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Complete List of Authors:	Shankland, Kenneth; University of Reading, Reading School of Pharmacy Buckton, Graham; Pharmaterials Majumder, Mridul; Pharmaterials Rawlinson-Malone, Clare; Bristol-Myers Squibb Pharmaceuticals Limited Williams, Adrian; University of Reading, School of Pharmacy Spillman, Mark; University of Reading, School of Pharmacy Shankland, Norman; CrystallografX Ltd.

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COMMUNICATION

A carbamazepine-indomethacin (1:1) cocrystal produced by milling

Mridul Majumder,[a,b] Graham Buckton[a,c], Clare Rawlinson-Malone,[d] Adrian C. Williams,[b] , Mark J. Spillman[b] , Norman Shankland [e] and Kenneth Shankland*[b]

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An X-ray amorphous mixture of carbamazepine and indomethacin transforms upon annealing to produce a novel 1:1 cocrystal, whose structure has been determined from laboratory powder X-ray diffraction (PXRD) data.

Carbamazepine (CBZ; Fig 1) crystallises in five known polymorphic forms, four of which are dimer based and one of which is catemer based,[1] whilst there are two reported crystal structures for indomethacin (IND; Fig. 1; ∇).[2] A large number of solvated forms and cocrystals of both materials has been reported.[3] Both have also been studied in the X-ray amorphous state[4] and this communication describes one product of a wider investigation into the formation of cocrystals *via* the amorphous state. It has been suggested that this is the most likely route of cocrystal formation for non-volatile solids that are held together by strong intermolecular bonds.[5] There is a strong expectation that any novel CBZ:IND cocrystal discovered will feature either an acid-amide or amide-amide $R_2^2(8)$ motif.§

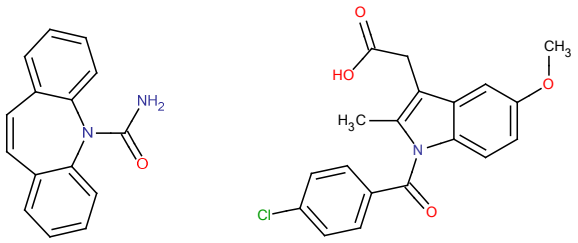

Fig. 1 The molecular structures of CBZ (left) and IND (right).

A 1:1 molar ratio mixture of CBZ form III and γ-IND was ground in a ball mill for ca. 4 hrs and then stored at 40°C/75% RH for 21 days. The resultant polycrystalline material was loaded into a 0.7mm borosilicate glass capillary and transmission PXRD collected at room temperature (Fig. 2).‡ After taking due account of the presence of reflections attributable to CBZ form III and γ-IND, the diffraction pattern indexed to a monoclinic unit cell of volume 2920Å^3, indicative of a 1:1 CBZ:IND cocrystal as the dominant phase. A Pawley-type refinement of the unit cell parameters in space group $P2_1/c$ was carried out simultaneously with Rietveld refinement of the CBZ and γ-IND crystal structures using TOPAS,[7] in order to extract an effectively phase-pure pattern for 1:1 CBZ:IND. The crystal structure was then solved from this data using DASH[8] and the structure refined against the original data using TOPAS.¶ The final refinement included a total of 39 parameters (17 background, 3 scale, 1 temperature factor, 6 positional, 6 rotational and 6 torsional), yielding R_{wp}=3.99.

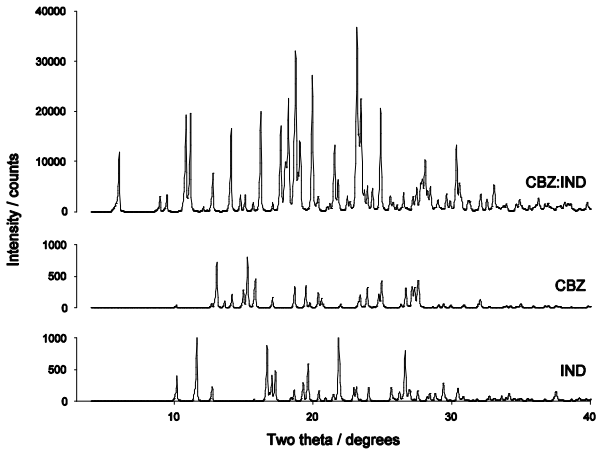

Fig. 2 The observed PXRD pattern for the 1:1 CBZ:IND powder sample after storage for 21 days, broken down into its three contributing phases: the 1:1 CBZ:IND cocrystal (top, ca. 97%), CBZ form III (middle, ca. 1.5%) and γ-IND (bottom, ca. 1.5%).

The resulting structure was further scrutinised by allowing all fractional coordinates to refine freely. As expected, the reduction in R_{wp} to 1.91 came at the expense of some chemical sense (mainly H-atom positions), but otherwise the geometry of each of the two molecules was well preserved. This, together with a satisfactory solid-state geometry optimization, confirms the correctness of the rigid-body refined crystal structure.¥

As anticipated, the bimolecular hydrogen-bonded ring motif is acid-amide (Fig. 3). The angle between the mean planes formed by atoms C17,O3,O4 in IND and N2,N3,O5 in CBZ is 27.7° (cf. a mean angle of 21.6° between corresponding planes in 17 published solvate and cocrystal structures of CBZ). Adjacent CBZ molecules pack as the supramolecular construct identified as B' in Fig. 2 of reference 11, an arrangement that is observed in 8 out of 56 published crystal structures containing CBZ .

The CBZ:IND cocrystal reported here can be generated reproducibly not only by ball milling, but also by co-grinding for as little as 15 minutes in a mortar and pestle. With this latter method, CBZ:IND is detectable by PXRD after ca. 48hrs storage at 25°C and the characteristic CBZ:IND peaks continue to grow in intensity and sharpen with time as crystallization proceeds.

Storage conditions do not appear to play a critical role in determining the outcome of the milling and grinding experiments, though the impact of storage time, temperature and relative humidity on the rate and extent of CBZ:IND formation has yet to be fully explored. It is notable that when starting with amorphous samples of CBZ and IND (as opposed to form III CBZ and γ-IND), co-grinding resulted in CBZ:IND formation, whilst a simple physical mix of either the two amorphous forms or the two crystalline forms did not (after 60 days of storage at 40°C/75% RH). The outcomes of liquid-assisted grinding experiments using CBZ and IND are currently under investigation.

With the increasing use of grinding / milling techniques to generate novel cocrystal forms, PXRD has an obvious role to play in crystal structure determination. The structure solution and refinement reported here emphasizes that the presence of 'contaminating' crystalline phases (whether residual starting materials, or recrystallised known structures) need not be an impediment to the high-quality crystal structure determination.

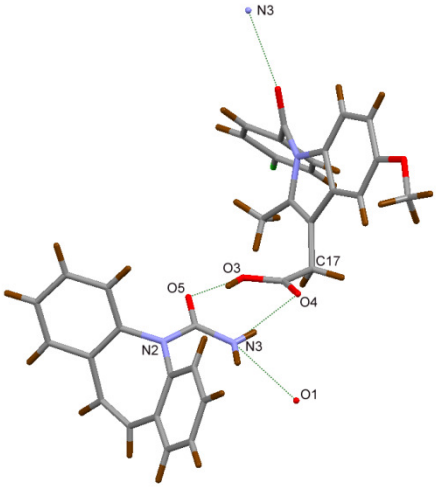

Fig. 3 The bimolecular hydrogen-bonded ring motif in the 1:1 CBZ:IND crystal structure.

Notes and references

[a] *Pharmaterials, Unit B, 5 Boulton Road, Reading RG2 0NH, UK. Fax: +44 (0) 1189 310679; Tel: +44 (0) 1189 209900; E-mail: mridul.majumder@pharmaterials.co.uk*
[b] *School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AD, UK.*
[c] *School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK.*
[d] *Bristol-Myers Squibb Pharmaceuticals Limited, Reeds Lane, Moreton, CH46 1QW, UK.*
[e] *Crystallografx Ltd, 2 Stewart St., Milngavie, Glasgow G62 6BW, UK.*

† Electronic Supplementary Information (ESI) available: Profile fits from Rietveld refinement and details of solid-state calculations. See DOI: 10.1039/b000000x/

∇The International Nonproprietary Name for indomethacin is indometacin.

§ Of the 309 crystal structures in the CSD v5.32 (Nov 2010)[6] that feature both X-COOH and X-$CONH_2$ groups, 74% possess an $R_2^2(8)$ motif. 127 of these exhibit *only* amide-acid type, 70 exhibit *only* amide-amide type, 2 exhibit *only* acid-acid type, and the remaining 30 exhibit some combination of these types.

‡ PXRD data were collected over the range 3–70° 2θ (2 kW; Cu $K\alpha_1$, 1.54056 A°; step size 0.017° 2θ), using a variable count time scheme. The Bruker D8 Advance diffractometer was equipped with a LynxEye detector.

¶ The data set was background subtracted and truncated to 50° 2θ for Pawley fitting (χ^2=1.1). The simulated annealing component of DASH was used to optimise the positions, orientations and conformations of molecular models of CBZ (derived from CSD refcode CBMZPN01, with 7 DoF) and IND (derived from CSD refcode INDMET03, with 10 DoF) against the diffraction data (168 reflections), yielding a favourable χ^2 of 10.8 for the best solution. A TOPAS-type rigid-body description of this solution was then refined against the original data set in the range 4°-65° 2θ to give a good final fit, R_{wp}=3.99, R_e=1.08. For the rigid-body refined fractional coordinates, with errors calculated by the bootstrap method, see CCDC reference number 827277.

¥ The rigid-body refined crystal structure was optimized in the program MOPAC2009 using PM6 parameterization.[9] A 15 molecule overlay of the experimental and PM6 crystal structures, in the program Mercury[10] returned RMSD = 0.255 Å, confirming good agreement between the experimental crystal structure (corresponding to a minimum in the Rietveld R_{wp} agreement factor) and the PM6 crystal structure (corresponding to a minimum in energy, specifically enthalpy of formation in the solid state).

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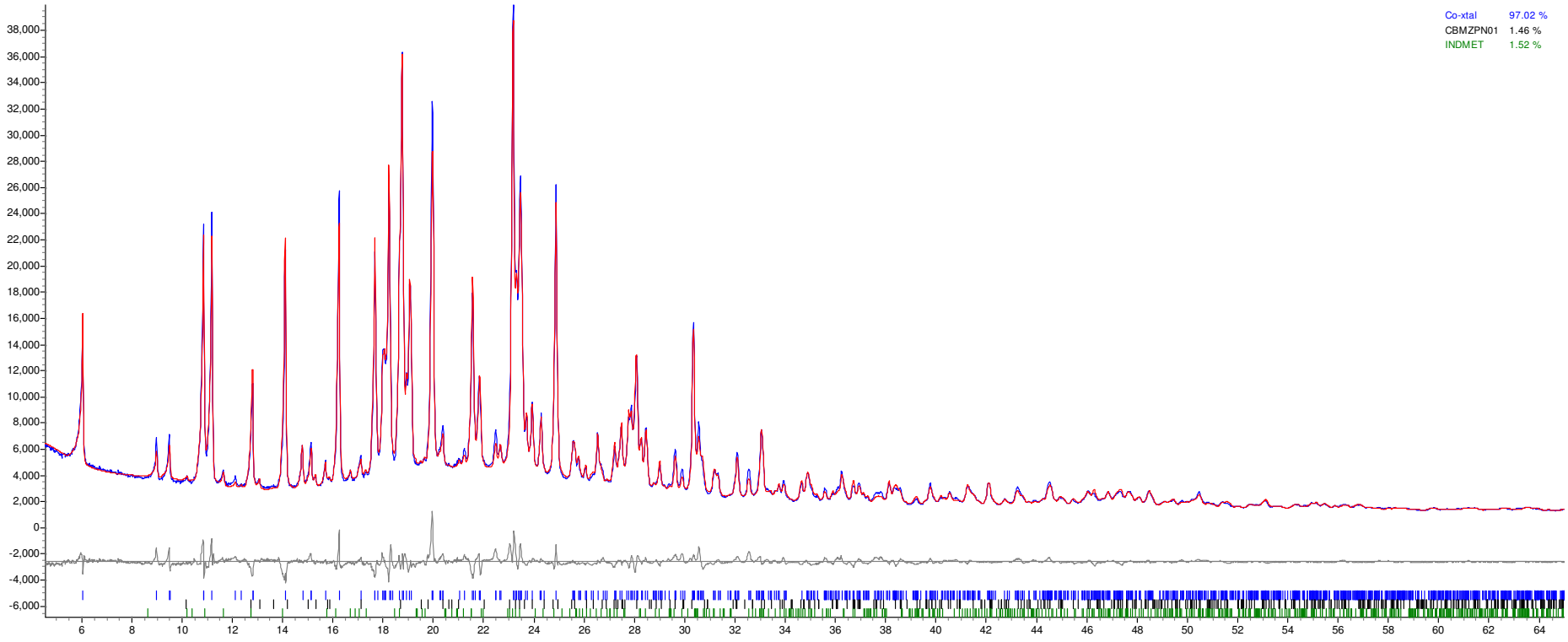
Electronic Supplementary Information

Profile plot of three phase Rietveld fit to the CBZ:IND diffraction data - full range



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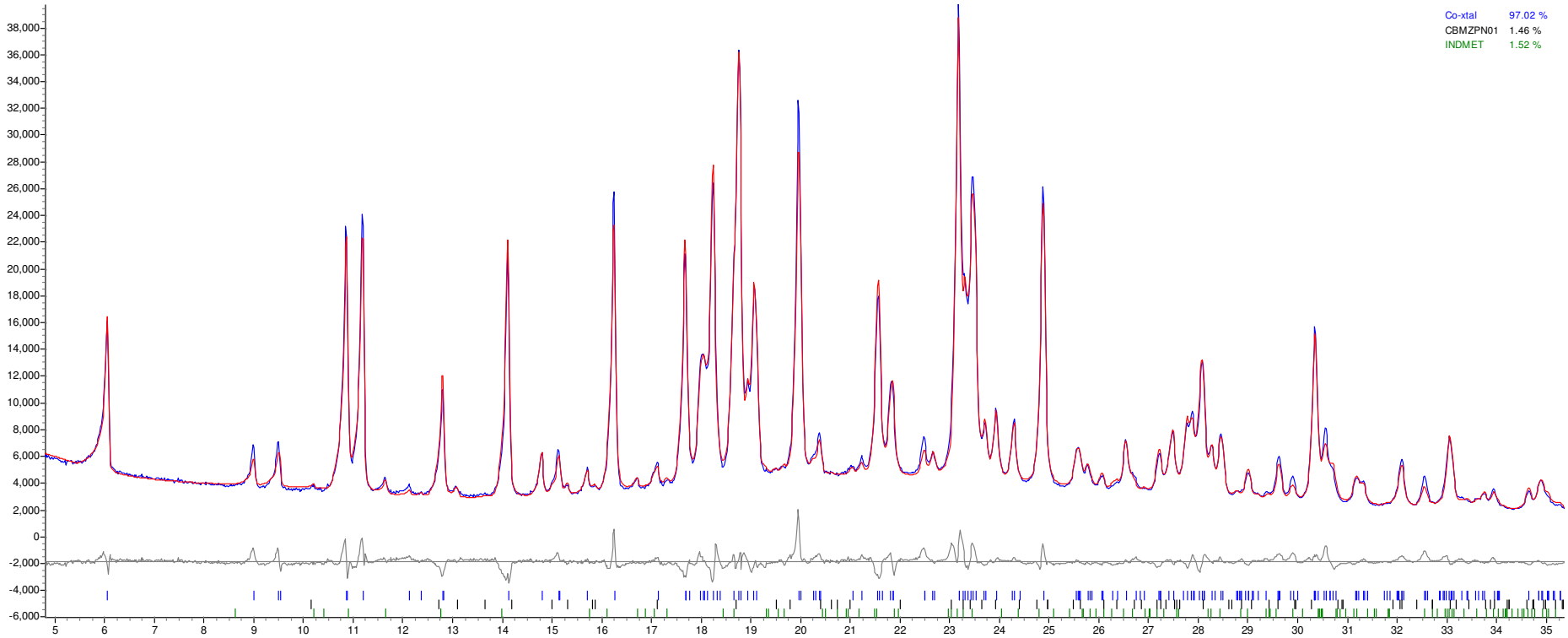

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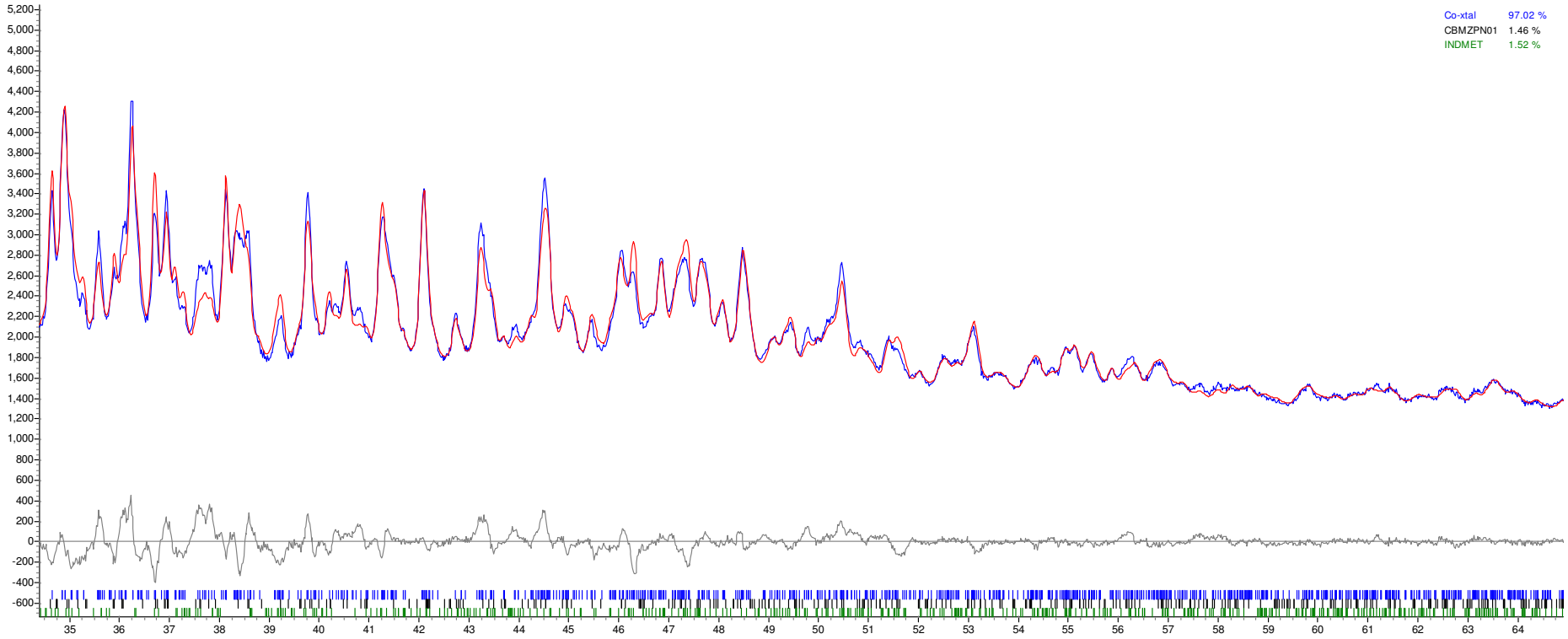

Solid state calculations

The refined crystal structure of $C_{15}H_{12}N_2O$:$C_{19}H_{16}ClNO_4$ was optimized in the program MOPAC2009, running on a PC equipped with 2.4GHz Intel Core2 Quad CPU and 4Gb memory, using PM6 parameterization.[2,3]

The input cluster of molecules (a packed unit cell of the experimental crystal structure, 284 atoms total) was created in Mercury[4] and the first atom in the resultant Cartesian coordinate listing was placed at the origin (all other atom positions adjusted accordingly). Translation vectors were applied[5] and the crystal structure geometry optimized using the eigenvector following routine, without the use of symmetry, allowing (*x*,*y*,*z*) of all 284 atoms, plus the lattice parameters, to optimize. The calculation was set to terminate when the gradient norm reached a value < 5 kcal mol^{-1} $Å^{-1}$ (the default) and ran to completion in 210 minutes [enthalpy of formation in the solid state, ΔH_f (solid) = -129.4 kcal mol^{-1}]. The output file was visualized using Mercury and showed a good correspondence with the experimental crystal structure, as evidenced by:

(i) small lattice parameter differences (Exp. – PM6): Δa = 0.215, Δb = -0.070, Δc = 0.318 Å; $\Delta\alpha$ = 0.03 , $\Delta\beta$ = 0.81, $\Delta\gamma$ = -0.34°; ΔV = -132.58 $Å^3$ ≈ -4.5%;

(ii) RMSD = 0.260 Å for a 15 molecule overlay of the experimental and PM6 crystal structures.

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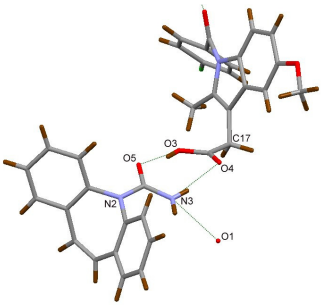

An X-ray amorphous mixture of carbamazepine and indomethacin transforms upon annealing to produce a novel 1:1 cocrystal, whose structure has been determined from laboratory powder X-ray diffraction (PXRD) data.

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: CBZ-INDO

Bond precision: C-C = 0.0051 A Wavelength=1.54056

Cell: a=10.2447(3) b=29.148(1) c=10.2114(3)
alpha=90 beta=106.636(2) gamma=90
Temperature: 293 K

	Calculated	Reported
Volume	2921.62(16)	2921.6(2)
Space group	P 21/c	P21/c
Hall group	-P 2ybc	?
Moiety formula	C19 H16 Cl N O4, C15 H12 N2 O	C15 H12 N2 O1, C19 H16 Cl1 N1 O4
Sum formula	C34 H28 Cl N3 O5	C34 H28 Cl1 N3 O5
Mr	594.04	594.05
Dx,g cm-3	1.350	1.350
Z	4	4
Mu (mm-1)	1.554	0.000
F000	1240.0	0.0
F000’	1245.09	
h,k,lmax		
Nref		
Tmin,Tmax		
Tmin’		

Correction method= Not given

Data completeness= Theta(max)=

R(reflections)= wR2(reflections)=

S = Npar=

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level A
ATOM007_ALERT_1_A _atom_site_aniso_label is missing
Unique label identifying the atom site.

Alert level C

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CRYSC01_ALERT_1_C The word below has not been recognised as a standard
           identifier.
           off
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   1 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   1 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   0 ALERT level G = General information/check it is not something unexpected

   2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   0 ALERT type 2 Indicator that the structure model may be wrong or deficient
   0 ALERT type 3 Indicator that the structure quality may be low
   0 ALERT type 4 Improvement, methodology, query or suggestion
   0 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

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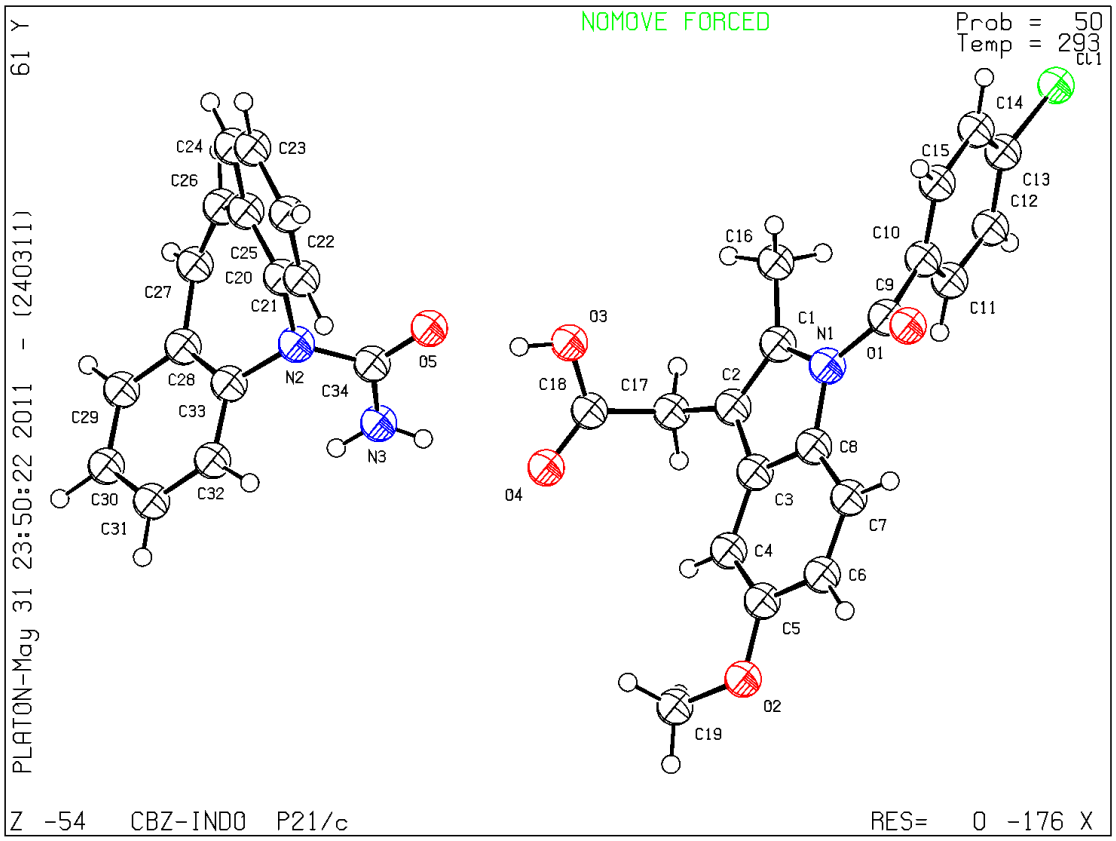

Comment on Alert level A

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Comment on Alert level C

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