Supporting Information

Indomethacin Polymorph $\delta$ Revealed To Be Two Plastically Bendable Crystal Forms by 3D Electron Diffraction: Correcting a 47-Year-Old Misunderstanding

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**References**
Experimental Procedures

Powder X-ray diffraction (PXRD)

PXRD patterns of IDM polymorphs were collected by a Rigaku D/MAX2200 diffractometer (Rigaku, Japan) with Cu Kα radiation (λ= 1.542 Å) at 40 kV and 26 mA. The samples were gently crushed and placed on a monocrystalline silicon sample holder. The scan was performed from 3 ° to 40 ° (2θ) at a rate of 2.5 °/min. The as-received IDM sample was used to obtain the PXRD pattern of γ-IDM. PXRD patterns of melt δ-IDM (θ-IDM), solution δ-IDM (δ-IDM) and α-IDM were obtained by using crystallographically pure samples. All experiments were triplicated.

Fourier Transform Raman Spectroscopy (FT-Raman)

The FT-Raman spectra were collected using a Nicolet NXR 9650 spectrometer (Thermo Scientific, USA) equipped with a Nd³⁺: YAG laser emitting at a wavelength of 1064 nm. The laser power was approximately 200 mW and the diameter of the laser spot was around 50 μm. The spectra were recorded from 100 to 3700 cm⁻¹ by 512 accumulated scans at a resolution of 8 cm⁻¹. All experiments were triplicated.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of IDM polymorphs were collected in attenuated total reflectance (ATR) mode using a Spectrum Two spectrometer (Perkin Elmer, Waltham, USA) with a PerkinElmer horizontal ATR accessory. The samples were scanned from 400 to 4000 cm⁻¹ at a resolution of 4 cm⁻¹.

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded using a Netzsch DSC 200-F3 (200 F3 Maia, Selb, Germany). The crystallographically pure samples of melt δ-IDM (θ-IDM) and solution δ-IDM (δ-IDM) (3-5 mg) were accurately weighed into alumina pans and heated at 10 °C/min under nitrogen purging conditions (40 ml/min). Data were analyzed using Proteus analysis software (NETZSCH, Version 5.2.1, Germany). All experiments were triplicated.

3D ED sample preparation and data collection

Single crystals were first separated from the supercooled melt and gently crushed between two glass slides. Cu TEM grids were then glow discharged for 40s using a PELCO easiGLOW with a current of 20 mA. The glow-discharged Cu TEM grid was gently placed over the crushed sample to pick up the broken fragments and then lightly tapped to remove any larger fragments, leaving only microcrystals on the grid. 3D ED (MicroED) data were collected on a JEOL JEM-2100 LaB6 TEM equipped with a fast Timepix hybrid pixel detector (512 x 512 pixels, Amsterdam Scientific Instruments) operating at 200 kV in selected area electron diffraction (SAED) mode. The software Instamatic[1] was used for electron diffraction data collection. Diffraction data were collected by continuously rotating the crystal at a rate of 1.13 ° s⁻¹. The exposure time was 0.3 s, meaning the individual diffraction images were integrated over 0.34° of reciprocal space. Several data sets from different crystals were acquired from starting angles between -60° to + 60°. The spot size and camera length were 3 and 25 cm, respectively.

3D ED data processing and structure solution

Rotation ED processing software (REDp)[2] was used to determine the unit cell and space group based on the symmetry and reflection conditions of the diffraction patterns (Figures S1 and S2). Data were processed using crystallography software (XDS).[3] Data sets were merged together based on their cross-correlation, in order to improve completeness and I/σ(I) and obtain a single data set suitable for structure solution and refinement (Tables S2, S3, S4 and S5). The structures were solved using the simulated annealing method as implemented in the program Sir2014.[4] The atom connectivity of γ-indomethacin (as reported in the CSD, reference code INDMET[5]) was used to create the rigid-body starting fragment in the form of a mol file. The general conditions can be found in Table S6. The structures with the lowest cost functions were refined by least-squares against the ED data using SHELXL[6] through the OLEX2 interface.[7] The unit cell parameters were refined against the PXRD data using the Pawley method[8] with the TOPAS-Academic v6 program package.[9]
### Table S1: Crystallographic information of IDM polymorphs.

[1-[(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid], C₁₉H₁₆ClNO₄, M = 357.8]

| Polymorph | Solved yr. | Solved method | Melt (9-IDM) | Solution (5-IDM) |
|-----------|------------|---------------|--------------|------------------|
| γ         | 1972[5]    | SCXRD         | 2021         | 2021             |
| α         | 2002[10]   | SCXRD         | ED           | ED               |

- **Solved temp.(K)**
  - 283-303
  - 203
  - Room temp.
  - Room temp.

- **Refcode**
  - INDMET
  - INDMET02
  - Not available
  - Not available

- **Deposition No.**
  - 1180373
  - 201766
  - 2119504
  - 2119505

- **Crystal system**
  - triclinic
  - monoclinic
  - monoclinic
  - monoclinic

- **Space group**
  - P̄1 (No. 2)
  - P2₁ (No. 4)
  - Cc (No. 9)
  - P2₁ (No. 4)

- **a (Å)**
  - 9.295 (2)
  - 5.462 (1)
  - 4.786 (1)
  - 18.301 (5)

- **b (Å)**
  - 10.969 (1)
  - 25.310 (9)
  - 56.999 (9)
  - 5.123 (1)

- **c (Å)**
  - 9.742 (1)
  - 18.152 (7)
  - 12.908 (2)
  - 18.564 (6)

- **α (°)**
  - 69.38 (1)
  - 90
  - 90
  - 90

- **β (°)**
  - 110.79 (1)
  - 94.38 (3)
  - 99.57 (1)
  - 95.80 (1)

- **γ (°)**
  - 92.78 (1)
  - 90
  - 90
  - 90

- **V (Å³)**
  - 865.773
  - 2510.879
  - 3472.189
  - 1731.577

- **Z**
  - 1
  - 3
  - 2
  - 2

- **Z**
  - 2
  - 6
  - 8
  - 4

- **Density (gcm⁻³)**
  - 1.37
  - 1.42
  - 1.37
  - 1.37

- **R-factor (%)**
  - 5.9
  - 5.4
  - 20.8
  - 19.0
Table S2: Melting point ($T_m$) and melting enthalpy ($\Delta H_m$) of melt $\delta$-IDM (θ-IDM) and solution $\delta$-IDM (δ-IDM) ($n=3$).

| Polymorph            | $T_m$, peak ($^\circ$C) | $T_m$, onset ($^\circ$C) | $\Delta H_m$ (KJ/mol) |
|----------------------|-------------------------|--------------------------|------------------------|
| Melt $\delta$-IDM (θ-IDM) | 134.2 ± 0.8             | 130.7 ± 1.0              | 26.5 ± 0.7             |
| Solution $\delta$-IDM (δ-IDM) | 133.6 ± 0.3             | 130.3 ± 0.3              | 30.8 ± 0.4             |
Table S3: Summary of the crystallographic information used for the structure solution of melt δ-IDM (θ-IDM).

| Dataset | $a$/Å | $b$/Å | $c$/Å | $\beta$/° | $V$/Å$^3$ |
|---------|-------|-------|-------|-----------|-----------|
| 1       | 5.045 | 57.046| 13.253| 97.169    | 3784.36   |
| 2       | 4.915 | 59.369| 13.344| 97.857    | 3857.21   |
| 3       | 5.054 | 58.921| 13.046| 98.779    | 3839.41   |
| 4       | 4.766 | 61.714| 12.630| 97.396    | 3683.94   |
| 5       | 4.878 | 56.232| 13.039| 100.559   | 3516.03   |
| 6       | 4.781 | 60.530| 12.826| 98.837    | 3667.71   |
| 7       | 4.890 | 58.838| 13.067| 99.796    | 3704.79   |
Table S4: Pair-wise cross-correlation of individual data sets of melt δ-IDM (θ-IDM).

| #i | Data sets | Number of common reflections | Correlation between i, j | Ratio of common intensities (i,j) | B-factor between i,j |
|----|-----------|-------------------------------|--------------------------|----------------------------------|---------------------|
| 1  | 2         | 131                           | 0.993                    | 0.9404                           | -0.2232             |
| 1  | 3         | 326                           | 0.925                    | 0.4011                           | -0.7305             |
| 2  | 3         | 127                           | 0.931                    | 0.4343                           | -0.3148             |
| 1  | 4         | 188                           | 0.864                    | 0.6855                           | -2.0166             |
| 2  | 4         | 123                           | 0.847                    | 0.4099                           | -0.0850             |
| 3  | 4         | 293                           | 0.743                    | 2.0251                           | -0.7831             |
| 1  | 5         | 238                           | 0.978                    | 0.9704                           | -0.1391             |
| 2  | 5         | 152                           | 0.706                    | 1.2862                           | 0.0013              |
| 3  | 5         | 328                           | 0.914                    | 3.3032                           | -0.7462             |
| 4  | 5         | 216                           | 0.876                    | 1.6765                           | -0.5048             |
| 1  | 6         | 288                           | 0.985                    | 0.1699                           | -0.6736             |
| 2  | 6         | 158                           | 0.967                    | 0.1833                           | -0.4610             |
| 3  | 6         | 258                           | 0.804                    | 0.5726                           | -0.3748             |
| 4  | 6         | 222                           | 0.829                    | 0.3534                           | 0.3104              |
| 5  | 6         | 228                           | 0.859                    | 0.1327                           | 0.2950              |
| 1  | 7         | 314                           | 0.941                    | 0.9007                           | -0.7310             |
| 2  | 7         | 148                           | 0.933                    | 0.8803                           | 0.0368              |
| 3  | 7         | 406                           | 0.940                    | 2.6863                           | -0.3363             |
| 4  | 7         | 345                           | 0.799                    | 1.6020                           | 0.8358              |
| 5  | 7         | 243                           | 0.961                    | 1.0743                           | 0.4301              |
| 6  | 7         | 302                           | 0.861                    | 4.9135                           | 0.3589              |
Table S5: Merging statistics of seven cRED datasets obtained from melt δ-IDM (θ-IDM).

| Resolution | Number of reflections | R-factor | |
|------------|----------------------|----------|------------------|
|            | Observed | Unique | Possible | Completeness | Observed | Expected | Compared | I/σ | R-meas | CC(1/2) |
| 3.70       | 207      | 29     | 43       | 67.4%        | 25.6%     | 25.3%     | 206      | 7.81 | 27.7%  | 93.2*    |
| 2.62       | 243      | 47     | 68       | 69.1%        | 27.0%     | 27.1%     | 239      | 6.24 | 29.4%  | 85.1*    |
| 2.14       | 538      | 75     | 98       | 76.5%        | 33.6%     | 31.0%     | 534      | 6.24 | 36.2%  | 95.7*    |
| 1.85       | 502      | 81     | 110      | 73.6%        | 31.5%     | 29.0%     | 497      | 6.21 | 34.2%  | 85.6*    |
| 1.66       | 469      | 81     | 109      | 74.3%        | 30.9%     | 29.6%     | 464      | 5.12 | 33.7%  | 93.1*    |
| 1.51       | 825      | 120    | 154      | 77.9%        | 35.4%     | 35.0%     | 818      | 4.73 | 38.5%  | 96.0*    |
| 1.40       | 851      | 119    | 156      | 76.3%        | 51.0%     | 49.1%     | 844      | 3.83 | 54.9%  | 82.4*    |
| 1.31       | 684      | 106    | 146      | 72.6%        | 54.3%     | 51.6%     | 682      | 3.34 | 59.1%  | 61.7*    |
| 1.23       | 692      | 114    | 160      | 71.2%        | 59.8%     | 53.7%     | 688      | 3.06 | 64.9%  | 79.0*    |
| 1.17       | 862      | 141    | 190      | 74.2%        | 61.7%     | 55.7%     | 852      | 2.86 | 67.2%  | 79.4*    |
| 1.12       | 803      | 152    | 199      | 76.4%        | 67.5%     | 63.3%     | 799      | 2.51 | 75.2%  | 60.0*    |
| 1.07       | 413      | 132    | 202      | 65.3%        | 75.4%     | 70.8%     | 380      | 1.85 | 87.2%  | 46.5*    |
| 1.03       | 200      | 86     | 193      | 44.6%        | 83.6%     | 84.9%     | 172      | 1.38 | 101.1% | 48.9*    |
| total      | 7289     | 1283   | 1828     | 70.2%        | 28.8%     | 28.0%     | 7175     | 3.73 | 31.2%  | 95.5*    |
Table S6: General conditions used for the simulated annealing calculations.

| General Conditions                          | Value                      |
|--------------------------------------------|----------------------------|
| Cost function                              | R structure factor         |
| Resolution (Å)                             | 2                          |
| Random seed                                | 1                          |
| Number of runs                             | 10                         |
| Starting temperature                       | 10 (automatic)             |
| Number of moves                            | 490 (automatic)            |
| Temperature reduction factor               | 0.9                        |
Table S7: Melt δ-IDM (θ-IDM) experimental crystallographic data and refinement data. The unit cell parameters were refined against PXRD data.

| Melt δ-IDM (θ-IDM) |  |
|--------------------|---|
| Crystal System     | Monoclinic |
| Space Group        | Cc (No. 9) |
| a, b, c (Å)        | 4.7859(9), 56.999(9), 12.908(2) |
| α, β, γ (°)        | 90, 99.57(1), 90 |
| Volume (Å³)        | 3472.189 |
| Z                  | 2 |
| Z                  | 8 |
| Density (gcm⁻³, calculated) | 1.37 |
| Crystal Width (μm) | 0.5 – 2 |

Data Collection

| No. of measured, and independent and observed reflections [Fo > 4σ(Fo)] | 7884, 2459, 1325 |
| Rint              | 0.2793 |
| Resolution (Å)    | 1.05 |
| Completeness (%)  | 74.5 |

Refinement

| R1 (calculated over all amplitudes for all reflections), wR2, S | 0.1914, 0.4694, 1.388 |
| No. of Reflections | 2459 |
| No. of parameters  | 207 |
| No. of restraints  | 137 |
| H-atom treatment   | HFIX |
Table S8: Summary of the crystallographic information used for the structure solution of solution δ-IDM (δ-IDM).

| Dataset | \(a\)/Å  | \(b\)/Å  | \(c\)/Å  | \(β\)/° | \(V\)/Å³  |
|---------|----------|----------|----------|---------|-----------|
| 14      | 18.33    | 5.23     | 18.67    | 95.717  | 1780.91   |
| 18      | 18.20    | 5.25     | 18.73    | 96.645  | 1777.63   |
| 21      | 18.76    | 5.19     | 18.46    | 96.320  | 1786.42   |
| 34      | 18.59    | 5.18     | 20.14    | 96.529  | 1926.83   |
| 35      | 18.90    | 5.16     | 19.34    | 93.779  | 1882.01   |
Table S9: Solution δ-IDM (δ-IDM) experimental crystallographic data and refinement data. The unit cell parameters were refined against PXRD data.

| Solution δ-IDM (δ-IDM) |  |
|-----------------------|--|
| **Crystal System**     | Monoclinic |
| **Space Group**        | P2₁ (No. 4) |
| **a, b, c (Å)**        | 18.301(5), 5.123(1), 18.564(6) |
| **α, β, γ (°)**        | 90, 95.80(1), 90 |
| **Volume (Å³)**        | 1731.577 |
| **Z**                  | 2 |
| **Z**                  | 4 |
| **Density (g cm⁻³, calculated)** | 1.37 |
| **Crystal Width (μm)** | 0.5 – 2.5 |

**Data Collection**

| No. of measured, and independent and observed reflections [Fo > 4σ(Fo)] | 3502, 1914, 1064 |
| Rint | 0.2117 |
| Resolution (Å) | 1.15 |
| Completeness (%) | 75.0 |

**Refinement**

| R1 (calculated over all amplitudes for all reflections), wR2, S | 0.1724, 0.4367, 1.229 |
| No. of Reflections | 1914 |
| No. of parameters | 392 |
| No. of restraints | 361 |
| H-atom treatment | HFIX |
Table S10: Table of torsion angle \( \theta(C4-C7-N1'-C16) \) (*) of IDM polymorphs.

![Chemical structure](image)

| \( \alpha \)-IDM | \( \gamma \)-IDM | Melt 5-IDM (9-IDM) | Solution 5-IDM (5-IDM) |
|-----------------|-----------------|--------------------|------------------------|
| Mol.1           | Mol.1           | Mol.1              | Mol.1                  |
| 154.54          | 159.85          | 151.09             | 26.26                  |
| Mol.2           | Mol.2           | 152.90             | 27.58                  |
| 153.64          | 152.90          |                    |                        |
| Mol.3           | Mol.2           |                    |                        |
| 22.74           | 27.58           |                    |                        |
Figure S1: PXRD patterns of IDM polymorphs.
Figure S2: FT-Raman spectra of IDM polymorphs. a) 100-3200 cm$^{-1}$; b) 1400-1800 cm$^{-1}$. 
Figure S3: FTIR spectra of IDM polymorphs. a) 400-1800 cm$^{-1}$; b) 1400-1800 cm$^{-1}$.
Figure S4: Low magnification TEM images of melt δ-IDM (δ-IDM) (left) and solution δ-IDM (δ-IDM) (right).
Figure S5: The reciprocal lattice of melt δ-IDM (δ-IDM). (a) – (c) Projections of the 3D reconstructed reciprocal space. (d) – (f) 2D slices of reciprocal lattice planes. The reflection conditions obtained from the 3D ED data show that the crystal space group is Cc (No. 9).
Figure S6: The reciprocal lattice of solution δ-IDM (δ-IDM). (a) – (c) Projections of the 3D reconstructed reciprocal space. (d) – (f) 2D slices of reciprocal lattice planes. The reflection conditions obtained from the 3D ED data show that the crystal space group is $P2_1$ (No. 4).
Figure S7: Profile fit after refinement of the melt δ-IDM (θ-IDM) crystal structure model against the powder XRD data using the Pawley method.
Figure S8: Profile fit after refinement of the solution δ-IDM (δ-IDM) crystal structure model against the powder XRD data using the Pawley method.
Figure S9: Overlay of solution δ-IDM (δ-IDM) (green) with the δ-IDM structure solved by Andrusenko et al.\cite{11} (blue). Viewed along the a-axis. The root-mean-square deviation (RMSD) is 0.236 Å (non-hydrogen atoms). The small differences between the two structures can arise from our differing refinement procedures. Solution δ-IDM was refined against 3D ED data while the model from Andrusenko et al. was refined against powder X-ray diffraction data. Both models have reasonable bond lengths and angles.

\[
\text{RMSD}(v, w) = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (v_{ix} - w_{ix})^2 + (v_{iy} - w_{iy})^2 + (v_{iz} - w_{iz})^2}
\]
Figure S10: Crystal growth direction determination of melt δ-IDM (θ-IDM). (a - b) Low magnification TEM images of melt δ-IDM (θ-IDM); (c - d) Corresponding diffraction patterns of melt δ-IDM (θ-IDM). By comparing the crystal orientation in real-space images with the corresponding diffraction patterns, the crystal growth direction can be confirmed to be along the shortest (h00) axis (Unit cell: a = 4.79 Å, b = 57.00 Å, c = 12.91 Å, β = 99.6°).
Figure S11: Crystal growth direction determination of solution $\delta$-IDM ($\delta$-IDM). (a - b) Low magnification TEM images of solution $\delta$-IDM ($\delta$-IDM); (c - d) Corresponding diffraction patterns of solution $\delta$-IDM ($\delta$-IDM). By comparing the crystal orientation in real-space images with the corresponding diffraction patterns, the crystal growth direction can be confirmed to be along the shortest (0k0) axis (Unit cell: $a = 18.30$ Å, $b = 5.12$ Å, $c = 18.56$ Å, $\beta = 95.80^\circ$).
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Author Contributions

Molly L. performed 3D ED data collection and analysis. S.L. and X.O. performed PXRD, FT-Raman, FTIR, DSC, and microdroplet crystallization experiments. Molly L. and S.L. wrote the manuscript together with input from all authors. X.Z., Ming L. and H.X. supervised the project.