Cyclic imides and an open-chain amide carboxylic acid from the facile reaction of cis-cyclohexane-1,2-carboxylic anhydride with the isomeric monofluoroanilines

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The structures of the cyclic imides cis-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione, $C_{14}H_{14}FNO_2$, (I), and cis-2-(4-fluorophenyl)-3a,4,5,6,7,7a-hexahydroisoindoline-1,3-dione, $C_{14}H_{14}FNO_2$, (III), and the open-chain amide acid rac-cis-2-[(3-fluorophenyl)carbamoyl]cyclohexane-1-carboxylic acid, $C_{14}H_{16}FNO_3$, (II), are reported. Cyclic imides (I) and (III) are conformationally similar, with comparable ring rotations about the imide N—C_{ar} bond [the dihedral angles between the benzene ring and the five-membered isoindole ring are 55.40 (8)° for (I) and 51.83 (7)° for (III)]. There are no formal intermolecular hydrogen bonds involved in the crystal packing of either (I) or (III). With the acid (II), in which the meta-related F-atom substituent is rotationally disordered (0.784:0.216), the amide group lies slightly out of the benzene plane [the interplanar dihedral angle is 39.7 (1)°]. Intermolecular amide–carboxyl N—H···O hydrogen-bonding interactions between centrosymmetrically related molecules form stacks extending down b, and these are linked across c by carboxyl–amide O—H···O hydrogen bonds, giving two-dimensional layered structures which lie in the (011) plane. The structures reported here represent examples of compounds analogous to the phthalimides or phthalanilic acids and have little precedence in the crystallographic literature.

Comment

cis-Cyclohexane-1,2-dicarboxylic acid (cis-CHDC) is of interest because, unlike the trans isomer which forms separable DL pairs, it exists as an unresolvable racemic mixture of (1R,2S) and (1S,2R) enantiomeric components (Eliel, 1962). This situation arises because of the low interconversion potential between these components, resulting in racemization. The 1:1 stoichiometric reaction of cyclohexane-1,2-dicarboxylic anhydride (cis-CHDC anhydride, which has the cis configuration) with Lewis bases usually gives the hydrogen cis-CHDC

proton-transfer salts, and the structures of a limited number of these have been determined: the racemic ammonium salt (a dihydrate; Smith & Wermuth, 2011a), the isomeric racemic anhydrous 2-aminopyridinium (Smith & Wermuth, 2011b) and 4-aminopyridinium salts (Smith & Wermuth, 2011d), and the chiral brucinium salt [a dihydrate in which the (1R)-carboxylate (2S)-carboxy cis-CHDC species has been captured; Smith et al., 2012]. The structure of the 1:1 adducts of cis-CHDC with 4,4′-bipyridine (Bhogala et al., 2005) and with isoquinoline (Smith & Wermuth, 2011c) are also known.

(I)

(II)

(III)
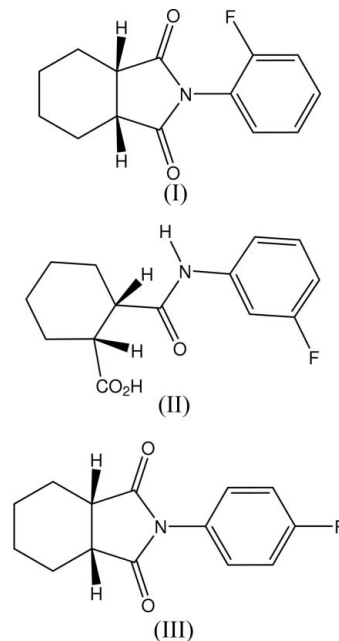
However, with certain bases, particularly the anilines, but including urea, formation of amide carboxylates or cyclic imides may occur, analogous to those formed with phthalic anhydride, the phthalimides and the phthalanilic acids. The mechanism for the formation of the cyclic imide from the amide carboxylic acid via the loss of a mole of water has been proposed and the reaction has been found to proceed efficiently in the presence of acetic acid (Perry & Parveen, 2001). Commonly, the N-substituted hexahydroisoindoline-1,3-diones were prepared from the reaction of the primary amine with cis-CHDC anhydride using a condensation reaction promoted by hexamethyldisilazine (HMDS) (Reddy et al., 1997). However, occasionally the reaction may proceed in a facile manner, e.g. in the case of phthalic anhydride with certain anilines (giving either a phthalanilic acid or the cyclic phthalimide), or cis-CHDC anhydride with the aniline or urea. The structures of the cis-CHDC cyclic imides with 5-benzyl-oxy-2,4-dichloroaniline (Wang et al., 2005) or with urea (Wang et al., 2007) represent the only reported examples and in these the configuration is naturally racemic cis-(R,S) or -(S,R). With the cis-CHDC amide acids, there is only one example in the crystallographic literature, an unusual diastereoisomeric amide formed with phenylethylamine (Takahashi et al., 2003). Another unusual structure is the asymmetric imide carboxylic
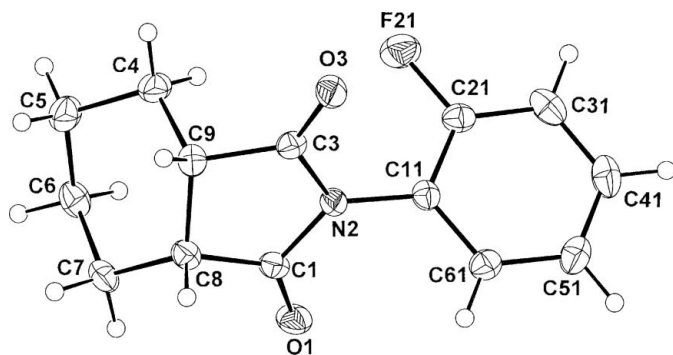
organic compounds

Figure 1
The molecular conformation and atom-numbering scheme for (I). Displacement ellipsoids are drawn at the 40% probability level.

Figure 3
The molecular conformation and atom-numbering scheme for (III). Displacement ellipsoids are drawn at the 40% probability level.

acid *cis*-2-(3-oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-yl)cyclohexane-1-carboxylic acid monohydrate, formed in the self-condensation of *cis*-CHDC anhydride with triethylamine (Newman *et al.*, 2000).

Our 1:1 reaction of a series of substituted anilines with *cis*-CHDC anhydride under mild reaction conditions in a 50% ethanol–water solution yielded, in some cases, both cyclic imides and amide acids, and those formed with the isomeric monofluoroanilins are reported here. With the 2- and 4-fluoroanilines, the isomeric cyclic imides *cis*-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione, (I), and *cis*-2-(4-fluorophenyl)-3a,4,5,6,7,7a-hexahydroisoindole-1,3-dione, (III), were formed, respectively, while with 3-fluoroaniline, *rac-cis*-[2-(3-fluorophenyl)carbamoyl]cyclohexane-1-carboxylic acid, (II), was obtained. The molecular structures of compounds (I)–(III) are shown in Figs. 1–3.

The two racemic cyclic imides, (I) and (III) (Figs. 1 and 3), from 2- and 4-fluoroanilins, respectively, show many structural similarities. Both are conformationally similar and have their five-membered isoindole ring systems distorted, with maximum deviations from planarity for either atom C8 or C9 of 0.152 (1) Å in (I) and 0.149 (1) Å in (III). There are also comparable benzene-ring rotations about the imide N—C_{ar} bond, as indicated by the dihedral angles of 55.40 (8)° in (I) and 51.83 (7)° in (III) between the benzene and isoindole

rings. Another feature common to both molecules is the strain within the cyclohexane ring system, which is indicated by the large displacement parameters observed for the constituent C atoms. This has also been observed in other examples of cyclic imides of this series and is at its most extreme in the 4-bromo derivative (Smith & Wermuth, 2012), in which two independent and conformationally different molecules constitute the asymmetric unit contents, one with the cyclohexane ring ordered and the other with it disordered, partial replacement of the (1*R*,2*S*)-substituted cyclohexane enantiomer by the (1*S*,2*R*) component having taken place. In the crystal packing of the two title imides, only weak aromatic C—H···O hydrogen-bonding interactions are found (Tables 1 and 3).

With the *cis*-amide carboxylic acid, (II) (Fig. 2), the benzene ring is rotationally disordered, with atom F31 on C31 [site-occupancy factor = 0.784 (4)] related to the minor component F51 on C51 [site-occupancy factor = 0.216 (4)]. The aminocarbonyl group defined by atoms C1/C12/O12/N11 is rotated out of the benzene plane [torsion angle C21—C11—N11—C12 = 42.1 (3)°], corresponding to a dihedral angle of 39.7 (1)° between these planes. The axially located carboxylic acid group is close to being coplanar with the C1—C2 bond of the cyclohexane ring [torsion angle C1—C2—C22—O21 =
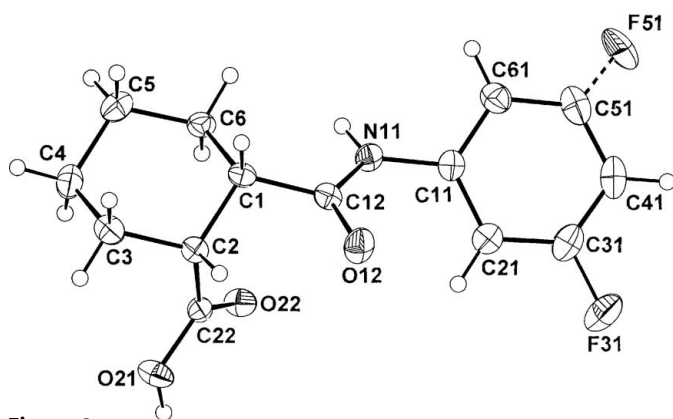

Figure 2
The molecular configuration and atom-numbering scheme for (II). Atom F51 is the minor component of the rotationally related disordered atom F31. Displacement ellipsoids are drawn at the 40% probability level.
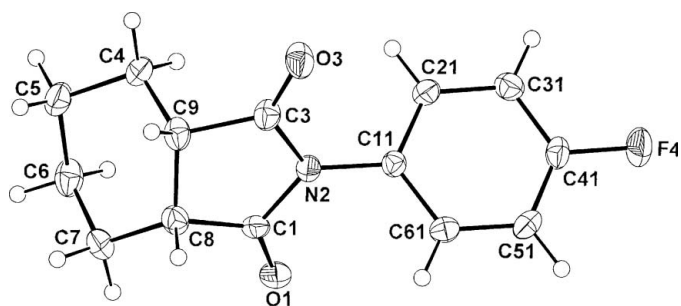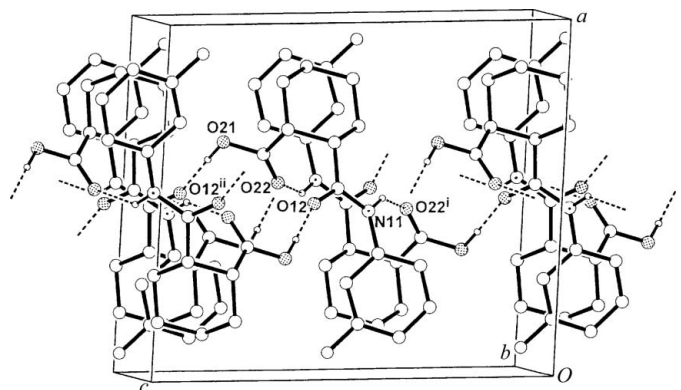

Figure 4
The two-dimensional hydrogen-bonded structure in (II), viewed down the *b*-cell direction of the unit cell, showing hydrogen-bonding interactions as dashed lines. Non-associative H atoms have been omitted, together with the minor-occupancy atom F51. Symmetry codes are as in Table 2.

$-176.93\ (14)°$]. In the crystal structure of (II), the molecules lie along the approximate a cell direction and form stacks down b through centrosymmetrically alternating molecular associations, and are linked by intermolecular amide–carboxyl N—H···O hydrogen bonds (Table 2). Lateral carboxyl–amide O—H···O hydrogen bonds link the stacks across c, giving a two-dimensional sheet structure extending along the (011) planes in the unit cell (Fig. 4).

The structures reported herein represent examples of two possible products, either amide carboxylic acids or cyclic imides, from the facile 1:1 stoichiometric reaction of *cis*-cyclohexane-1,2-dicarboxylic anhydride with substituted anilines, and have few analogues reported in the crystallographic literature.

Experimental

The title compounds were synthesized by heating together under reflux for 15 min cyclohexane-1,2-dicarboxylic anhydride (1 mmol) and, respectively, 2-, 3- or 4-fluoroaniline (1 mmol) in ethanol–water (50 ml, 1:1 v/v). After reducing the volume to 30 ml, the solutions were filtered while hot and allowed to evaporate to incipient dryness at room temperature over a period of several weeks, giving either colourless plates [for (I) and (II)] or prisms [for (III)] from which specimens were cleaved for the X-ray analyses.

Compound (I)

Crystal data

$C_{14}H_{14}FNO_2$	$\gamma = 97.260\ (4)°$
$M_r = 247.26$	$V = 590.86\ (5)\ \text{Å}^3$
Triclinic, $P\bar{1}$	$Z = 2$
$a = 8.0316\ (4)\ \text{Å}$	Mo $K\alpha$ radiation
$b = 8.1702\ (4)\ \text{Å}$	$\mu = 0.10\ \text{mm}^{-1}$
$c = 9.2085\ (5)\ \text{Å}$	$T = 200\ \text{K}$
$\alpha = 98.595\ (4)°$	$0.40 \times 0.30 \times 0.25$ mm
$\beta = 93.324\ (4)°$	

Data collection

Oxford Gemini-S CCD area-detector diffractometer	7051 measured reflections
	2305 independent reflections
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2010)	1783 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.022$
$T_{min} = 0.969$, $T_{max} = 0.989$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	163 parameters
$wR(F^2) = 0.098$	H-atom parameters constrained
$S = 1.08$	$\Delta\rho_{max} = 0.24$ e Å^{-3}
2305 reflections	$\Delta\rho_{min} = -0.20$ e Å^{-3}

Compound (II)

Crystal data

$C_{14}H_{16}FNO_3$	$V = 1275.29\ (16)\ \text{Å}^3$
$M_r = 265.28$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 11.3688\ (8)\ \text{Å}$	$\mu = 0.11\ \text{mm}^{-1}$
$b = 8.7802\ (6)\ \text{Å}$	$T = 200\ \text{K}$
$c = 12.7989\ (10)\ \text{Å}$	$0.45 \times 0.40 \times 0.05$ mm
$\beta = 93.436\ (7)°$	

Table 1
Weak interaction geometry (Å, °) for (I).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
C31—H31···O1[i]	0.93	2.56	3.3589 (18)	144
C51—H51···O3[ii]	0.93	2.57	3.4064 (18)	150

Symmetry codes: (i) $-x + 1, -y + 1, -z + 2$; (ii) $x - 1, y, z$.

Table 2
Hydrogen-bond and weak interaction geometry (Å, °) for (II).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
N11—H11···O22[i]	0.839 (18)	2.281 (18)	2.967 (2)	139.1 (15)
O21—H22···O12[ii]	0.92 (3)	1.69 (2)	2.613 (2)	176 (2)
C3—H3A···O21	0.97	2.49	2.847 (2)	102
C21—H21···O12	0.93	2.50	2.891 (2)	106

Symmetry codes: (i) $-x + 1, -y + 1, -z + 1$; (ii) $-x + 1, y + \frac{1}{2}, -z + \frac{3}{2}$.

Data collection

Oxford Gemini-S CCD area-detector diffractometer	8075 measured reflections
	2499 independent reflections
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2010)	1530 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.051$
$T_{min} = 0.881$, $T_{max} = 0.980$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.092$	
$S = 0.86$	
2499 reflections	$\Delta\rho_{max} = 0.18$ e Å^{-3}
190 parameters	$\Delta\rho_{min} = -0.16$ e Å^{-3}

Compound (III)

Crystal data

$C_{14}H_{14}FNO_2$	$V = 1203.59\ (6)\ \text{Å}^3$
$M_r = 247.26$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 10.7554\ (3)\ \text{Å}$	$\mu = 0.10\ \text{mm}^{-1}$
$b = 6.6709\ (2)\ \text{Å}$	$T = 200\ \text{K}$
$c = 16.8466\ (4)\ \text{Å}$	$0.45 \times 0.40 \times 0.35$ mm
$\beta = 95.275\ (3)°$	

Data collection

Oxford Gemini-S CCD area-detector diffractometer	7621 measured reflections
	2362 independent reflections
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2010)	1826 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.023$
$T_{min} = 0.960$, $T_{max} = 0.990$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	163 parameters
$wR(F^2) = 0.091$	H-atom parameters constrained
$S = 1.03$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
2362 reflections	$\Delta\rho_{min} = -0.21$ e Å^{-3}

The H atoms involved in hydrogen-bonding interactions in (II) (H11 and H22) were located by difference methods and their positional and isotropic displacement parameters were refined. The other H atoms in all three structures were included in the respective

refinements at calculated positions (C—H = 0.93–0.97 Å), with $U_{iso}(H) = 1.2U_{eq}(C)$, using a riding-model approximation. For (II), atom F31 was found to be disordered, having a rotationally related component F51 [site-occupancy factors for F31 and F51 refined to 0.784 (4) and 0.216 (4), respectively].

For all three compounds, data collection: *CrysAlis PRO* (Oxford Diffraction, 2010); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008) within *WinGX* (Farrugia, 1999); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3250). Services for accessing these data are described at the back of the journal.

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Table 3
Weak interaction geometry (Å, °) for (III).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C21—H21$\cdots$O1^i	0.93	2.49	3.1151 (16)	125
C51—H51$\cdots$O3^{ii}	0.93	2.51	3.3728 (17)	155

Symmetry codes: (i) $x, y + 1, z$; (ii) $-x + \frac{3}{2}, y - \frac{1}{2}, -z + \frac{1}{2}$.

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