

Conformational studies of hydantoin-5-acetic acid and orotic acid

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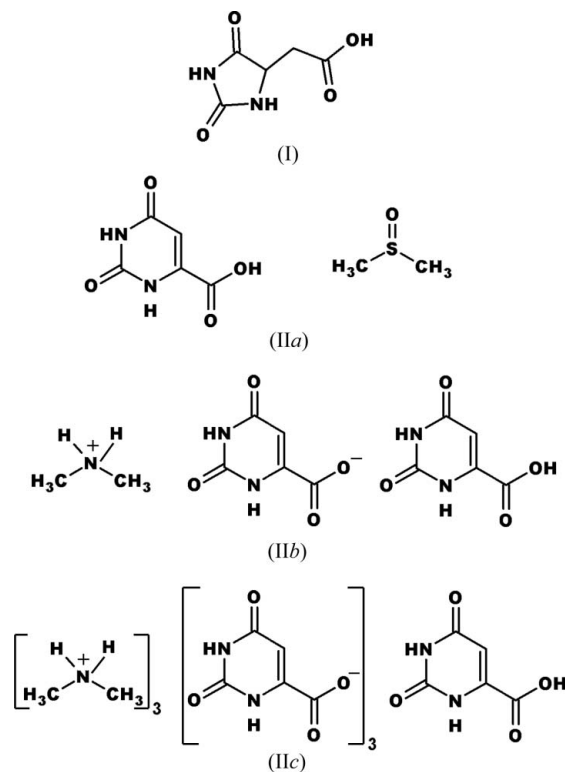
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Hydantoin-5-acetic acid [2-(2,5-dioxoimidazolidin-4-yl)acetic acid] and orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid) each contain one rigid acceptor–donor–acceptor hydrogen-bonding site and a flexible side chain, which can adopt different conformations. Since both compounds may be used as cofomers for supramolecular complexes, they have been crystallized in order to examine their conformational preferences, giving solvent-free hydantoin-5-acetic acid, C₅H₆N₂O₄, (I), and three crystals containing orotic acid, namely, orotic acid dimethyl sulfoxide monosolvate, C₅H₄N₂O₄·C₂H₆OS, (IIa), dimethylammonium orotate–orotic acid (1/1), C₂H₈N⁺·C₅H₃N₂O₄[−]·C₅H₄N₂O₄, (IIb), and dimethylammonium orotate–orotic acid (3/1), 3C₂H₈N⁺·3C₅H₃N₂O₄[−]·C₅H₄N₂O₄, (IIc). The crystal structure of (I) shows a three-dimensional network, with the acid function located perpendicular to the ring. Interestingly, the hydroxy O atom acts as an acceptor, even though the carbonyl O atom is not involved in any hydrogen bonds. However, in (IIa), (IIb) and (IIc), the acid functions are only slightly twisted out of the ring planes. All H atoms of the acidic functions are directed away from the rings and, with respect to the carbonyl O atoms, they show an antiperiplanar conformation in (I) and synperiplanar conformations in (IIa), (IIb) and (IIc). Furthermore, in (IIa), (IIb) and (IIc), different conformations of the acid O=C–C–N torsion angle are observed, leading to different hydrogen-bonding arrangements depending on their conformation and composition.

Comment

Active pharmaceutical ingredients (APIs) usually contain functional groups that are involved in recognition processes. Their polymorphic nature often leads to new opportunities in drug development. APIs are mostly administered as salts or together with a pharmaceutically inactive carrier compound, which possibly changes the desired pharmaceutical effects

(Almarsson & Zaworotko, 2004). The design of cocrystals with an API presents an alternative route to obtain new dosage forms without affecting the pharmaceutical activity (Ghosh *et al.*, 2011; Vishweshwar *et al.*, 2005). The most promising approach for the design of cocrystals deals with supramolecular synthons (Blagden *et al.*, 2008). The most-studied synthon is that formed between an amide and a carboxylic acid (Rodríguez-Cuamatzi *et al.*, 2007). Since carboxylic acids form robust and directed hydrogen bonds (Blagden *et al.*, 2007), they are ideal candidates as cofomers for APIs (Almarsson & Zaworotko, 2004). Although carboxylic acids are able to improve the stability of API-containing complexes (Seaton & Parkin, 2011), they show conformational polymorphism. Therefore, the possible conformations of carboxylic acids must be examined prior to their use as cofomers for APIs. For this reason, we crystallized hydantoin-5-acetic acid, (I), and orotic acid, (II), under several different sets of conditions.



Compounds (I) and (II) contain heterocyclic ring structures, rigid acceptor–donor–acceptor hydrogen-bonding sites and rotatable acid functionalities. Various crystallization attempts with hydantoin-5-acetic acid yielded only the solvent-free structure, (I), while crystallization experiments with (II) resulted in three structures, namely a dimethyl sulfoxide monosolvate, (IIa), and two dimethylammonium orotate–orotic acid compounds with 1:1, (IIb), and 3:1, (IIc), compositions. Both (IIb) and (IIc) crystallized from dimethylformamide but at different temperatures, *viz.* (IIb) at room temperature and (IIc) at 277 K.

Although a racemic mixture was used, compound (I) crystallized in the chiral orthorhombic space group *P*2₁2₁ with one molecule in the asymmetric unit. It is unknown if the crystal is an inversion twin or spontaneous resolution has

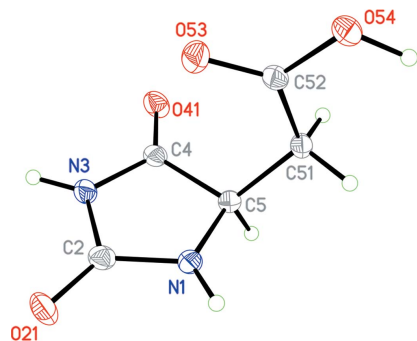


Figure 1
A perspective view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

taken place upon crystallization. The molecule contains a centre of chirality at C5, the absolute configuration of which was not determined due to the absence of significant anomalous scatterers (Fig. 1). The planar side chain (r.m.s. deviation for all non-H atoms = 0.006 Å) is perpendicular [dihedral angle = 89.28 (6)°] to the planar hydantoin ring (r.m.s. deviation = 0.026 Å for all non-H atoms). Hydroxy atom H54 points away from the hydantoin ring and the O—H bond is *trans* to the C=O bond [O53—C52—O54—H54 = 180 (2)°].

The crystal packing of (I) shows sheets of hydantoin-5-acetic acid molecules, which are parallel to the (01 $\bar{2}$) plane (Fig. 2). The sheets are characterized by $R_3^3(15)$ interactions (Bernstein *et al.*, 1995) with one O—H \cdots O and two N—H \cdots O hydrogen bonds (Table 1). Adjacent sheets are connected *via* $R_4^4(20)$ patterns which consist of two N—H \cdots O and two O—H \cdots O hydrogen bonds, building a three-dimensional network in the form of a zigzag pattern (Fig. 3). Interestingly, the N—H \cdots O interactions of the $R_4^4(20)$ patterns are connected *via* atom O54 of the carboxyl group and not *via* carbonyl atom O53.

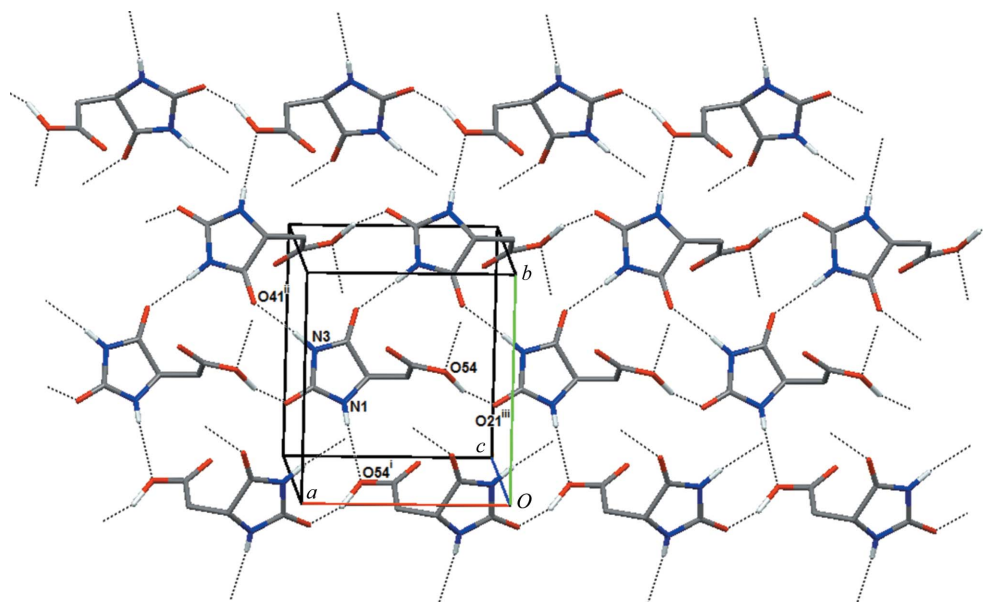
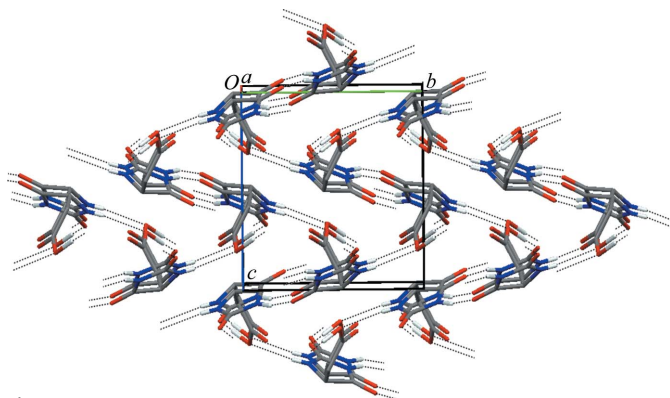


Figure 2
A partial packing diagram for (I). Only H atoms which participate in hydrogen bonds are shown. Hydrogen bonds are drawn as dashed lines. [Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x + \frac{1}{2}, -y + \frac{3}{2}, -z + 1$; (iii) $x - 1, y, z$.]

The orotic acid dimethyl sulfoxide (DMSO) monosolvate (IIa) crystallizes in the monoclinic space group $P2_1/c$, with one planar orotic acid molecule (r.m.s. deviation = 0.038 Å for all non-H atoms) and one DMSO molecule in the asymmetric unit (Fig. 4). The carbonyl O atom of the acid functionality is located in an antiperiplanar arrangement with respect to atom N5 [torsion angle N5—C4—C41—O42 = 176.17 (18)°] and is synperiplanar to atom H43. In the asymmetric unit, the DMSO and orotic acid molecules are connected *via* an O—H \cdots O hydrogen bond.

In the packing of (IIa), two orotic acid molecules are connected to form a centrosymmetric dimer. These dimers are further connected *via* DMSO molecules by N—H \cdots O and O—H \cdots O hydrogen bonds (Table 2) to form chains running in the [1 $\bar{2}$ 0] and [120] directions, respectively (Fig. 5).

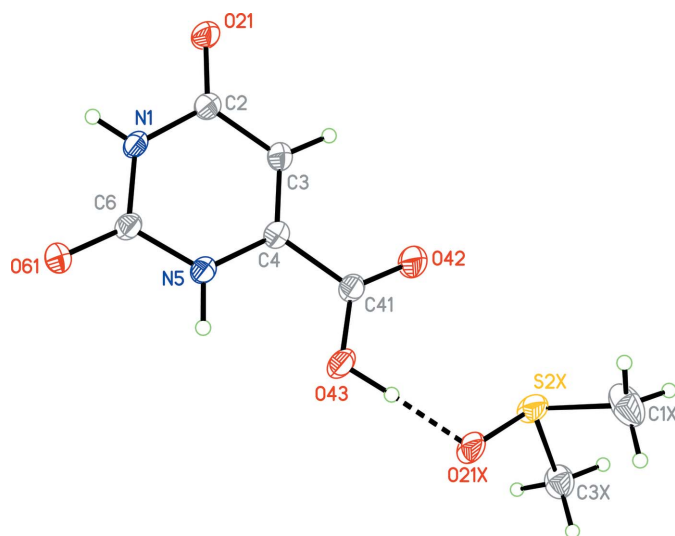
Compound (IIb) crystallizes from dimethylformamide (DMF) in the triclinic space group $P\bar{1}$. Since we did not use a water-free solvent, acidic hydrolysis of DMF, followed by an acid–base reaction with orotic acid, has taken place, resulting in the formation of a dimethylammonium cation (DMC) and an orotate anion. The asymmetric unit of (IIb) contains an orotic acid molecule (*A*) and an orotate anion (*B*), both of which are planar (r.m.s. deviation for all non-H atoms of molecule *A* = 0.054 Å; r.m.s. deviation of all non-H atoms of anion *B* = 0.081 Å), and one DMC cation [angle C1X—N2X—C3X = 113.4 (2)°] (Fig. 6). In the asymmetric unit, molecule *A* and anion *B* are connected through a short O—H \cdots O acid bridge [O \cdots O = 2.482 (3) Å; Table 3], while DMC forms an N—H \cdots O hydrogen bond with anion *B*. Both molecule *A* and anion *B* show slightly twisted acid functionalities, with dihedral angles between the —COO groups and the ring planes [r.m.s. deviations for all non-H atoms of the ring = 0.018 (molecule *A*) and 0.009 Å (anion *B*)] of 6.5 (5)° in molecule *A* and 10.7 (4)° in anion *B*. Moreover, molecule *A* and anion *B*


Figure 3

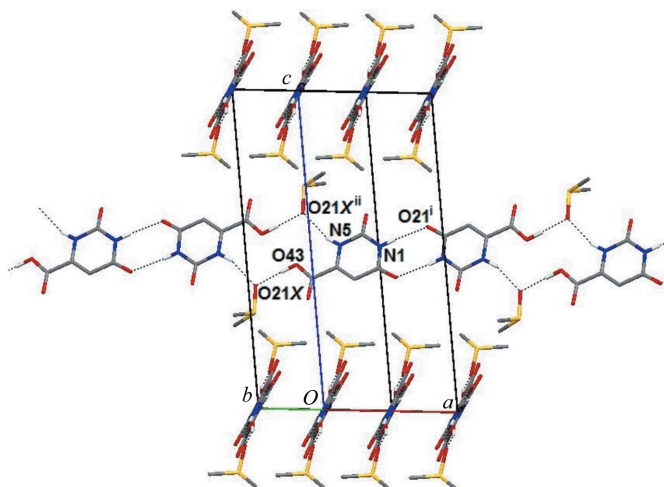
A partial packing diagram for (I), viewed along the *a* axis (red in the electronic version of the paper, pointing into the paper); the *b* axis (in green) points from left to right and the *c* axis (in blue) points downwards. Only H atoms which participate in hydrogen bonds are shown. Dashed lines indicate hydrogen bonds.

are oriented at an angle of $9.25 (5)^\circ$ (for all non-H atoms of *A* and *B*) with respect to each other. Both molecule *A* and anion *B* contain bond lengths of their COO groups which are indicative of double [C41A–O42A = 1.226 (3) Å and C41B–O42B = 1.222 (3) Å] and single bonds [C41A–O43A = 1.281 (3) Å and C41B–O43B = 1.293 (3) Å]. The torsion angle N5A–C4A–C41A–O42A is $-3.9 (3)^\circ$ in molecule *A*, while the corresponding angle in anion *B* is N5B–C4B–C41B–O42B of $9.0 (3)^\circ$. In contrast with (IIa), anion *B* prefers a synperiplanar conformation between atoms N5 and O42 in (IIb).

The crystal packing of (IIb) shows slightly rippled chains (r.m.s deviation of all non-H atoms of the rings = 0.087 Å) of molecules *A* and anions *B*, in turn characterized by an $R_2^2(8)$ pattern of two N–H···O hydrogen bonds and, alternately, one O–H···O interaction. Adjacent chains are connected *via*


Figure 4

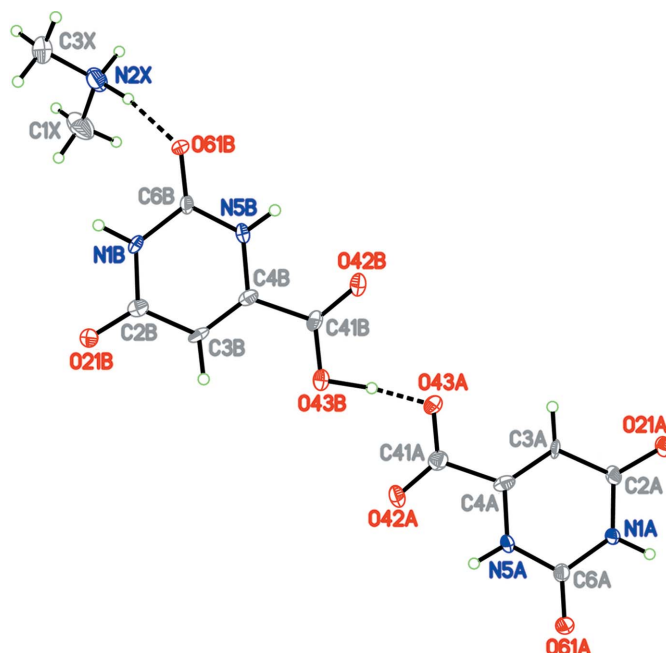
A perspective view of (IIa), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The hydrogen bond is shown as a dashed line.


Figure 5

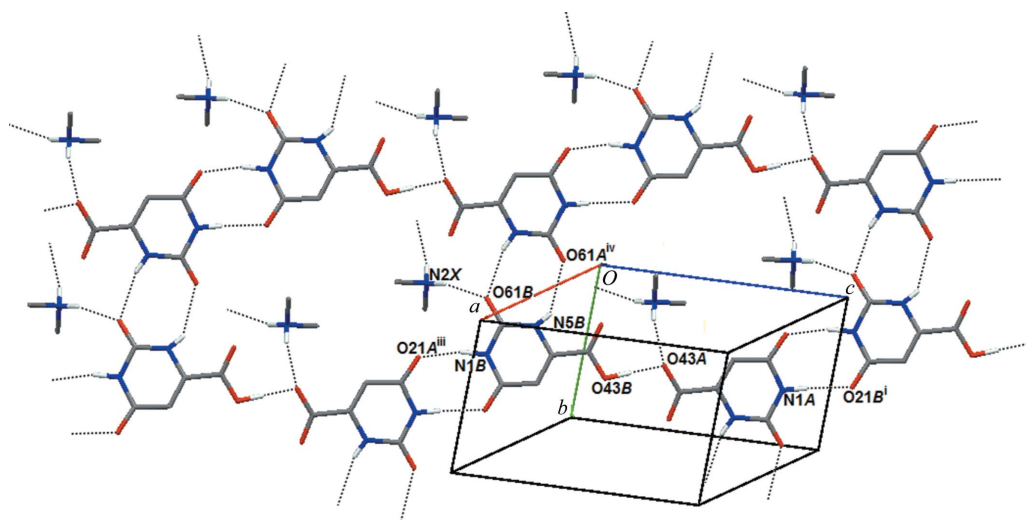
A partial packing diagram for (IIa). Only H atoms which participate in hydrogen bonds are shown. Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $-x + 2, -y - 1, -z + 1$; (ii) $-x + 1, -y + 1, -z + 1$.]

$R_2^2(8)$ patterns of two N–H···O hydrogen bonds, resulting in honeycomb-shaped layers parallel to (111). In addition, the DMC cation connects molecule *A* and anion *B* *via* two N–H···O interactions. Furthermore, ‘double layers’ are formed between adjacent layers by N–H···O interactions between DMC cations and molecules *A* and anions *B*, respectively (Fig. 7).

Dimethylammonium orotate–otrotic acid (3/1), (IIc), crystallizes in the monoclinic space group $P2_1$. As in (IIb), acid hydrolysis of DMF followed by an acid–base reaction with orotic acid has taken place, yielding three DMC cations [C–N–C angles = 112.1 (6) (cation *X*), 113.7 (8) (cation *Y*) and


Figure 6

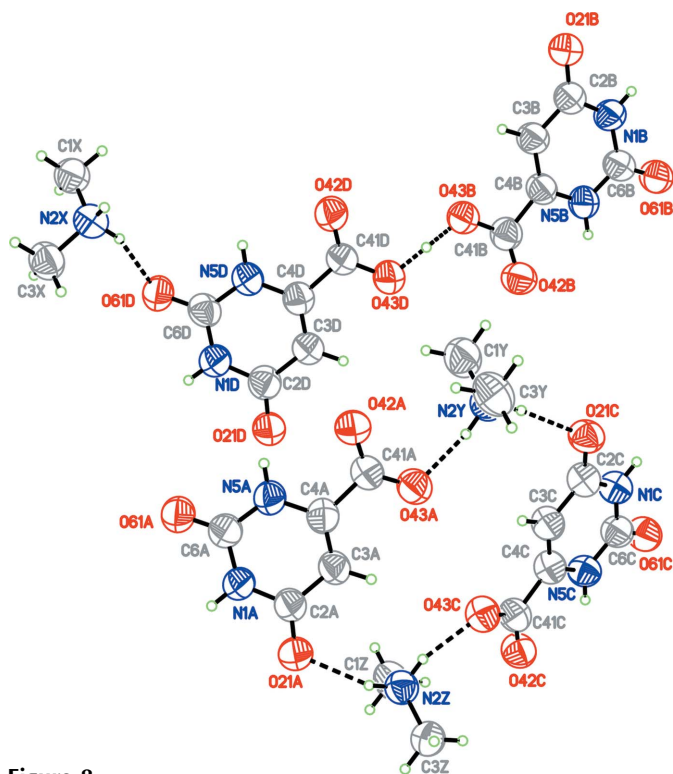
A perspective view of (IIb), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

**Figure 7**

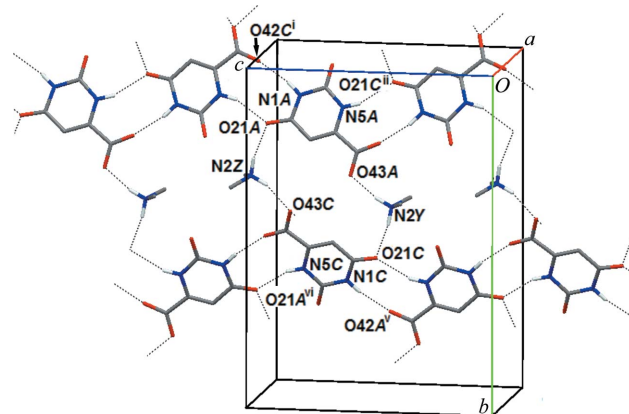
A partial packing diagram for (II*b*). Only H atoms which participate in hydrogen bonds are shown. Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $x - 1, y, z + 1$; (iii) $x + 1, y, z - 1$; (iv) $x, y - 1, z - 1$.]

113.8 (7)° (cation Z)], two orotate anions (*A* and *C*) and, interestingly, two partially deprotonated orotic acid molecules (*B* and *D*), sharing one H atom of the acid function, within the asymmetric unit (Fig. 8). All orotate anions and orotic acid molecules are essentially planar [r.m.s. deviations of all non-H atoms = 0.103 (anion *A*), 0.070 (molecule *B*), 0.027 (anion *C*) and 0.063 Å (molecule *D*)] and contain slightly twisted acid functionalities, with dihedral angles between the COO groups and the ring planes [r.m.s. deviations of all non-H atoms of the

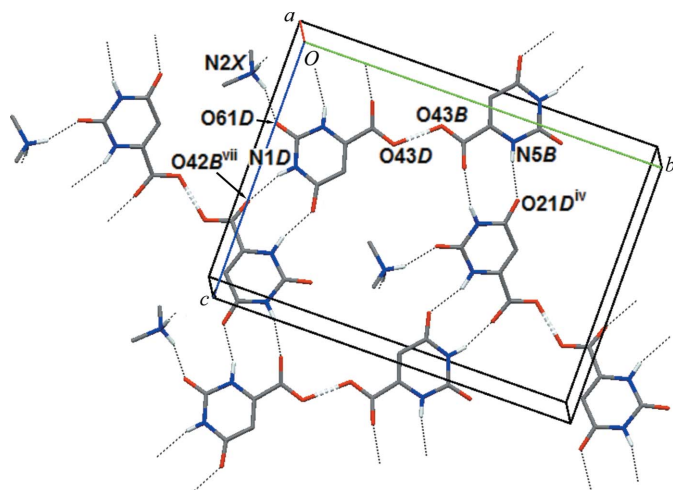
ring = 0.021 (anion *A*), 0.014 (molecule *B*), 0.020 (anion *C*) and 0.017 Å (molecule *D*)] of 13.4 (6)° in *A*, 9.2 (6)° in *B*, 2.9 (7)° in *C* and 7.9 (6)° in *D*. In *A* and *C*, similar bond lengths of both carboxy O atoms indicate delocalized charges [C41*A*–O42*A* = 1.240 (9) Å and C41*A*–O43*A* = 1.258 (9) Å, and C41*C*–O42*C* = 1.248 (9) Å and C41*C*–O43*C* = 1.282 (9) Å], while in *B* and *D* the bond lengths of atoms O42 and O43 are indicative of single [C41*B*–O43*B* = 1.297 (8) Å and C41*D*–O43*D* = 1.294 (8) Å] and double bonds [C41*B*–O42*B* = 1.207 (9) Å and C41*D*–O42*D* = 1.232 (9) Å]. In accordance with (II*b*) and in contrast with (II*a*), molecules *B* and *D* in (II*c*) prefer a synperiplanar conformation between atoms N5 and O42 [N5*B*–C4*B*–C41*B*–O42*B* = 7.9 (11)° and N5*D*–C4*D*–C41*D*–O42*D* = 7.6 (11)°]. In the asymmetric unit, *A* is connected to *C* via two bridging DMC cations (*Y* and *Z*), providing an $R_4^4(18)$ pattern with four N–H...O hydrogen bonds, while the third DMC cation, *X*, interacts with molecule *D* through one N–H...O hydrogen bond. Mol-

**Figure 8**

A perspective view of (II*c*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

**Figure 9**

A partial packing diagram for (II*c*), showing the layer built of entities *A*, *C*, *Y* and *Z*. Only H atoms which participate in hydrogen bonds are shown. Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + 2$; (ii) $-x + 1, y - \frac{1}{2}, -z + 1$; (v) $-x + 1, y + \frac{1}{2}, -z + 1$; (vi) $-x + 1, y + \frac{1}{2}, -z + 2$.]


Figure 10

A partial packing diagram for (IIc), showing the layer built of entities *B*, *D* and *X*. Only H atoms which participate in hydrogen bonds are shown. Hydrogen bonds are drawn as dashed lines. [Symmetry codes: (iv) $-x + 2, y + \frac{1}{2}, -z + 1$; (vii) $-x + 2, y - \frac{1}{2}, -z + 1$.]

ecules *B* and *D* are connected *via* a short O—H...O acid bridge formed between atoms O43*B* and O43*D* [O...O = 2.433 (6) Å; Table 4].

In the crystal packing of (IIc), two different alternating layer structures parallel to (100), built by entities *A*, *C*, *Y* and *Z* in one case and entities *B*, *D* and *X* in the other, can be observed. The former layer structure contains chains of alternating *A* and *C* entities running along [001], characterized by N—H...O hydrogen-bonded $R_2^2(8)$ patterns. In addition, adjacent chains of *A* and *C* entities are connected to form rippled layers (r.m.s deviation of all non-H atoms of the rings of *A* and *C* = 0.487 Å) through DMC cations *Y* and *Z*, providing N—H...O hydrogen-bonded $R_4^4(18)$ patterns and $R_8^6(24)$ interactions of eight N—H...O hydrogen bonds in turn (Fig. 9). In the second case, distorted honeycomb-shaped and slightly rippled layers (r.m.s deviation of all non-H atoms of the rings of entities *B* and *D* = 0.283 Å), which are related to those in (IIb), are observed (Fig. 10). Molecules *B* and *D* are arranged alternately and form hydrogen-bonded chains, characterized by $R_2^2(8)$ N—H...O interactions, running in the direction of the *c* axis. In contrast with (IIb), adjacent chains are linked to form layers by O—H...O interactions involving the short acid bridge. Furthermore, the DMC cations *X* in (IIc) connect both layer structures *via* two N—H...O interactions to form a three-dimensional network, while in (IIb) double layers are formed.

In order to study the preferred conformation of the CH—CH₂—C=O torsion angle in (I) and the N—C—C=O torsion angle in (II), a Cambridge Structural Database (CSD, Version 5.32 of November 2010, plus five updates; Allen, 2002) substructure search for hydantoin derivatives (I) and for orotic acid (II) was undertaken. The search for (I) did not yield comparable structures, while for (II), excluding metal-coordinated orotic acid molecules, four entries containing orotate [CSD refcodes AMOROT (Solbakk, 1971), HOXHEI (Nichol & Clegg, 2009), KEDZEZ (Nichol & Clegg, 2006) and

TUWCOE (Portalone, 2010)] and two entries with orotic acid molecules [OROTAC (Takusagawa & Shimada, 1973) and OROTAC01 (Portalone, 2008)] were found. In addition, a cocrystal of orotate with protonated pyrimethamine has been reported recently by our group (Tutughiamarso & Bolte, 2011). All CSD entries confirm the synperiplanar conformation between the N atom and the carbonyl O atom, as shown in (IIb) and (IIc). This result is in agreement with a DFT calculation (Bekiroglu & Kristiansson, 2002). In contrast, only the antiperiplanar conformation could be observed in (IIa).

Experimental

Solvent evaporation experiments with a racemic mixture of commercially available hydantoin-5-acetic acid (5.2 mg, 0.033 mmol) in H₂O (250 µl) at room temperature yielded crystals of (I). Single crystals of (II) were obtained during crystallization attempts by solvent evaporation with commercially available orotic acid [(IIa): 2.1 mg, 0.014 mmol in DMSO (50 µl) at room temperature; (IIb): 1.7 mg, 0.011 mmol in DMF (150 µl) at room temperature; (IIc): 4.5 mg, 0.029 mmol in DMF (450 µl) at 277 K].

Compound (I)

Crystal data

C₅H₆N₂O₄
M_r = 158.12
 Orthorhombic, *P*2₁2₁2₁
a = 7.6148 (5) Å
b = 8.5592 (6) Å
c = 9.3406 (6) Å

V = 608.79 (7) Å³
Z = 4
 Mo *K*α radiation
 μ = 0.15 mm⁻¹
T = 173 K
 0.50 × 0.10 × 0.10 mm

Data collection

Stoe IPDS II two-circle diffractometer
 10371 measured reflections

692 independent reflections
 607 reflections with *I* > 2σ(*I*)
*R*_{int} = 0.107

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.025$
 $wR(F^2) = 0.055$
S = 0.99
 692 reflections
 113 parameters

H atoms treated by a mixture of independent and constrained refinement
 $\Delta\rho_{\max} = 0.14 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.15 \text{ e \AA}^{-3}$

Compound (IIa)

Crystal data

C₅H₄N₂O₄·C₂H₆O₅
M_r = 234.23
 Monoclinic, *P*2₁/*c*
a = 9.3710 (6) Å
b = 5.9752 (3) Å
c = 17.8433 (13) Å
 β = 97.447 (6)°

V = 990.68 (11) Å³
Z = 4
 Mo *K*α radiation
 μ = 0.33 mm⁻¹
T = 173 K
 0.35 × 0.25 × 0.20 mm

Data collection

Stoe IPDS II two-circle diffractometer
 Absorption correction: multi-scan (MULABS; Blessing, 1995; Spek, 2009)
*T*_{min} = 0.893, *T*_{max} = 0.937

18676 measured reflections
 1865 independent reflections
 1383 reflections with *I* > 2σ(*I*)
*R*_{int} = 0.076

Table 1
Hydrogen-bond geometry (Å, °) for (I).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1...O54 ⁱ	0.86 (3)	2.14 (3)	2.996 (2)	175 (2)
N3—H3...O41 ⁱⁱ	0.91 (3)	1.93 (3)	2.831 (2)	168 (2)
O54—H54...O21 ⁱⁱⁱ	1.02 (4)	1.61 (4)	2.604 (2)	165 (3)

Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$; (iii) $x - 1, y, z$.**Table 2**
Hydrogen-bond geometry (Å, °) for (IIa).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1...O21 ⁱ	0.81 (3)	2.04 (3)	2.846 (2)	175 (2)
N5—H5...O21X ⁱⁱ	0.95 (3)	1.99 (3)	2.912 (2)	164 (2)
O43—H43...O21X	0.98 (3)	1.59 (3)	2.5675 (18)	176 (2)

Symmetry codes: (i) $-x + 2, -y - 1, -z + 1$; (ii) $-x + 1, -y + 1, -z + 1$.**Table 3**
Hydrogen-bond geometry (Å, °) for (IIb).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1A—H1A...O21B ⁱ	0.95 (4)	1.90 (4)	2.836 (3)	172 (3)
N5A—H5A...O61B ⁱⁱ	0.84 (3)	2.12 (3)	2.947 (3)	165 (3)
N1B—H1B...O21A ⁱⁱⁱ	0.88 (3)	1.94 (3)	2.807 (3)	169 (3)
O43B—H43...O43A	1.13 (4)	1.37 (4)	2.482 (3)	167 (4)
N5B—H5B...O61A ^{iv}	0.83 (3)	2.11 (3)	2.931 (3)	169 (3)
N2X—H2X1...O61B	1.06 (5)	1.92 (5)	2.973 (3)	174 (4)
N2X—H2X2...O43A ^v	0.92 (3)	2.11 (3)	2.982 (3)	159 (3)

Symmetry codes: (i) $x - 1, y, z + 1$; (ii) $x, y + 1, z + 1$; (iii) $x + 1, y, z - 1$; (iv) $x, y - 1, z - 1$; (v) $-x + 1, -y, -z$.**Refinement**

$R[F^2 > 2\sigma(F^2)] = 0.032$

$wR(F^2) = 0.072$

$S = 0.91$

1865 reflections

150 parameters

H atoms treated by a mixture of independent and constrained refinement

$\Delta\rho_{\max} = 0.17 \text{ e } \text{Å}^{-3}$

$\Delta\rho_{\min} = -0.32 \text{ e } \text{Å}^{-3}$

Compound (IIb)**Crystal data** $M_r = 357.29$ Triclinic, $P\bar{1}$ $a = 8.111 (1) \text{ Å}$ $b = 8.9503 (11) \text{ Å}$ $c = 11.6804 (15) \text{ Å}$ $\alpha = 112.366 (3)^\circ$ $\beta = 97.263 (2)^\circ$ $\gamma = 104.621 (2)^\circ$ $V = 734.94 (16) \text{ Å}^3$ $Z = 2$ Mo $K\alpha$ radiation $\mu = 0.14 \text{ mm}^{-1}$ $T = 173 \text{ K}$ $0.20 \times 0.20 \times 0.10 \text{ mm}$ **Data collection**

Siemens SMART three-circle diffractometer

4208 measured reflections

2555 independent reflections

1341 reflections with $I > 2\sigma(I)$ $R_{\text{int}} = 0.072$ **Refinement**

$R[F^2 > 2\sigma(F^2)] = 0.061$

$wR(F^2) = 0.104$

$S = 0.86$

2555 reflections

254 parameters

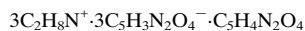
H atoms treated by a mixture of independent and constrained refinement

$\Delta\rho_{\max} = 0.25 \text{ e } \text{Å}^{-3}$

$\Delta\rho_{\min} = -0.30 \text{ e } \text{Å}^{-3}$

Table 4
Hydrogen-bond geometry (Å, °) for (IIc).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1A—H1A...O42C ⁱ	0.88	1.93	2.801 (8)	168
N5A—H5A...O21C ⁱⁱ	0.88	2.11	2.953 (8)	161
N1B—H1B...O42D ⁱⁱⁱ	0.88	1.93	2.790 (8)	165
N5B—H5B...O21D ^{iv}	0.88	1.98	2.837 (8)	163
O43B—H43B...O43D	1.21	1.22	2.433 (6)	179
N1C—H1C...O42A ^v	0.88	1.94	2.805 (8)	167
N5C—H5C...O21A ^{vi}	0.88	2.10	2.936 (8)	159
N1D—H1D...O42B ^{vii}	0.88	1.97	2.817 (8)	160
N5D—H5D...O21B ^{viii}	0.88	2.01	2.852 (8)	160
N2X—H2X1...O43C ⁱⁱ	0.92	1.91	2.805 (9)	164
N2X—H2X2...O61D	0.92	1.88	2.755 (8)	159
N2Y—H2Y1...O43A	0.92	1.79	2.695 (8)	167
N2Y—H2Y2...O21C	0.92	1.90	2.813 (8)	171
N2Z—H2Z1...O43C	0.92	1.88	2.776 (8)	163
N2Z—H2Z2...O21A	0.92	1.99	2.843 (8)	154

Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + 2$; (ii) $-x + 1, y - \frac{1}{2}, -z + 1$; (iii) $-x + 2, y + \frac{1}{2}, -z$; (iv) $-x + 2, y + \frac{1}{2}, -z + 1$; (v) $-x + 1, y + \frac{1}{2}, -z + 1$; (vi) $-x + 1, y + \frac{1}{2}, -z + 2$; (vii) $-x + 2, y - \frac{1}{2}, -z + 1$; (viii) $-x + 2, y - \frac{1}{2}, -z$.**Compound (IIc)****Crystal data** $M_r = 759.67$ Monoclinic, $P2_1$ $a = 7.0176 (14) \text{ Å}$ $b = 18.026 (4) \text{ Å}$ $c = 12.906 (3) \text{ Å}$ $\beta = 94.94 (3)^\circ$ $V = 1626.5 (6) \text{ Å}^3$ $Z = 2$ Mo $K\alpha$ radiation $\mu = 0.13 \text{ mm}^{-1}$ $T = 173 \text{ K}$ $0.18 \times 0.16 \times 0.06 \text{ mm}$ **Data collection**Stoe IPDS II two-circle diffractometer
15886 measured reflections2968 independent reflections
2207 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.091$ **Refinement**

$R[F^2 > 2\sigma(F^2)] = 0.065$

$wR(F^2) = 0.169$

$S = 1.02$

2968 reflections

479 parameters

1 restraint

H-atom parameters constrained

$\Delta\rho_{\max} = 0.30 \text{ e } \text{Å}^{-3}$

$\Delta\rho_{\min} = -0.31 \text{ e } \text{Å}^{-3}$

The H atoms of (I), (IIa) and (IIb) were initially located in difference Fourier syntheses, while in (IIc) the H atom of the carboxyl group between molecules *B* and *D*, and two of the six DMC H atoms, could not be observed. Since both molecules *B* and *D* show bond lengths indicative of single and double bonds, the H atom of the carboxyl group was placed in the middle of the line between the two O atoms, with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O43B})$.

H atoms bonded to C atoms in all structures were refined using a riding model, with methyl C—H = 0.98 Å, secondary C—H = 0.99 Å and aromatic C—H = 0.95 Å, and with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for methyl or $1.2U_{\text{eq}}(\text{C})$ for secondary and aromatic H atoms. In (I), (IIa) and (IIb), H atoms bonded to N and O atoms were refined isotropically, while in (IIc) they were refined using a riding model, with amide N—H = 0.88 Å and protonated N—H = 0.92 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{N})$.

Due to the weak anomalous signals in the racemic mixture of (I) and in (IIc), 452 Friedel pairs for (I) and 2966 Friedel pairs for (IIc) were merged before refinement. The absolute structures of (I) and (IIc) were not determined.

The displacement ellipsoids of (IIc) (Fig. 8) are significantly enlarged, although the data for this compound were definitely collected at 173 K. The only explanation we have for this is that the molecules in the crystals are not perfectly ordered but adopt slightly different positions in different unit cells.

Data collection: *X-AREA* (Stoe & Cie, 2001) for (I), (IIa) and (IIc); *SMART* (Siemens, 1994) for (IIb). Cell refinement: *X-AREA* for (I), (IIa) and (IIc); *SAINT* (Siemens, 1994) for (IIb). Data reduction: *X-AREA* for (I), (IIa) and (IIc); *SAINT* for (IIb). For all compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *Mercury* (Macrae *et al.*, 2008) and *XP* (Sheldrick, 2008); software used to prepare material for publication: *pubCIF* (Westrip, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3419). Services for accessing these data are described at the back of the journal.

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