an observable polymorph as it has a very small shear elastic constant. b The crystal structure is denoted by the molecular conformer and one of the MOLPAK-generated starting structures that resulted in this minimum. c The sum of the lattice energy and the B3LYP/6-31G(d,p) relative conformational energy from Table 1. d The smallest eigenvalue of the shear submatrix of the elastic constant tensor.
MZ: $a = 12.1$, $b = 6.5$, $c = 11.32$, $\beta = 111.5^\circ$
Possible polymorphs of Aspirin


Form I:
- $a = 11.233$ Å
- $b = 6.544$ Å
- $c = 11.231$ Å
- $\beta = 95.89^\circ$
- $V = 821.22$ Å$^3$

Form II:
- $a = 12.124$ Å
- $b = 6.686$ Å
- $c = 11.475$ Å
- $\beta = 68.4^\circ$
The Predictably Elusive Form II of Aspirin

P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson, M. J. Zaworotko


Form I:
- \(a = 11.233 \, \text{Å}\)
- \(b = 6.544 \, \text{Å}\)
- \(c = 11.231 \, \text{Å}\)
- \(\beta = 95.89^\circ\)
- \(V = 821.22 \, \text{Å}^3\)

Form II:
- \(a = 12.095 \, \text{Å}\)
- \(b = 6.491 \, \text{Å}\)
- \(c = 11.323 \, \text{Å}\)
- \(\beta = 111.509^\circ\)
- \(V = 827.1 \, \text{Å}^3\)

R1=16.22%, 2theta(max)=40°, T=100K,
a=12.095, b=6.591, c=11.323, \( \beta =115.323, P2_1/c \)

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U iso</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.3768(8)</td>
<td>0.1410(16)</td>
<td>0.8883(9)</td>
<td>0.006(3)</td>
</tr>
<tr>
<td>O2</td>
<td>0.4895(8)</td>
<td>0.1874(16)</td>
<td>1.0905(9)</td>
<td>0.005(3)</td>
</tr>
<tr>
<td>O3</td>
<td>0.2102(8)</td>
<td>0.4195(15)</td>
<td>0.7699(8)</td>
<td>0.000(3)</td>
</tr>
<tr>
<td>O4</td>
<td>0.0931(8)</td>
<td>0.2184(15)</td>
<td>0.8366(9)</td>
<td>0.002(3)</td>
</tr>
<tr>
<td>C1</td>
<td>0.3474(13)</td>
<td>0.445(3)</td>
<td>0.9920(14)</td>
<td>0.009(4)</td>
</tr>
<tr>
<td>C2</td>
<td>0.2510(13)</td>
<td>0.521(2)</td>
<td>0.8878(13)</td>
<td>0.003(4)</td>
</tr>
<tr>
<td>C3</td>
<td>0.1997(14)</td>
<td>0.705(3)</td>
<td>0.8916(15)</td>
<td>0.013(4)</td>
</tr>
<tr>
<td>C4</td>
<td>0.2369(13)</td>
<td>0.810(3)</td>
<td>1.0089(14)</td>
<td>0.013(4)</td>
</tr>
<tr>
<td>C5</td>
<td>0.3295(12)</td>
<td>0.745(2)</td>
<td>1.1119(13)</td>
<td>0.003(4)</td>
</tr>
<tr>
<td>C6</td>
<td>0.3826(13)</td>
<td>0.559(2)</td>
<td>1.1056(14)</td>
<td>0.008(4)</td>
</tr>
<tr>
<td>C7</td>
<td>0.4100(12)</td>
<td>0.244(2)</td>
<td>0.9939(13)</td>
<td>0.002(4)</td>
</tr>
<tr>
<td>C8</td>
<td>0.1306(12)</td>
<td>0.258(2)</td>
<td>0.7574(13)</td>
<td>0.002(4)</td>
</tr>
<tr>
<td>C9</td>
<td>0.1018(14)</td>
<td>0.164(3)</td>
<td>0.6273(14)</td>
<td>0.014(4)</td>
</tr>
</tbody>
</table>
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 $2\theta$: 20 and 26°.
Possible polymorphs of Aspirin

X-Ray crystal structure of 'Form II'

A.D. Bond, R. Boese, G.R. Desiraju,

With a crystal of Form I (R=4%) the structure can be refined as Form II after re-indexing, achieving a similar R-value (14%) at 2-Theta = 40° and with U=0 for four non-H atoms,- anisotrop refinement resulted in non-positive values.
A Second Polymorph of Aspirin?

“Aspirin Form II was repeatedly obtained during attempted 1:1 co-crystallization of aspirin and Levitiracetam from hot acetonitrile and was subsequently also observed in the presence of a molar equivalent of acetamide”
On the Polymorphism of Aspirin: Crystalline Aspirin as Intergrowths of Two “Polymorphic” Domains**

The crucial experimental result was first obtained after we freshly synthesized aspirin from salicylic acid (see the Supporting Information) and prepared single crystals by rapidly cooling a solution in hot acetonitrile (Table 1). Single-

A.D. Bond, R. Boese, G.R. Desiraju,
Aspirin in the crystal lattice
Aspirin in the crystal lattice

Two different methyl groups!
Aspirin: the two "polymorphs" in \( P2_1/c \)

In Form I the dimers are linked by C-H⋯O interactions with an inversion center.

In the hypothetical "Form II" the dimers are linked by C-H⋯O interactions with a two-fold screw axis (catemers).

\( b\)-axis points out of plane

\[ \beta=95.4^\circ \]
\[ a=11.23 \, \text{Å} \]

\[ \beta=111.51^\circ \]
\[ a=12.09 \, \text{Å} \]
Aspirin: the two "polymorphs" in $P2_1/c$

The two cells can be transformed into each other by non-crystallographic transformation procedure.

The inversion centers are turned into 2-fold screw axes and vice versa.

Two cells may be taken to characterize the domain structure, that of Form I and of the hypothetical "Form II", both existing in one entity.

The ratio with different proportions can be refined from single crystal data.
The New Aspirin: a domain structure

Form I with unit cell, horizontal layers in one sequence AAA (red).

Form I with unit cell, middle layer shifted by half of the c-axis, resulting in a stacking sequence ABA (blue).

Blue lines indicate the unit cells Form II; three unit cells with an ABA sequence.

Sequences with an order ABAAAAABABABABAAAAAAAABABA etc. are possible; resulting in domains of different number and size.
Preparation and characterization of ‘Form AB‘

From freshly synthesized acetyl salicylic acid crystals of Form AB can be produced, which do not represent ‘mixed crystals’, are not disordered, are no twins and no solid solutions.

The new type of polymorph, identified as Form AB, consists of two intergrown forms, the known Form I and a hypothetical ‘Form II’.

Depending on the crystallization conditions, the composition of the domains are variable. The properties can be explained by the domain structure.

Crucial is the control on producing traces of Aspirin anhydride and transferring it with a suitable solvent into the crystallization process at the right time and right condition!
Intergrowths domain character in reconstructed reciprocal lattice sections:

Predominatly domains of Form I with low proportions of Form II: The clear reflections originate from large domains.

Predominatly domains of Form II with low proportions of Form I, the strikes (diffuse scattering) originate from small domains.
Optical diffraction of increasing voids/dislocations

Fourier transformation – diffuse scattering
The Domain Structure
The Domain Structure

- Inversion center
- 2-fold screw axes
The Domain Structure

Inversion center

2-fold screw axes
The Domain Structure

Inversion center

Dopant molecule
The Domain Structure

dopant molecule

Aspirin dimer

Aspirinanhydride

-H₂O
The Domain Structure

Form I

A new entity with specific properties

hypothesetical pure form II

domain structure

A new entity with specific properties
PXRDs

Form I
Derived from single crystal data

Form II
Derived from idealized single crystal data

Experimental, from different procedures
Solid State NMR

$^{13}$C-Methyl groups

Form AB (ca. 70% Form B)

Form I

Form AB (ca. 20% Form B)
"Actually, most doctors now insist on $\mathcal{P}_{4,1,2,1,2}$ aspirin"

courtesy A. Gavezzotti
Relative conductivity versus time

Dissolution after one minute

0.266 g/L

0.533 g/L

0.803 g/L

AS Form AB

AST(A)

rel. conduct. [μs/cm]

time (s)

1 min

Comparison of ASS AB with ASS Form I

Instrument Specifikation:
Varian Cary 300 Bio UV/Vis Spectrometer
Double beam instrument
Complete range of measurement: 190-900 nm (range used: 250-310; selected 276 nm)
Data were recorded from a solution at 37.5 °C in a 1 mm flow cell, pumped through the cell and filtered from a 150 mL vessel, continuously stirred.
Is a metastable form of Aspirin of any interest?

Is a quick release Aspirin of any interest?

YES!
Bayer Quick Release Crystals

This is probably due to a special formulation
Synopsis: Full three-dimensional diffuse scattering data have been recorded for both polymorphic forms [(I) and (II)] of aspirin and these data have been analysed using Monte Carlo computer modelling. The observed scattering in form (I) is well reproduced by a simple harmonic model of thermally induced displacements. The data for form (II) show, in addition to thermal diffuse scattering (TDS) similar to that in form (I), diffuse streaks originating from stacking fault-like defects as well as other effects that can be attributed to strain induced by these defects. Online 10 November 2010

[ doi:10.1107/S0108768110037055 ]
Abstract
Single crystals of aspirin form II can be obtained by crystallisation of aspirin in the presence of aspirin anhydride in organic solvents such as acetonitrile or tetrahydrofuran. The crystals are stable under ambient conditions for months and do not show any phase transition on application of isotropic pressure up to 2.2 GPa.
the end