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ORIGINAL PAPER

Cyclic Imide and Open-Chain Amide Carboxylic Acid Derivatives from the Facile Reaction of *cis*-Cyclohexane-1,2-Dicarboxylic Anhydride with Three Substituted Anilines

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Abstract The structures of the compounds from the reaction of *cis*-cyclohexane-1,2-dicarboxylic anhydride with 4-chloroaniline [*rac*-2-[(4-chlorophenyl)carbamoyl]-*cis*-cyclohexane-1-carboxylic acid] (**1**), 4-bromoaniline [2-(4-bromophenyl)-3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione] (**2**) and 3-carboxy-4-hydoxyaniline (5-aminosalicylic acid) [2-(3-carboxy-4-hydroxyphenyl)- 3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione] (**3**) have been determined at 200 K. Crystals of the open-chain amide carboxylic acid **1** are orthorhombic, space group *Pbcn*, with unit cell dimensions $a = 20.1753(10)$, $b = 8.6267(4)$, $c = 15.9940(9)$ Å, and $Z = 8$. Compounds **2** and **3** are cyclic imides, with **2** monoclinic having space group $P2_1$ and $Z = 4$, with cell dimensions $a = 11.5321(3)$, $b = 6.7095(2)$, $c = 17.2040(5)$ Å, $\beta = 102.527(3)°$. Compound **3** is orthorhombic, space group $P2_12_12_1$ with $Z = 4$ and cell dimensions $a = 6.4642(3)$, $b = 12.8196(5)$, $c = 16.4197(7)$ Å. Molecules of **1** form hydrogen-bonded cyclic carboxylic acid dimers [graph set $R_2^2(8)$] which are extended into a two-dimensional layered structure through amide-group associations: **3** forms into one-dimensional zigzag chains through carboxylic acid-··imide O-atom hydrogen bonds, while compound **2** is essentially unassociated. With both cyclic imides **2** and **3**, disorder is found which involves the presence of partial enantiomeric replacement of the *cis*-1,2-substituted cyclohexane ring systems.

Keywords *cis*-cyclohexane-1,2-dicarboxylic acid · Cyclic imides · Open-chain amide carboxylic acids

Introduction

Cyclohexane-1,2-dicarboxylic anhydride is of interest as a reagent because in its reactions it confers the *cis* configuration [(1*R*,2*S*) or (1*S*,2*R*)] upon the reaction products. With the *cis*-isomer of cyclohexane-1,2-dicarboxylic acid (CHDC), because of the low interconversion potential between these components, unlike the *trans*-isomer [(1*R*,2*R*) or (1*S*,2*S*)], the *dl* enantiomeric pairs are inseparable, forming racemic pairs [1]. The structures of both the racemic and chiral *trans* forms have been determined [2, 3], together with that of the racemic *cis* form [4]. The 1:1 stoichiometric reaction of cyclohexane-1,2-dicarboxylic anhydride with Lewis bases usually gives the racemic hydrogen *cis*-CHDC proton-transfer salts and the structures of a limited number of these have now been determined: the ammonium salt (a dihydrate) [5], the 2-aminopyridinium salt [6], the 4-aminopyridinium salt [7] and the 4-carbamoylpiperidinium salt [8] (all three anhydrous). However, the chiral brucinium salt is also known [9] in which the (1*R*)-carboxylate-(2*S*)-carboxy-*cis*-CHDC species has been captured.

With the substituted anilines, formation of cyclic imides or open-chain amide carboxylic acids may occur, analogous to those formed with phthalic anhydride, (the phthalimides and the phthalanilic acids), often under mild reaction conditions [10]. The structures of the cyclic CHDC imides formed with 5-benzyloxy-2,4-dichloroaniline [11] and with urea [12] were the only ones reported until our recent work [13, 14] provided a number of examples of both cyclic imides and open-chain amide carboxylic acids from the reaction of CHDC anhydride with *X*-monosubstituted anilines (imides:

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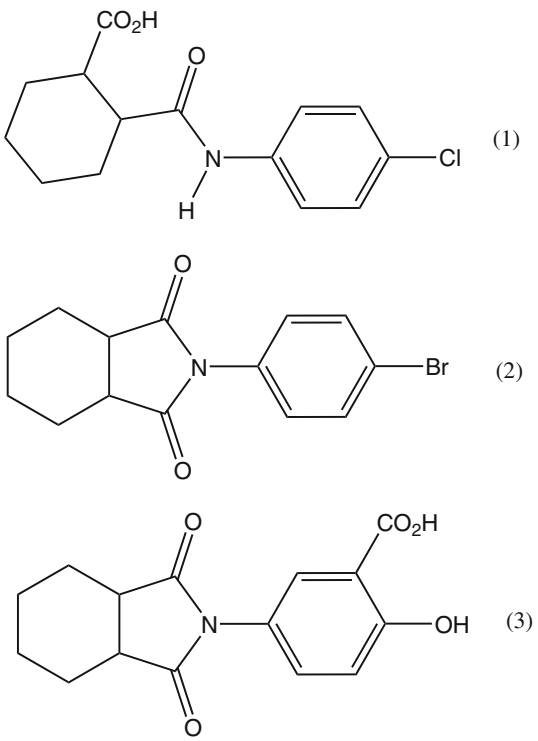
X = *o*-F, *p*-F, *p*-OCH_3, *m*-CO_2H, *p*-CO_2H; amide acids: R = *m*-F, *o*-OCH_3). All products were obtained under mild 1:1 stoichiometric reaction conditions in aqueous ethanolic solutions.

Herein we report the structures of the crystalline products obtained under similar mild reaction conditions from the 1:1 reaction of *cis*-cyclohexane-1,2-dicarboxylic anhydride with 4-chloroaniline, the open-chain amide carboxylic acid [2-[(4-chlorophenyl)carbamoyl]-*cis*-cyclohexane-1-carboxylic acid] (**1**); with 4-bromoaniline [2-(4-bromophenyl)-3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione] (**2**) and with 3-carboxy-4-hydroxyaniline (5-aminosalicylic acid) [2-(3-carboxy-4-hydroxyphenyl)- 3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione] (**3**) (both cyclic imides) (Scheme 1).

Experimental

Preparation

Compounds **1-3** were synthesized by heating together under reflux for 10 min, 1 mmol quantities of *cis*-cyclohexane-1,2-dicarboxylic anhydride and the appropriate aniline (4-chloroaniline for **1**, 4-bromoaniline for **2** and 5-aminosalicylic acid for **3**), in 50 mL of 50 % ethanol–water. After concentration to ca. 30 mL, partial room temperature evaporation of the hot-filtered solutions gave colourless plates of **1** and **2** or pale brown needles of **3** from which specimens were cleaved for the X-ray analyses.



Scheme 1 The compounds **1**, **2** and **3**

Crystallography

X-ray diffraction data for **1**–**3** were acquired at 200(2) K on an Oxford Diffraction Gemini Ultra CCD-detector diffractometer employing graphite crystal monochromatized Mo K_α radiation (λ = 0.71073 Å). Data collection and reduction and absorption correction (multi-scan) were completed using CrysAlis PRO [15]. The structures were solved using direct methods (SIR92 [16]) and refined with SHELXL97 [17] operating within WinGX [18]. Hydrogen atoms potentially involved in hydrogen-bonding interactions for compounds **1** and **3** were located by difference methods but their positional parameters were constrained in the final refinement cycles with thermal parameters riding [U_{iso}(H) = 1.2 U_{eq}(O)]. Other H atoms in all compounds were included in the refinements at calculated positions and treated as riding with C–H = 0.93–0.98 Å and U_{iso}(H) = 1.2 U_{eq}(C). Disorder was identified within the cyclohexane ring in only the B molecule in **2**, resulting from a partial presence of the [C8(*R*),C9(S)] *cis*-enantiomer (C) [site occupancy factor = 0.27(1)] with the larger occupancy [C8(*S*),C9(*R*)] (B) *cis*-enantiomer (S.O.F. = 0.73). The disordered atoms C4C and C7C were subsequently refined isotropically. With **3** the disorder was more extensive, affecting most of the perhydroisoindoline-1,2-dione system, also from partial replacement of the major [C8(*R*),C9(S)] component [S.O.F. = 0.85(1)] by the minor component [C8(*S*),C9(*R*)] (A) [S.O.F. = 0.15(1)], which was also refined isotropically. Absolute configuration of the *cis*-CHDC species in compounds **2** and **3** could not be confirmed from the analyses and with **3**, in the absence of a suitable heavy atom in the structure, Friedel pairs (2868) were merged in the final cycles of refinement. General crystallographic details are given in Table 1. The atom numbering schemes employed for all species are shown in Figs. 1, 2 and 3 [19].

Results and Discussion

In the structure of the racemic open-chain amide carboxylic acid **1** (Fig. 1) the *p*-chlorophenyl ring is rotated slightly out of the plane of the interlinking carboxamide side-chain giving a slight twisting [intra-ring torsion angles C2–C1–C12–N11, C1–C12–N11–C11 and C12–N11–C11–C61: −179.7(2), 173.0(3) and 152.1(3)°, respectively]. Present also is an intramolecular aromatic ring C21–H···O12(ketone) interaction [2.902(3) Å]. The carboxylic acid group is rotated out of the C1–C2–C3 molecular plane of the cyclohexane ring [torsion angle C1–C2–C21–O22, 148.9(2)°]. The 1,2-disubstituted cyclohexane ring as expected has the *cis*-configuration.

Table 1 Crystal data for compounds **1–3**

Compound	**1**	**2**	**3**
CCDC reference	862425	862424	862423
Molecular formula	$C_{14}H_{16}ClNO_3$	$C_{14}H_{14}BrNO_2$	$C_{15}H_{15}NO_5$
M_r	281.73	308.16	289.28
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	*Pbcn*	$P2_1$	$P2_12_12_1$
a (Å)	20.1753(10)	11.5321(3)	6.4642(3)
b (Å)	8.6267(4)	6.7095(2)	12.8196(5)
c (Å)	15.9940(9)	17.2040(5)	16.4197(7)
β (°)	90	102.527(3)	90
V (Å^3)	2783.7(2)	1299.46(7)	1360.68(10)
Z	8	4	4
D_c (g cm^{-3})	1.344	1.568	1.412
μ (mm^{-1})	0.278	3.156	0.107
F(000)	1,184	1,288	608
Reflections total, θ_{max} (°)	9279, 26.0	9056, 26.0	5237, 28.9
Crystal size (mm)	0.38 × 0.22 × 0.10	0.40 × 0.30 × 0.05	0.35 × 0.10 × 0.08
Collection range			
h	−15 to 24	−11 to 14	−5 to 8
k	−10 to 6	−8 to 8	−16 to 16
l	−12 to 19	−21 to 21	−20 to 17
Reflections (independent)	2735	5041	1818
Reflections [$F^2 > 2\ \sigma(F^2)$]	1616	3774	1624
R_{int}	0.0527	0.0236	0.0264
$R1$[a] [$F^2 > 2\sigma(F^2)$]	0.0609	0.0299	0.0433
$wR2$[a] (all data)	0.1412	0.0513	0.1011
S[a]	0.94	0.83	1.10
n_p	172	333	222
Residuals (max/min) (eÅ^{-3})	0.299/−0.222	0.400/−0.370	0.175/−0.173
Transmission factors (max/min)	0.880/0.980	0.714/0.980	0.969/0.990

[a] $R1 = (\Sigma\ |F_o| - |F_c|)/\Sigma\ |F_o|)$; $wR2 = \{\Sigma\ [w(F_o^2 - F_c^2)^2]/\Sigma\ [w(F_o^2)^2]\}^{1/2}$; $S = \{\Sigma\ [w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$

In the crystal packing the carboxylic acid group forms classic centrosymmetric head-to-head cyclic intermolecular hydrogen-bonding associations [graph set $R_2^2(8)$] [20] [O21–H···O22, 2.662(3) Å: symmetry code (ii) $-x + 1$, $-y + 1$, $-z + 1$], the dimers formed being extended into a two-dimensional sheet structure through amide N11–H···O12^{ii}(ketone) hydrogen bonds [2.862(3) Å: symmetry code (i) $-x + 1$, $y - ½$, z] (Fig. 2). This structure is similar to that of the analogous compound *N*-(4-chlorophenyl)phthalanilic acid [21].

The two *cis*-cyclic imides **2** and **3** show many structural similarities.

Both compounds are conformationally similar with variations resulting from ring rotations about the imine N–C(phenyl) bond, as indicated by the minimum C–N2–C–C torsion angles of 49.8(4)° and −61.1(4)° for the two independent molecules in **2** and −65.7(3)° in **3**. A common feature of both **1** and **2** is the conformational stress within the cyclohexane ring system as indicated by the relatively higher thermal activities observed in the constituent carbon atoms, resulting in disorder which is more extreme in **3**. This activity has also been present in other examples of cyclic imides of this series [13, 14] but not to the extent observed in **2** and **3**.

With compound **2**, there are two independent cyclic imide molecules (A and B) in the asymmetric unit (Figs. 3, 4). In both of these, the *cis*-configuration is present as expected, with ordered A having a [C8A(*R*),C9A(*S*)] assignment and the major component of the B molecule, [C8B(*S*),C9B(*R*)], with the minor (C) component [C8C(*R*),C9C(*S*)], A and B representing a partial racemic pair. With the molecule B, there is significant disorder in most of the atoms of the cyclohexane ring, with atoms C4B and C7B [site occupancy factor = 0.73(1)] having alternative 'flipped' chair conformational sites [C4C and C7C: S.O.F. = 0.27(1)], C having the [C8(*R*),C9(*S*)] configuration. The two ring systems are

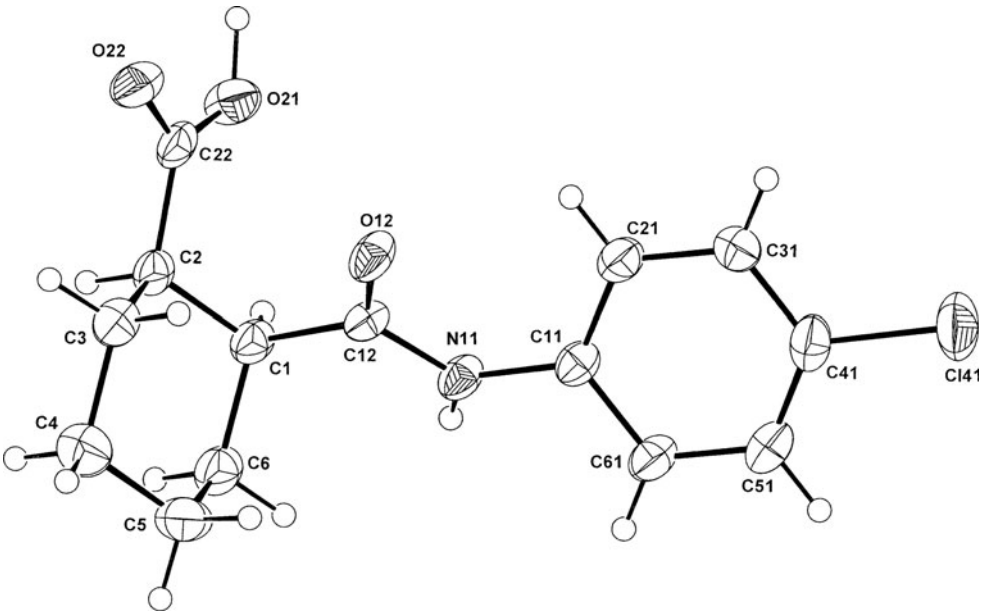


Fig. 1 Atom numbering scheme for **1**, with non-hydrogen atoms shown as 40 % probability ellipsoids [15]

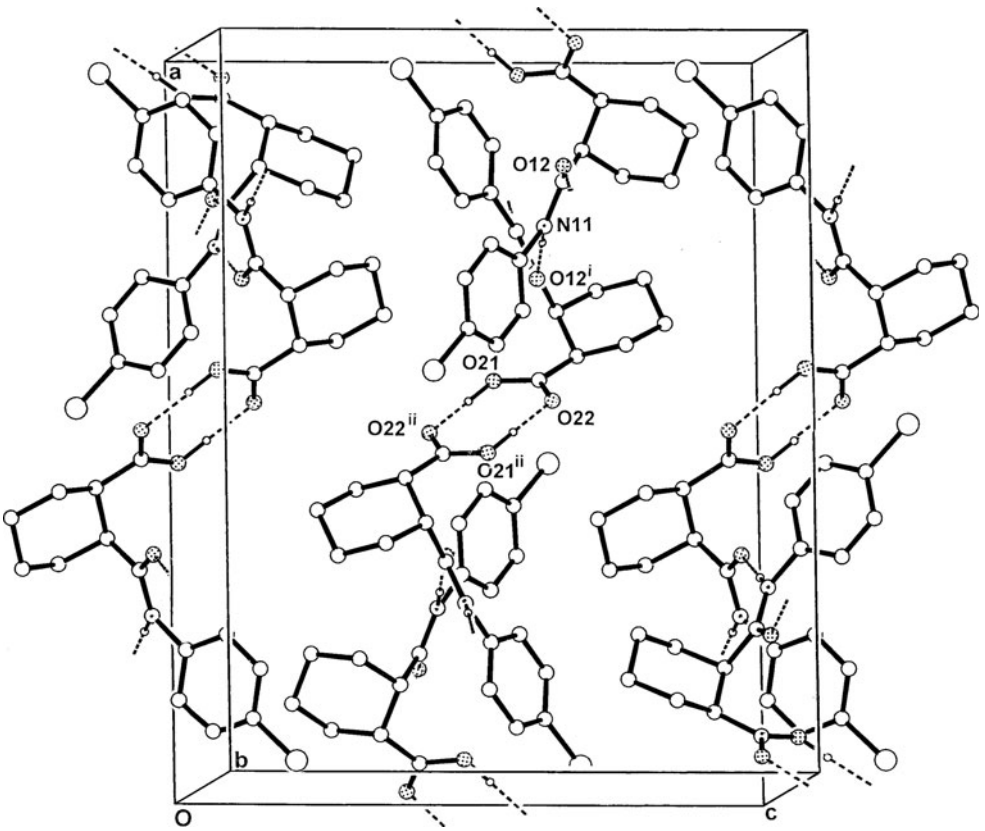


Fig. 2 The hydrogen-bonded chain structures in **1** showing the head-to-head cyclic dimeric carboxylic acid hydrogen-bonding associations and the extension through N–H···O hydrogen bonds. Non-associative H-atoms are omitted

also different with respect to the rotation about the N–C(phenyl) bond as indicated previously and both this and the disorder are therefore responsible for the presence of the two independent pseudo-racemic molecules in the $P2_1$ asymmetric unit rather than forming the common centrosymmetrically related racemic pairs found in most examples [13, 14].

There are only minor intermolecular aromatic C–H···O interactions in the crystal structure [C21B–H···O1B^{i}, 3.153(4) Å, and C61A–H···O3A^{ii}, 3.058(3) Å; symmetry codes: (i) x, $y - 1$, z; (ii) x, $y + 1$, z].

The cyclic imide **3** also has disorder in the cyclohexane moiety of the molecule which is more extensive than in **2**,

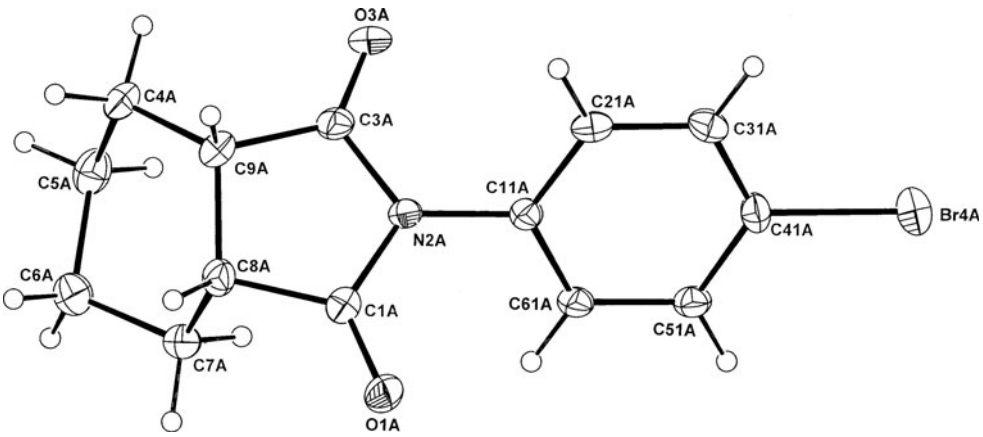


Fig. 3 The ordered (*A*) molecule in the asymmetric unit of **2**, showing 40 % probability ellipsoids

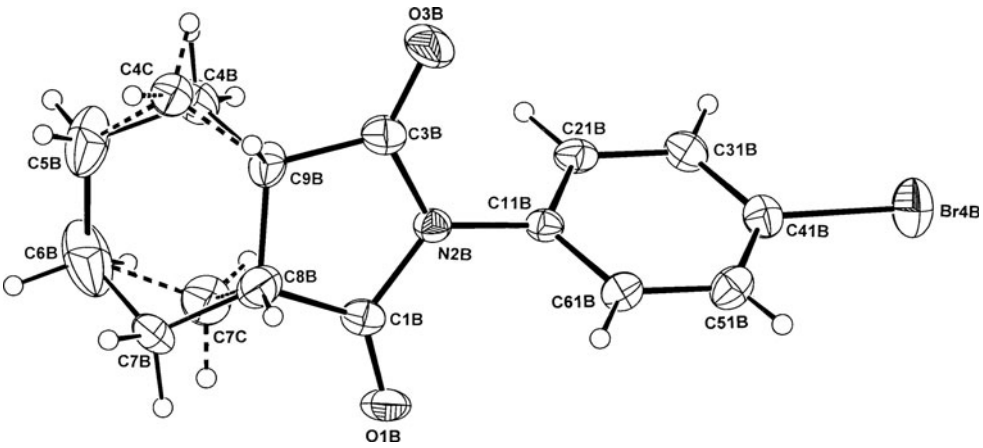


Fig. 4 The partially disordered (*B*) molecule in the asymmetric unit of **2**, showing 30 % probability ellipsoids

involving most of the perhydroisoindole-1,3-dione atoms (Fig. 5). Both components have the *cis*-configuration with the major component [site occupancy factor = 0.85(1) having a slightly distorted chair conformation while the minor component adopts a more distorted chair conformation. The minimum torsion angle between the benzene ring and the isoindoline ring (C21–C11–N1–C1) is −65.7(3)°, while the carboxylic acid group is essentially coplanar with the benzene ring [torsion angle C21–C31–C311–O32, 175.2(2)°]. This conformation is maintained by an intramolecular hydrogen bond between the hydroxyl and carboxyl groups [O41–H···O32, 2.603(3)°; O–H···O angle 138°], which is similar to that found in the parent salicylic acid [22].

In the crystal packing (Fig. 6), the molecules form one-dimensional zigzag chains through intermolecular carboxylic

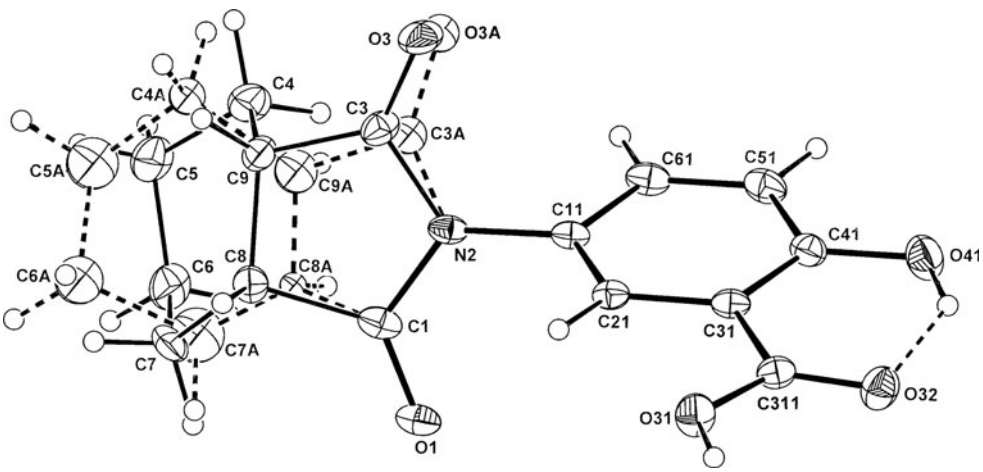


Fig. 5 The molecular conformation and atom numbering scheme for the disordered molecule of **3**, showing 30 % probability ellipsoids

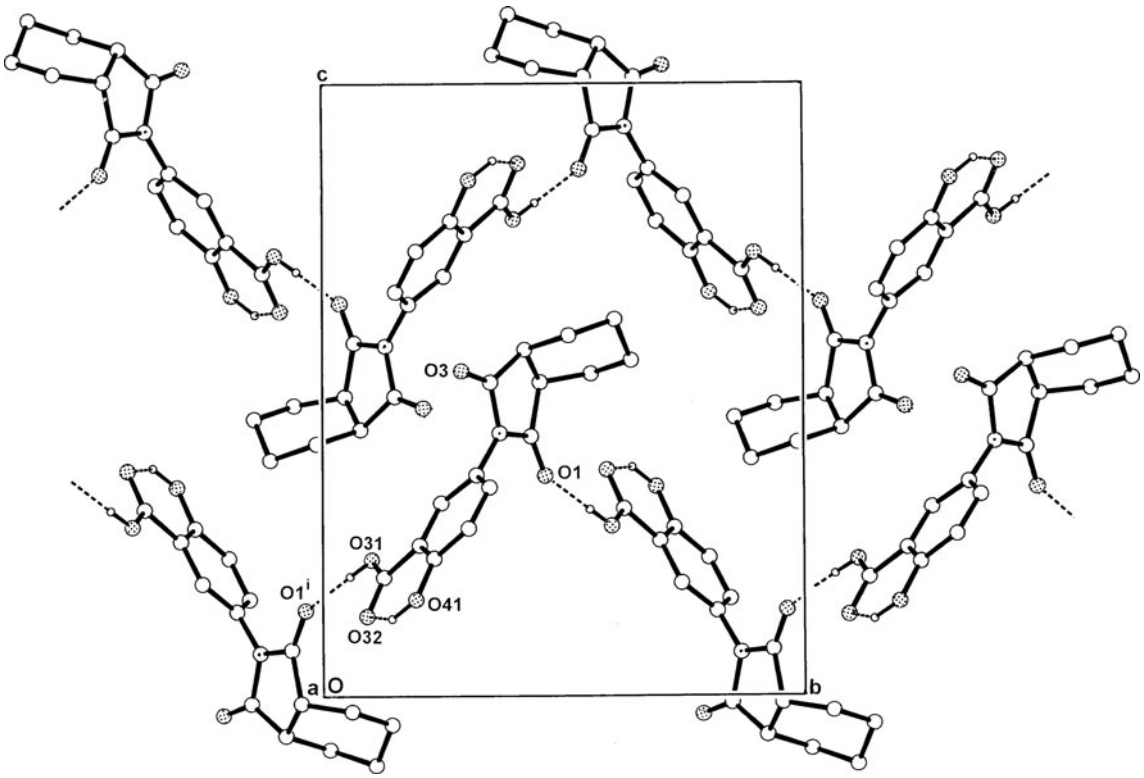


Fig. 6 A perspective view of **3** in the unit cell viewed down the *a* axial direction. The minor disordered component (*A*) of the hexahydroisoindole ring system and non-associative H-atoms are omitted

acid O–H···O(isoindoline) hydrogen bonds [O31–H···O1^{i}, 2.707(3) Å: O–H···O angle 179°: symmetry code (i) $-x$, $y - ½$, $-z + ½$]. These chains extend across the *b* cell direction in the unit cell.

Conclusion

This work provides further examples of the structures of cyclic imides and open-chain amide carboxylic acids from the facile reaction of *cis*-cyclohexane-1,2-dicarboxylic anhydride with substituted anilines. Within this relatively small set of known structures (currently 11 examples, including **1**–**3**), there is a much higher incidence of cyclic imides (8) compared to amide acids (3). However, functional group influence upon which form is preferred is not apparent from the examples structurally characterized in this and previous work with this series of compounds.

Supplementary material

CCDC entries 862423, 862424 and 862425 contain the supplementary crystallographic data for compounds **3**, **2** and **1**, respectively, from this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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