Unusual polymorphs of *rac*-3-phenylpyrrolidine-2,5-dione with Z' = 1, 2, and 3

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ARTICLE

Unusual polymorphs of *rac*-3-phenylpyrrolidine-2,5-dione with Z' = 1, 2, and 3

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3-Phenylpyrrolidine-2,5-dione (PPD) is the pharmacologically relevant metabolite of the clinically used antiepileptic drug phensuximide. In 1973, Argay and Kálmán (*Acta Crystallogr., Sect. B,* 1973, **29**, 636-638) described an orthorhombic modification (Polymorph I) of *rac*-PPD with one molecule in the asymmetric unit (*Pna*2_1; Z' = 1) and mentioned the existence of another, monoclinic modification (Polymorph II). By varying the crystallization conditions, we were able to obtain diffraction-quality crystals of the monoclinic Polymorph II ($P2_1/c$; Z' = 2) and of novel triclinic Polymorph III (*P*-1; Z' = 3). In this paper, we report a detailed structural comparison of these variable-Z' polymorphs of *rac*-PPD. We found a remarkable diversity of intermolecular interactions (medium-strength N-H...O hydrogen bonds, weak C-H...O hydrogen bonds, carbonyl-carbonyl interactions, edge-to-face aromatic-aromatic interactions). We also explored the relative stability of these polymorphs (as indicated by crystal lattice energies and thermal analysis data). Our results are expected to aid in developing a better understanding of solid-state structure of cyclic imide-based antiepileptic drugs.

Introduction

Many clinically used drugs are administered as solid pharmaceutical formulations of active pharmaceutical ingredients (APIs). For such drugs, their supramolecular structure affects their solubility (and, thus, bioavailability and therapeutic efficacy upon oral administration) and stability upon storage.[1-4] The knowledge of the relationship between supramolecular structure and pharmaceutically relevant solid-state properties is of critical importance in producing well-defined solid APIs (including polymorphism control), in modulating such properties *via* technological processing, in developing the optimal storage conditions, and in rationally guiding the prescribing practices.

α-Substituted cyclic imides are known to be effective anticonvulsants.[5,6] For example, ethosuximide (3-ethyl-3-methylpyrrolidine-2,5-dione), methsuximide (1,3-methyl-3-phenylpyrrolidine-2,5-dione), and phensuximide (1-methyl-3-phenylpyrrolidine-2,5-dione) are approved by the US Food and Drug Administration for the treatment of epilepsy. The latter two compounds metabolize through *N*-demethylation, with 3-phenylpyrrolidine-2,5-dione (PPD) being the metabolite of phensuximide (Fig. 1). Importantly, these *N*-demethylated metabolites are largely responsible for the pharmacological effect of these drugs and thus can serve as starting structures for the design of novel drug leads.

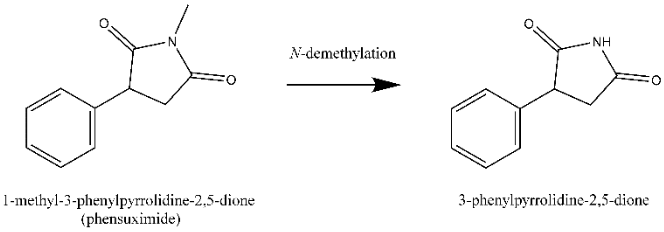

Fig. 1 Metabolic *N*-demethylation of phensuximide.

Kuhnert-Brandstätter and Bösch[7] used crystallization from melts to produce three polymorphic modifications of phensuximide. Although no crystal structures were reported, these modifications were characterized using differential scanning calorimetry (DSC) and infrared (IR) spectroscopy.

Concerning PPD, Argay and Kálmán[8] described the crystal structure of an orthorhombic modification of *rac*-PPD (which we designated as Polymorph I; CSD entry PHPYRO) and mentioned the existence of another, monoclinic modification (which we designated as Polymorph II). The crystal structure of the latter modification has not been reported so far.

In this paper, we present a detailed study of Polymorph II and of a newly discovered modification, which we designated as Polymorph III. Notably, Polymorphs I, II, and III differ in the number of symmetry-independent molecules in the asymmetric unit and thus present an interesting case of polymorphism seldom observed in cyclic imides.

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Electronic Supplementary Information (ESI) available: Summary of crystallization conditions, crystallographic data for Polymorph II, parameters of N-H...O hydrogen bonds for Polymorph II, parameters of C-H...O hydrogen bonds, summary of IR frequencies, and IR spectra in the N-H stretch region. See DOI: 10.1039/x0xx00000x

Experimental

Chemicals

Rac-PPD was purchased from Enamine Ltd (Monmouth Junction, NJ). Ethanol (absolute, 200 proof) was purchased from PHARMCO-AAPER, and hexanes and acetone from MilliporeSigma (Burlington, MA).

Crystallization

To produce Polymorph II, crystals were grown by slow evaporation of 15 mg/ml solutions of *rac*-PPD in hexanes/acetone (2:1, vol/vol) in 10×75 mm glass test tubes at room temperature in a desiccator. To produce Polymorph III, crystals were grown by slow evaporation of 40 mg/ml solutions of *rac*-PPD in absolute ethanol in 12×75 mm glass test tube at room temperature in a desiccator (in many instances, similar crystallization conditions instead produced Polymorph II).

Structure determination *via* single-crystal X-ray diffraction analysis

The data were collected on a Bruker-AXS SMART APEX II CCD diffractometer using graphite-monochromatized MoKα radiation (λ = 0.71073 Å) in the φ and ω scan mode and corrected for absorption using the *SADABS* program.[9] The crystal structures were solved by direct methods[10] and refined by a full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms.

The hydrogen atoms were objectively localized in the difference Fourier maps and refined isotropically. All calculations were carried out using the Bruker *SHELXTL* program.[11]

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. The accession codes for Polymorph II are CCDC 1957488 (100 K), CCDC 1957489 (175 K), CCDC 1888876 (215 K), and CCDC 1957490 (298 K). The accession code for Polymorph III is CCDC 1888875. These CIFs can be obtained free of charge *via* https://www.ccdc.cam.ac.uk/structures/.

IR spectroscopy

IR spectra were recorded at room temperature (20-22 °C) on a Nicolet iS5 FT-IR spectrometer controlled by OMNIC ver. 9.8.372 software (Thermo Fisher Scientific, Madison, WI). The spectral range was 4000 cm^{-1} to 525 cm^{-1} and the resolution was set at 4 cm^{-1}. Thirty-two spectra were collected and averaged for each sample or background measurement. Other acquisition settings were as follows: 2 levels of zero filling, Happ-Genzel apodization, and Mertz phase correction. The frequencies of the peaks and shoulders were determined from the second derivatives of the spectra.

For finely ground crystals, an iD7 single-bounce monolithic diamond attenuated total reflectance (ATR) accessory (Thermo Fisher Scientific, Madison, WI) was used. A three-segment (4000-3380 cm^{-1}, 3380-1875 cm^{-1}, and 1875-525 cm^{-1}) linear Baseline Correction and an Advanced ATR Correction were applied.

For solutions, Pearl liquid transmission accessory with 50-μm pathlength Oyster cell with wedged CaF_2 windows (Specac Inc., Fort Washington, PA) was used.

Melting point determination

Melting curves were recorded on an OptiMelt MPA100 automated melting point system with digital image processing technology controlled by MeltView ver. 1.107 software (Stanford Research Systems, Sunnyvale, CA). A heating rate of 1 °C/min was used. The clear point was defined as the 10% threshold.

Differential thermal analysis (DTA) measurements

DTA traces for 3.3- to 7.9-mg samples of intact or ground crystals of Polymorphs II and III were recorded in open aluminium pans on a Hitachi STA 7200 simultaneous thermogravimetric analyzer (Hitachi High Technologies America, Schaumburg, IL). A heating rate of 10 °C/min was used. The furnace compartment was continuously purged with nitrogen at 100 ml/min.

For $\Delta_{fus}H$ calculations, peak areas were normalized to a peak area for indium ($\Delta_{fus}H$ 28.59 J/g).

Hirshfeld surface analysis

Molecular Hirshfeld surfaces and corresponding "fingerprint" plots for the crystal structures in question were calculated using the CrystalExplorer software (ver. 17.5, available from http://crystalexplorer.scb.uwa.edu.au/).[12] For the "fingerprint" plots (calculated at the resolution setting "Very high"), the distance from the surface to the nearest nucleus exterior to the surface (d_e) was plotted against the distance from the surface to the nearest nucleus interior to the surface (d_i). The overall approach for Hirshfeld surface analysis has been described in detail by Spackman with collaborators.[13,14]

Crystal lattice energy calculations

Energies of the crystal lattices (kJ / mol) were computed using the atom-atom force field with subdivision of the interaction energies into Coulombic, polarization, London dispersion, and Pauli repulsion components (AA-CLP) method implemented in the CLP-PIXEL computer program package (ver. 3.0, available from http://www.angelogavezzotti.it).[15,16] Default settings were used, and the hydrogen atom positions were assigned by the software.

Statistics

Data from replicate experiments are presented as M±SD.

Statistical significance of the differences in mean values was tested by means of unpaired two-tailed *t*-test using GraphPad QuickCalcs web-based calculator (https://www.graphpad.com/quickcalcs/).

Results and discussion

Molecular structures

Our study indicates that depending on the crystallization conditions, *rac*-PPD can form at least three distinct polymorphic modifications. Argay and Kálmán[8] previously described an orthorhombic modification (Polymorph I; $Pna2_1$; Z' = 1) formed upon crystallization from ethanol. They also mentioned the existence of another, monoclinic modification (Polymorph II; $P2_1/c$; Z' = 2) - presumably, formed in the same crystallization conditions. However, the quality of their crystals apparently prevented them from solving the structure of Polymorph II. We were able to obtain high-quality crystals of Polymorph II upon crystallization from hexanes/acetone (2:1, vol/vol) or from absolute ethanol. In some cases, crystallization from absolute ethanol also produced a novel triclinic Polymorph III (*P*-1; Z' = 3).

Despite extensive trials (absolute ethanol or 95% ethanol, different temperatures, different vessels - see Table S1), we were unable to obtain Polymorph I as per Argay and Kálmán[8] (unfortunately, they did not specify the exact crystallization conditions for Polymorph I, only stating that it was crystallized from ethanol). Thus, this might be yet another example of "disappearing" polymorphs, a phenomenon extensively reviewed by Bernstein and collaborators.[17,18]

The crystallographic data for the X-ray structures of Polymorphs II and III are given in Table 1; for comparison, the data of Argay and Kálmán[8] for Polymorph I are also shown there.

Structures of Polymorph II were determined at four different temperatures (Table S2); no substantial differences were observed.

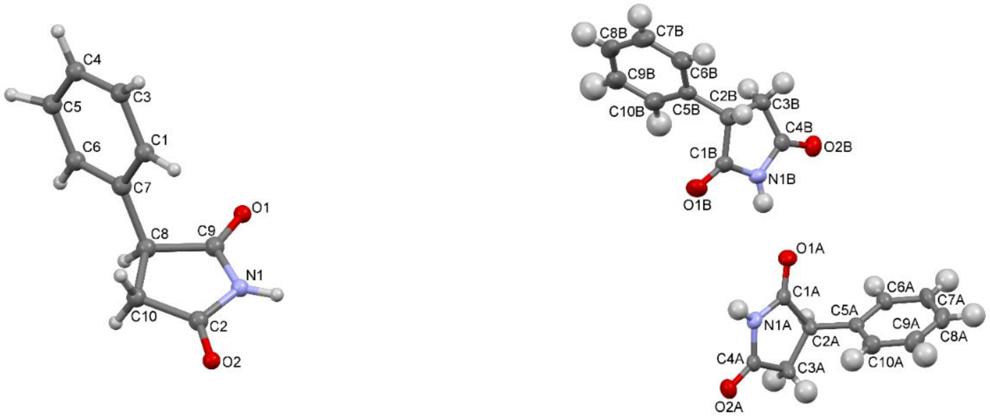
Table 1 Crystallographic and refinement data

Parameter	Polymorph I (PHPYRO[8])	Polymorph II	Polymorph III
T, K	295	215	100
λ, Å	1.5418	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic	Triclinic
Space group	$Pna2_1$	$P2_1/c$	*P*-1
a, Å	8.66(1)	15.564(5)	9.285(5)
b, Å	17.31(1)	5.716(2)	10.118(5)
c, Å	6.05(1)	20.595(8)	15.913(8)
α, deg.	90	90	80.568(6)
β, deg.	90	107.363(6)	81.516(6)
γ, deg.	90	90	65.604(6)
V, Å^3	907.68	1749(1)	1338(1)
Z; Z'	4; 1	8; 2	6; 3
d_c, g/cm^3	1.269	1.331	1.305
$F(000)$	n.a.	736	552
Index range	n.a.	$-20 \leq h \leq 20$ $-7 \leq k \leq 7$ $-27 \leq l \leq 27$	$-13 \leq h \leq 13$ $-14 \leq k \leq 14$ $-22 \leq l \leq 22$
No. of reflections collected	n.a.	22399	19911
No. of unique reflections	870	4257	8123
No. of reflections with $I > 2s(I)$	748	2869	5607
Data/restraints/parameters	n.a.	4257/0/307	8123/0/460
R_1; wR_2 ($I > 2s(I)$)	0.054; n.a.	0.0429; 0.0866	0.0470; 0.1132
Goodness-of-fit on F^2	n.a.	1.017	1.030
T_{min}; T_{max}	n.a.	0.6544; 0.7460	0.6404; 0.7461

One of the most interesting features of these polymorphs is the different number of symmetry-independent molecules in the asymmetric unit: Z' = 1 for Polymorph I, Z' = 2 for Polymorph II, and Z' = 3 for Polymorph III (Fig. 2). Based on CSD search for succinimide and glutarimide structures with Z'>1, variable-Z' polymorphism is quite uncommon among cyclic imides. For example, although *rac*-3-methyl-3-phenylpyrrolidin-2,5-dione has two symmetry-independent molecules in the asymmetric unit, only one crystal structure was observed irrespective of crystallization conditions.[19] The only cyclic imide, for which variable-Z' (Z' = 1 for Form 1 and Z' = 2 for Form 2) polymorphism has been previously noted, is 3-azabicyclo[3.3.1]nonane-2,4-dione.[20,21]

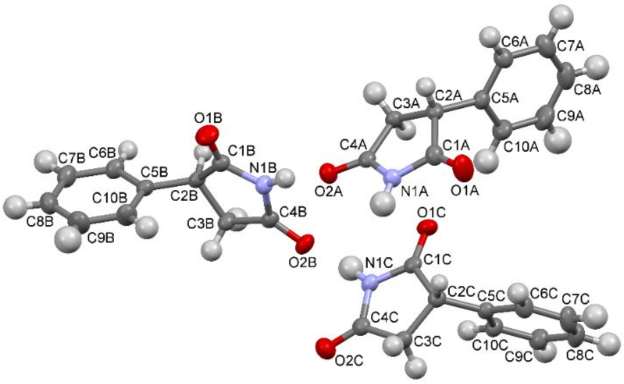
Generally, the bond lengths and bond angles are very similar in all of these PPD molecules. For example, the endocyclic angle C1-C2-C3 is essentially the same (differences are less than one degree) due to the very limited ring puckering. However, some conformational differences between molecules of the same polymorph and between molecules in the different polymorphs can be observed (see the superposition of the molecules in Fig. 3 and the corresponding dihedral angles in Table 2). Fairly small differences (approximately one to three degrees) are observed in the exocyclic angles C1-C2-C5, C9-C8-C7, C3-C2-C5 and C10-C8-C7. The most significant difference (up to 17 deg.) is observed in the relative orientation of pyrrolidine-2,5-dione and phenyl rings.

Considering the angles in Table 2, one can see that Molecule A in Polymorph II adopts virtually the same conformation as the PPD molecule in Polymorph I. However, the conformation of Molecule B in Polymorph II is considerably different, with the phenyl ring being less (by 13 degrees) tilted relatively to the pyrrolidine-2,5-dione ring and the exocyclic angle C1-C2-C5 being larger. The three molecules of Polymorph III are similar to each other, with only modest (2 to 6 degrees) differences in the two abovementioned angles.



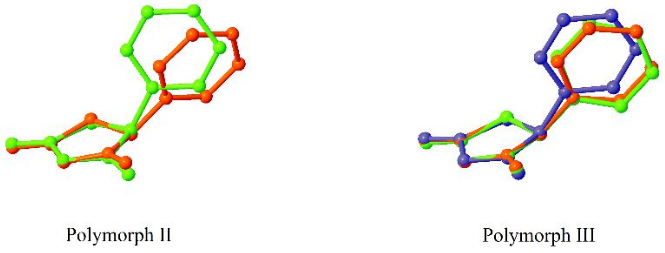
Polymorph I

Polymorph II



Polymorph III

Fig. 2 Symmetry-independent molecules in the asymmetric units of Polymorphs I (295 K; CSD entry PHPYRO[8]), II (215 K), and III (100 K). For Polymorphs II and III, heavy atoms are shown as thermal ellipsoids (50% probability level).



Polymorph II

Polymorph III

Fig. 3 Superposition of symmetry-independent molecules in the asymmetric units of Polymorphs II (Molecule A is shown in green, and Molecule B - in red) and III (Molecule A is shown in green, Molecule B - in red, and Molecule C - in blue).

Table 2 Selected dihedral angles (deg.) in symmetry-independent molecules of PPD in Polymorphs I-III

Dihedral angle	I[1]	IIA[2]	IIB[2]	IIIA	IIIB	IIIC
C1-C2-C3 or C9-C8-C10 (endo)	103.1	103.3(1)	103.35(13)	103.6(1)	103.4(1)	103.6(1)
C1-C2-C5 or C9-C8-C7 (endo)	111.0	110.3(1)	114.03(13)	114.9(1)	114.8(1)	112.2(1)
C3-C2-C5 or C10-C8-C7 (exo)	116.3	116.3(1)	116.47(14)	115.9(1)	116.3(1)	114.9(1)
The angle between pyrrolidine-2,5-dione and phenyl rings	82.8	84.0(1)	70.43(8)	87.9(1)	81.4(1)	84.6(1)

[1] Argay and Kálmán[8] (atoms have been renumbered to correspond to the numbering scheme in Fig. 2);

[2] stucture determined from data collected at 215 K.

Crystal structures and intermolecular interactions

Formation of robust H-bonded (N-H...O) supramolecular synthons defines the molecular packing in all three polymorphs (Figs 4-6). The existence of one donor group and two acceptor groups in each PPD molecule allows for the diversity of noncovalent interactions and packing motifs observed in Polymorphs I-III.

The intermolecular N-H...O hydrogen bonds in *rac*-PPD crystals (Table 3) are medium-strength bonds typical for imides, amides, lactams, and related compounds. No substantial differences in H-bond geometry between different polymorphs can be seen (Table 3). Furthermore, for Polymorph II, no substantial differences in H-bond geometry are seen in structures determined at four different temperatures (Table S3).

Due to the fact that not all carbonyl groups participate in N-H...O hydrogen bonds, all three polymorphs also contain multiple weak (H...O 2.38-2.70 Å) C-H...O hydrogen bonds. Many of these bonds involve *ortho*-hydrogens of the phenyl rings and aliphatic protons of the succinimide rings. These weak H-bonds[22-24] (catalogued in Table S4) likely play a substantial role in the stabilization of the crystal structures in question.

Argay and Kálmán[8] initially suggested that the supramolecular synthon in Polymorph I ($Pna2_1$; Z' = 1) is a cyclic dimer. However, a more careful inspection of the data indicates that PPD molecules in Polymorph I in fact form not dimers but infinite chains along the *c* axis (Argay *et al.*[25]; see Fig. 4). We previously observed similar molecular chains in the structures of enantiopure forms of a closely related succinimide derivative, 3-methyl-3-phenylpyrrolidine-2,5-dione.[19] Such infinite chains/molecular helices seem to be a very common H-bonded supramolecular synthon in substituted succinimides (reviewed in Argay *et al.*[25]). In addition to serving as an H-bond acceptor for a medium-strength N1-H9...O1 bond (Table 3), oxygen in the C1=O1 carbonyl also forms a weak hydrogen bond with *m*-H of the phenyl ring of a neighboring molecule. Oxygen in the C4=O2 carbonyl forms a weak hydrogen bond with the *o*-H of the phenyl ring of a neighboring molecule.

In Polymorph II ($P2_1/c$; Z' = 2), PPD Molecules A form infinite chains along the *b* axis, and PPD Molecules B are attached to these chains as pendants (Fig. 5). Consequently, while in Molecule A both of the carbonyls are involved in N-H...O hydrogen bonds, in Molecule B none of the carbonyls are involved in such H-bonds. At the same time, both of the carbonyls of Molecule A form weak H-bonds with aliphatic protons of the succinimide ring. In Molecule B, the C1=O1 carbonyl forms a bifurcated weak H-bond with *o*-Hs of phenyl rings of the opposite (across a center of symmetry) Molecules A and B. The C4=O2 carbonyl of Molecule B is unusual in that it does not participate in any (weak or medium-strength) hydrogen bonds - possibly due to a competition from carbonyl-carbonyl interactions (see below).

In Polymorph III (P-1; Z' = 3), PPD molecules form hexamers (Fig. 6). In each hexamer, a dimer of Molecules A is formed *via* an 8-member N-H...O-bonded cycle. Two Molecules B are attached as pendants to each cyclic dimer. In turn, each Molecule B is N-H...O-bonded to one molecule C. This arrangement results in 8 (one of the carbonyls in Molecules A, one of the carbonyls in Molecules B and both of the carbonyls in Molecules C) out of 12 carbonyls of the hexamer not being involved in N-H...O hydrogen bonds. Instead, these carbonyls form a number of weak C-H...O hydrogen bonds as follows: (i) the C1A=O1A carbonyl forms a bifurcated weak H-bond with *o*-H of the phenyl ring of the neighboring Molecule B and with *m*-H of the phenyl ring of the neighboring Molecule C; (ii) the C1B=O1B carbonyl forms a bifurcated weak H-bond with *o*-H of the phenyl ring of the neighboring Molecule C (H...O 2.65 Å) and with aliphatic proton of the succinimide ring the neighboring Molecule A (H...O 2.38 Å); (iii) the C4B=O2B carbonyl forms a weak H-bond with aliphatic proton of the succinimide ring the neighboring Molecule C; (iv) the C1C=O1C carbonyl forms a bifurcated weak H-bond with *o*-Hs of the phenyl rings of the neighboring Molecules A and B; (v) the C4C=O2C carbonyl forms a bifurcated weak H-bond with *o*-H of the phenyl ring of the neighboring Molecule C and with aliphatic proton of the succinimide ring the neighboring Molecule B.

Additionally, C4=O2 carbonyls in Molecule B of Polymorphs II and III are involved in antiparallel stacking interactions (motif II as per Allen *et al.*[26]) with the same carbonyls in the opposite (across a center of symmetry) Molecule B (C...O 3.04-3.05 Å, C=O...C and O...C=O angles 84-96 deg.).

Further insight into intermolecular interactions[27,28] in *rac*-PPD crystals can be gained from "fingerprint" plots calculated from molecular Hirshfeld surfaces (Fig. 7). The characteristic sharp spikes (d_i ~ 1.1 Å) correspond to the N-H...O hydrogen bonds. For Polymorph III, the diffuse area between these spikes likely corresponds to the cyclic H-bonded dimer at the center of the hexamer (see Fig. 6).

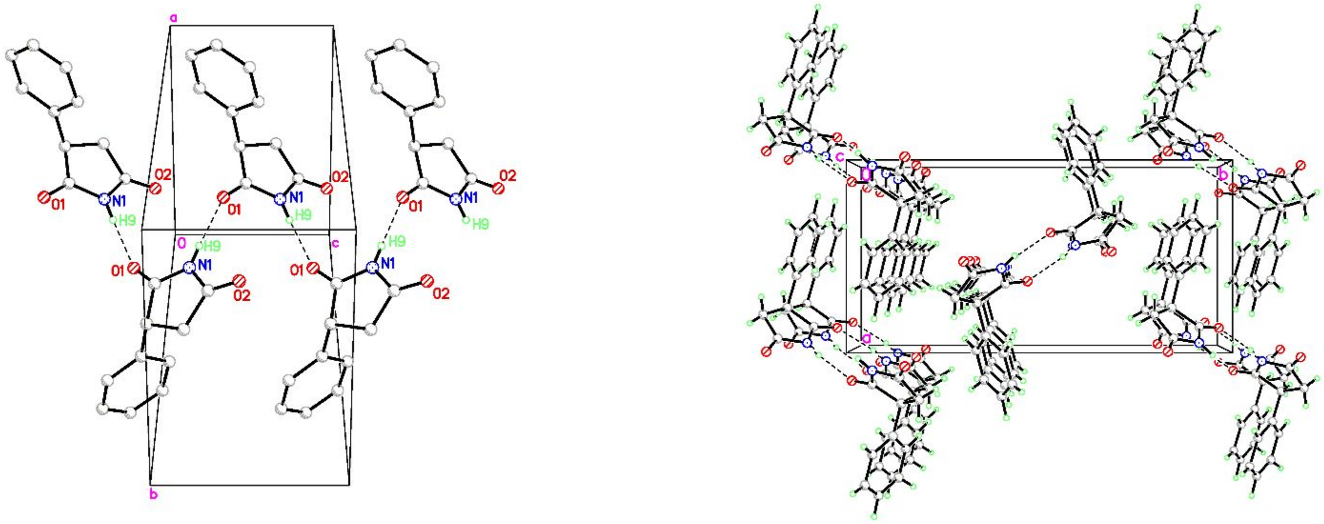


Fig. 4 Crystal structure of Polymorph I (*Pna*2$_1$; Z' = 1; CSD entry PHPYRO[8]). The chain of H-bonded PPD molecules along the *c* axis (hydrogen atoms - except the ones at nitrogen atoms - are omitted for clarity) is shown in the left panel, and packing of the chains in crystal is shown in the right panel.

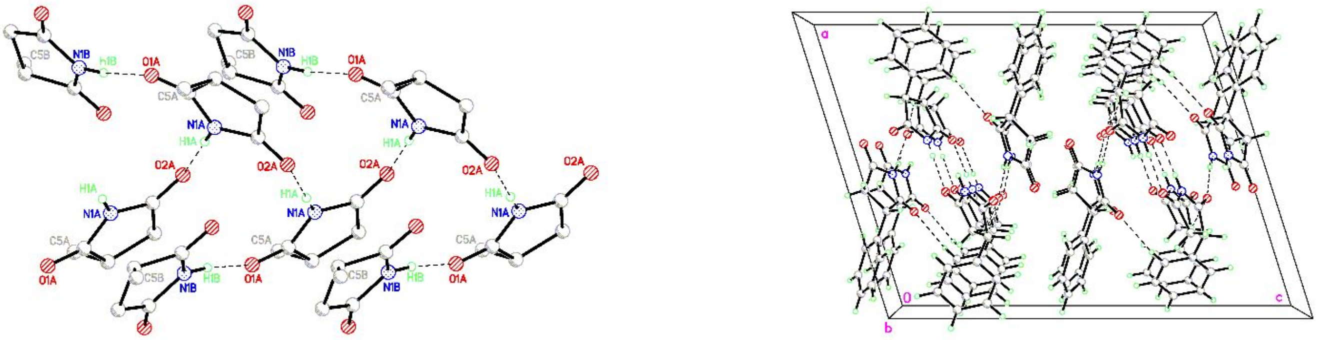


Fig. 5 Crystal structure of Polymorph II (*P*2$_1$/*c*; Z' = 2) determined from data collected at 215 K. The chain of H-bonded PPD molecules along the *b* axis (hydrogen atoms - except the ones at nitrogen atoms - and the phenyl groups are omitted for clarity) is shown in the left panel, and packing of the chains in crystal is shown in the right panel.

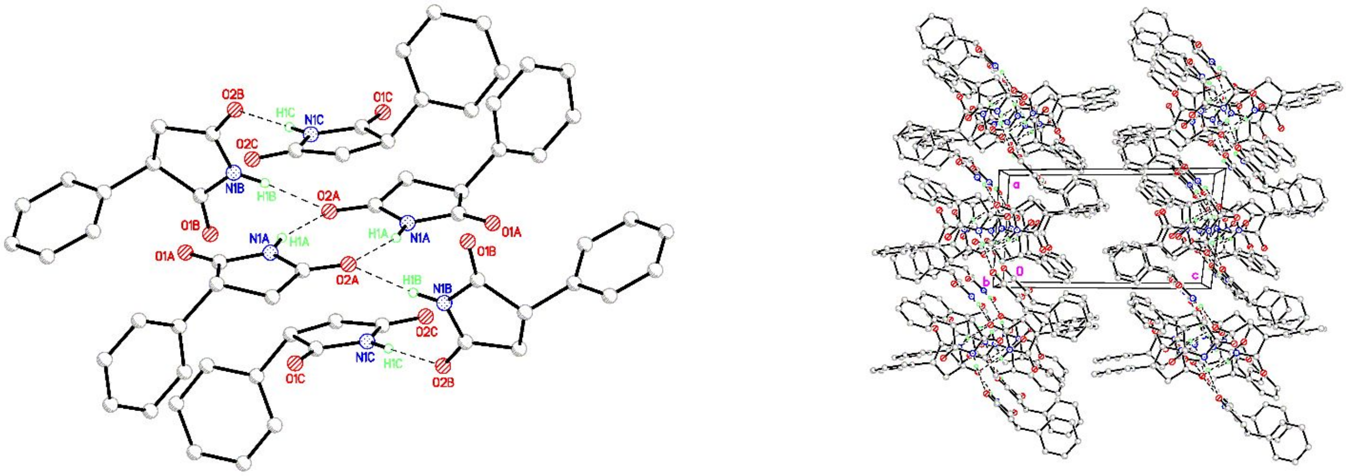


Fig. 6 Crystal structure of Polymorph III (*P*-1; Z' = 3). The H-bonded molecular hexamer (hydrogen atoms - except the ones at nitrogen atoms - are omitted for clarity) is shown in the left panel, and packing of the hexamers in crystal is shown in the right panel.

Table 3 N-H...O hydrogen bond distances (Å) and angles (deg.) in Polymorphs I-III

Polymorph	D-H...A	d (D-H)	d (H...A)	d (D...A)	∠ (D-H...A)
I (295 K)	N1-H9...O1	0.83	2.04	2.859	172
II (215 K)	N1A-H1A...O2A^{1}	0.87(2)	1.97(2)	2.835(2)	179(2)
	N1B-H1B...O1A	0.91(2)	2.02(2)	2.910(2)	165(2)
III (100 K)	N1A-H1A...O2A^{2}	0.90(2)	2.07(2)	2.936(2)	162(2)
	N1B-H1B...O2A^{2}	0.88(2)	1.95(2)	2.820(2)	170(2)
	N1C-H1C...O2B	0.91(2)	2.01(2)	2.916(2)	172(2)

Symmetry transformations used to generate equivalent atoms: ^{1} -x+1, y+1/2, -z+1/2; ^{2} -x+1, -y+1, -z

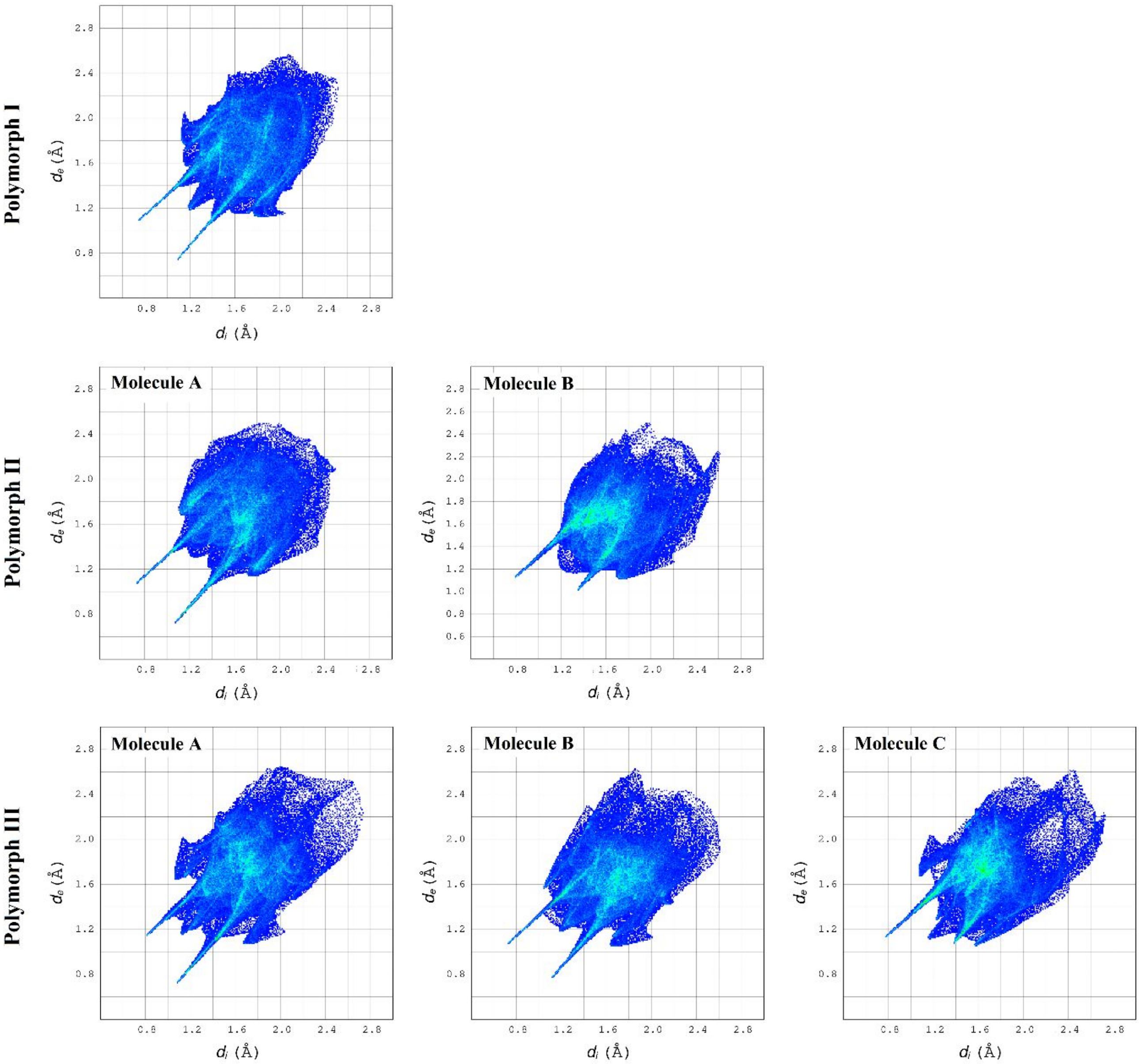


Fig. 7 "Fingerprint" plots for molecular Hirshfeld surfaces of Polymorphs I (*Pna*2_1; Z'=1), II ($P2_1/c$; Z' = 2), and III (*P*-1; Z' = 3). The structures were determined from data obtained at 295K, 215K, and 100 K, respectively.

The "wings" ($d_i \sim 1.7$ Å, $d_e \sim 1.1$ Å,) in the "fingerprint" plots of Polymorph III are indicative of C-H...π interactions. Indeed, careful inspection of the crystal structure revealed two edge-to-face aromatic-aromatic interactions. One of them (H-to-centroid distance 2.692 Å, centroid-to-centroid distance 4.971 Å) is between Molecule B of one hexamer ("face" phenyl group) and Molecule A of another hexamer ("edge" phenyl group). The second one (H-to-centroid distance 2.724 Å, centroid-to-centroid distance 4.712 Å) is between Molecule A of one hexamer ("face" phenyl group) and Molecule C of another hexamer ("edge" phenyl group). Taylor with collaborators[29] observed that edge-to-face aromatic-aromatic interactions are frequently associated with Z' > 1 in centrosymmetric structures.

A feature observed in the "fingerprint" plot of Polymorph I is the blunt spike at (d_e, d_i) ~ 1.2 Å corresponding to short H...H contacts (van der Waals interactions). In Polymorphs II and III this spike seems to be split suggesting that the short H...H contacts in those polymorphs may involve three rather than two hydrogen atoms.

It is instructive to compare the wealth of intermolecular interactions observed in these polymorphs of *rac*-PPD with such interactions in other cyclic imides. In the crystal structure of a closely related succinimide derivative, *rac*-3-methyl-3-phenylpyrrolidine-2,5-dione (Z'=2), one can observe medium-strength H-bonds, weak H-bonds, and carbonyl-carbonyl interactions.[19] Carbonyls in Molecule A are involved in N-H...O and C-H...O hydrogen bonds (the latter ones with *p*-Hs of the phenyl ring), while carbonyls in Molecule B are involved in N-H...O bonds and carbonyl-carbonyl interactions. On the other hand, only N-H...O and C-H...O hydrogen bonds (the latter ones with *m*-Hs of the phenyl ring) are observed in enantiopure forms of 3-methyl-3-phenylpyrrolidine-2,5-dione (Z'=1).[19] Both C-H...O hydrogen bonds and carbonyl-carbonyl interactions were observed[30] in *rac*-1,3-dimethyl-3-phenylpyrrolidine-2,5-dione, an *N*-substituted succinimide derivative incapable of forming N-H...O hydrogen bonds. The weak C-H...O hydrogen bonds are also found in crystal structures of other substituted succinimides,[31-33] unsubstituted succinimide,[34,35] and phthalimide.[36,37] The latter compound also has parallel displaced aromatic-aromatic interactions.

Overall, Polymorphs II and III of *rac*-PPD seem to have very diverse and extensive intermolecular interactions. Thus, *rac*-PPD might be a useful (albeit challenging!) benchmark for computational prediction of polymorphism.

Solid-state IR spectra

Since IR spectra are sensitive to molecular geometry and hydrogen bonding, solid-state IR spectroscopy can be very useful in distinguishing polymorphic modifications of organic compounds.[38,39]

However, ATR IR spectra of finely ground crystals of Polymorphs II and III turned out to be very similar (although clearly distinct from IR spectrum of *rac*-PPD in solution). Fig. 8 shows the C=O stretch region. The part of the Imide I envelope corresponding to asymmetric (out-of-phase) stretching of the C=O bond in *rac*-PPD crystals is quite complex, with four strongly overlapped bands in the 1687-1738 cm^{-1} range. In Polymorph III, the contribution of the 1697 cm^{-1} component is larger and the contribution of the 1721 cm^{-1} and 1687 cm^{-1} components is smaller than in Polymorph II.

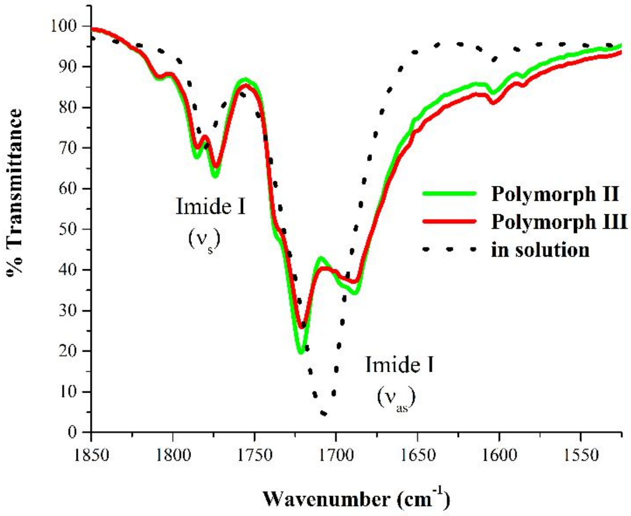


Fig. 8 IR spectra in the C=O stretch region of Polymorphs II and III (ground crystals). The spectrum of 50-mM solution of *rac*-PPD in MeOH-d4 is also shown. To facilitate the comparison, the spectra were normalized based on the area between 1520 and 1880 cm^{-1} (imide I envelope).

In the N-H stretch region of the IR spectra, no substantial differences between Polymorph II and Polymorph III are observed (Fig. S1). The band assignments for C=O stretch and NH stretch regions are given in Table S5.

The lack of major differences in IR spectra is not surprizing in light of the very similar H-bond geometry in Polymorphs II and III (Table 3).

Crystal lattice energies and thermal analysis data

The possible reasons (including the thermodynamic ones) for the existence of polymorphs with multiple symmetry-independent molecules in the asymmetric unit have been recently under extensive consideration.[25,40-43]

We felt that crystal lattice energies might aid in differentiating the polymorphs with Z' = 1 and Z' > 1. Table 4 shows the crystal lattice energy values calculated for Polymorphs I-III from their atomic coordinates using the atom-atom Coulomb-London-Pauli (AA-CLP) model for intermolecular energies.[15,16] Notably, the crystal lattice energy difference between Polymorphs II or III and Polymorph I (12.5 to 16.3 kJ / mol) is quite substantial - as per Nyman and Day,[44] 95% of polymorph pairs have energy difference less than 7.2 kJ / mol. The higher Coulombic contribution in Polymorphs II and III may reflect the more extensive N-H...O and C-H...O hydrogen bonding found in these forms.

The total lattice energies are in agreement with the observed crystal densities - Polymorph I has the lowest density and highest crystal lattice energy (likely due to a less tight packing), while Polymorph II has highest density and lowest crystal lattice energy. It seems that Polymorph I may be a metastable modification, which would explains why, despite extensive trials, we were unable to obtain this polymorph in our own crystallization experiments. On the other hand, the relatively small energy difference between Polymorphs II and III may explain the fact that both of them could be obtained from the same solvent (absolute ethanol) depending on minor variations (such as vessel geometry) in crystallization conditions. Nevertheless, the somewhat lower energy of Polymorph II compared to Polymorph III might have been sufficient to ensure its preferential crystallization - out of eight crystallization trials in absolute or 95% ethanol, only one trial yielded Polymorph III (the rest of the trials produced Polymorph II). Although, of course, one must also consider entropic contributions to crystallization kinetics and polymorph stability.

In many cases, crystal structure determinations of different polymorphs are carried out using datasets collected at different temperatures (as it was the case in this study). Gavezzotti, on pages 218 and 219 of his "Molecular Aggregation" book,[45] demonstrated that temperature at which XRD data were collected is without a major effect on calculated crystal lattice energies. Our own data with Polymorph II (Table 4) confirm the above assertion - the differences in total lattice energy for structures determined from datasets collected over the 100 K to 298 K range do not exceed 1.8 kJ / mol.

Differential thermal analysis (DTA) data for Polymorphs II and III (Fig. 9 and Table 5) are in line with the above conclusions regarding relative stability of these polymorphs. Since the melting points of these two forms are very close, the shape of the DTA traces cannot shed light on their possible thermodynamic relationship. However, such relationship can be deduced from enthalpies of fusion (Table 5) using the "heat-of-fusion rule" formulated by Burger and Ramburger.[46,47] Since the higher melting form (Polymorph II) has higher enthalpy of fusion than the lower melting form (Polymorph III), we can conclude that these two forms are monotropically related (Polymorph II is stable over the entire temperature range).

It has been suggested[48] that, among a set of polymorphic modifications with different Z' values, the modification with Z' = 1 would be the stable form while the modifications with Z' > 1 would be metastable forms. Our observations with *rac*-PPD are not compatible with such a model. The polymorphs with higher Z' values are actually more stable than the polymorph with Z' = 1 (Tables 4 and 5). We previously observed a similar trend in polymorphic modifications of phenazine derivatives.[49]

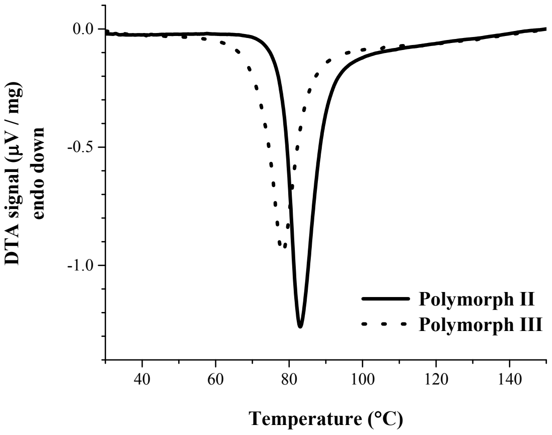


Fig. 9 DTA traces of Polymorphs II and III.

Table 4 Crystal lattice energies and crystal densities of Polymorphs I-III

Polymorph	T (K) for structure determination	Coulombic energy (kJ / mol)	Polarization energy (kJ / mol)	London dispersion energy (kJ / mol)	Pauli repulsion energy (kJ / mol)	Total lattice energy (kJ / mol)	Crystal density (g / cm^3)
I (*Pna*2$_1$; Z'=1)	295	-41.4	-26.9	-89.2	53.0	-104.9	1.269
II (*P*2$_1$/*c*; Z'=2)	100	-47.3	-32.8	-106.8	67.3	-119.7	1.366
	175	-48.2	-32.2	-102.3	61.2	-121.5	1.334
	215	-47.9	-32.1	-101.7	60.5	-121.2	1.331
	298	-47.2	-31.7	-99.5	58.0	-120.5	1.327
III (*P*-1; Z'=3)	100	-48.2	-31.2	-99.0	60.9	-117.4	1.305

Table 5 Thermal analysis data for Polymorphs II and III

Polymorph	m.p. (°C)	DTA data		
		T_{onset} (°C)	T_{peak} (°C)	$\Delta_{fus}H$ (J / g)
II (*P*2$_1$/*c*; Z'=2)	80.0±1.0[1]	77.3±0.8[2]	82.0±1.3[3]	101.2±0.3[4]
III (*P*-1; Z'=3)	76.7±0.2[1]	71.1±0.2[2]	78.7±0.6[3]	81.9±1.3[4]

[1] the difference is statistically significant at 99.92% confidence (n = 4)
[2] the difference is statistically significant at 99.98% confidence (n = 3)
[3] the difference is statistically significant at 98.52% confidence (n = 3)
[4] the difference is statistically significant at 99.99% confidence (n = 3)

Conclusions

Rac-PPD is an interesting example of a compound forming H-bonded systems with varying number of symmetry-independent molecules in the asymmetric unit. The results reported in this paper invite the following conclusions:

- The H-bonded synthons formed by *rac*-PPD are remarkably diverse - a simple infinite chain (Polymorph I; *Pna*2$_1$; Z' = 1), an infinite chain "decorated" with pendants (Polymorph II; *P*2$_1$/*c*; Z' = 2), and a hexamer (Polymorph III; *P*-1; Z' = 3).
- The hexameric crystal structure of Polymorph III is quite unusual for this class of compounds. A distinct structural feature of this polymorph is edge-to-face π...π interactions.
- Despite the diversity of the synthons, the geometry of all N-H...O hydrogen bonds is very similar.

Correspondingly, only very small differences are observed in IR spectra of Polymorph II *versus* Polymorph III.

- In addition to the medium-strength N-H...O hydrogen bonds, all three polymorphs also stabilized by a multitude of weak C-H...O hydrogen bonds. Furthermore, carbonyl-carbonyl interactions exist in Polymorphs II and III.
- Crystal lattice energies calculated from the atomic coordinates are in agreement with the observed melting points and densities. The energy difference between Polymorphs II and III is small, which might explain the fact that Polymorphs II and III can be produced in very similar experimental conditions.
- The previously reported Polymorph I is likely a metastable modification obtainable only within a narrow set of experimental conditions. Due to the lack of a detailed description of the crystallization conditions in the original paper by Argay and Kálmán,[8] we were unable to obtain and reinvestigate Polymorph I in this study.
- Directional N-H...O hydrogen bonding is the structural hallmark of cyclic imides and related compounds, and the occurrence of polymorphic modifications of *rac*-PPD with Z' > 1 is likely due to the need to preserve the H-bonding while still achieving a sufficiently tight packing of molecules in crystal.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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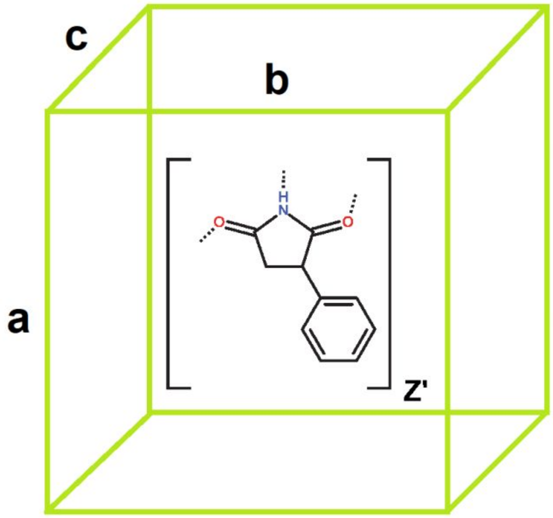
Table of Contents Entry for

Unusual polymorphs of *rac*-3-phenylpyrrolidine-2,5-dione with Z' = 1, 2, and 3

Tatiana V. Timofeeva, Victoria Sena, Boris B. Averkiev, Shabari N. Bejagam, Muhammad Usman, and Arcadius V. Krivoshein



We report two new polymorphs of *rac*-3-phenylpyrrolidine-2,5-dione and discuss the structural aspects of variable-Z' polymorphism in this compound.