Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Crystallographic characterization of the first reported crystalline form of the potent hallucinogen (*R*)-2-amino-1-(8-bromobenzo[1,2-*b*;5,4-*b*′]difuran-4-yl)propane or 'bromodragonfly': the 1:1 anhydrous proton-transfer compound with 3,5-dinitrosalicylic acid

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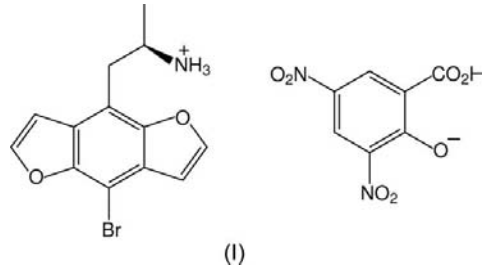
Received 28 February 2010
Accepted 7 April 2010
Online 15 April 2010

The 1:1 proton-transfer compound of the potent substituted amphetamine hallucinogen (*R*)-2-amino-1-(8-bromobenzo-[1,2-*b*;5,4-*b*′]difuran-4-yl)propane (common trivial name 'bromodragonfly') with 3,5-dinitrosalicylic acid, namely 1-(8-bromobenzo[1,2-*b*;5,4-*b*′]difuran-4-yl)propan-2-aminium 2-carboxy-4,6-dinitrophenolate, $C_{13}H_{13}BrNO_2^+\cdot C_7H_3N_2O_7^-$, forms hydrogen-bonded cation–anion chain substructures comprising undulating head-to-tail anion chains formed through $C(8)$ carboxyl–nitro O—H···O associations and incorporating the aminium groups of the cations. The intrachain cation–anion hydrogen-bonding associations feature proximal cyclic $R_3^3(8)$ interactions involving both an N^+—H···$O_{phenolate}$ and the carboxyl–nitro O—H···O associations and aromatic π–π ring interactions [minimum ring centroid separation = 3.566 (2) Å]. A lateral hydrogen-bonding interaction between the third aminium H atom and a carboxyl O-atom acceptor links the chain substructures, giving a two-dimensional sheet structure. This determination represents the first of any form of this compound and is in the (*R*) absolute configuration. The atypical crystal stability is attributed both to the hydrogen-bonded chain substructures provided by the anions, which accommodate the aminium proton-donor groups of the cations and give crosslinking, and to the presence of the cation–anion aromatic ring π–π interactions.

Comment

The bromo-substituted difuran amphetamine derivative 2-amino-1-(8-bromobenzo[1,2-*b*;4,5-*b*′]difuran-4-yl)propane (BDF), with the common trivial name of 'bromodragonfly' due to its visual molecular configuration, was first synthesized in the racemic form by the Nichols group (Parker *et al.*, 1998), who described it as a potent hallucinogen with an activity significantly enhanced compared with that of LSD (D-lysergic acid *N*,*N*-diethylamide). It is in fact the first compound with LSD activity having an aromatic nucleus other than benzene or indole and is recognized as the most potent known ligand for agonist binding to both the serotonin 5-HT_{2A} and 5-HT_{2C} receptors (5-HT is 5-hydroxytryptamine) (Chambers *et al.*, 2001). With amphetamines generally, the (*R*)-enantiomer is the most physiologically active form with respect to hallucinogenic activity, whereas the (*S*)-form is more active as a central nervous system (CNS) stimulant (Hardman *et al.*, 1996). Both the (*R*)- and the (*S*)-enantiomers of BDF have subsequently been synthesized and their relative physiological activities tested, also by the Nichols group (Chambers *et al.*, 2001). It is therefore remarkable, considering the physiological activity of this compound, that it is not currently on the list of restricted substances in many countries. This is despite the detection of this enantiopure (*R*) compound in a number of commercial products, *e.g.* speciality paints and paint materials imported into Australia. The enantiopure BDF was isolated without resolution from such products as part of this determination (Cotton *et al.*, 2008) and the reason for its presence in them can only be speculated upon.



(I)

Although the crystal structures of amphetamine and a number of variously ring-substituted analogues, in particular the 2,5-dimethoxy-substituted amphetamines, have been determined (*e.g.* *rac*-4-ethyl-2,5-dimethoxyamphetamine; Kennard *et al.*, 1974), no structures of the bis-furan-substituted types are known. With the bromo analogues, the bis-furan derivatives exhibit enhanced physiological activity compared with the dimethoxy derivatives (Chambers *et al.*, 2001). The problem with BDF has been that of obtaining crystalline samples suitable for X-ray analysis. From a number of preparations of salts of BDF with carboxylic acids, we obtained suitable crystals with only one, the relatively strong 3,5-dinitrosalicylic acid (DNSA) (pK_a = 2.2), from aqueous ethanolic solution. This acid has proved to be particularly effective for the generation of stable and mainly anhydrous 1:1 crystalline salts with both aliphatic and aromatic Lewis bases, and we have determined the crystal structures of a large number of these (*e.g.* Smith *et al.*, 2002, 2003, 2007). Addi-

  doi:10.1107/S0108270110012850

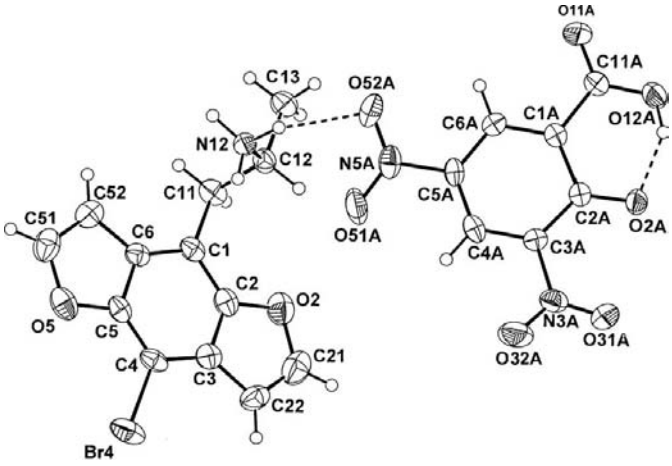


Figure 1
The molecular configuration and atom-numbering scheme for the BDF cation and the DNSA anion (suffix *A*) in (I). Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii. Intra- and interspecies hydrogen bonds are shown as dashed lines.

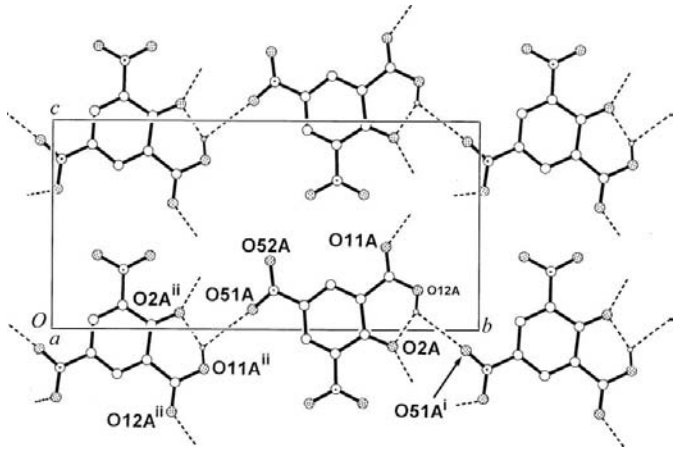


Figure 2
The DNSA anion chain substructures extending along the *b*-axis direction in the unit cell. The BDF cations have been omitted, along with H atoms not involved in the motif shown. Hydrogen bonds are shown as dashed lines. For symmetry codes, see Table 1.

tional notable structures are of the 1:1 proton-transfer compounds with the alkaloids strychnine (Smith *et al.*, 2005) and brucine (Smith *et al.*, 2006). The chemically stable crystalline anhydrous 1:1 salt of BDF with DNSA, *viz.* 1-(8-bromobenzo[1,2-*b*;5,4-*b*′]difuran-4-yl)propan-2-aminium 2-carboxy-4,6-dinitrophenolate, (I), provided the structure which is reported here.

In the structure of (I), as expected, DNSA protonates the amine group of the isopropane side chain of BDF. Fig. 1 shows the BDF cation and the DNSA anion (the *A* molecule), which associate *via* a linear N—H···O_{nitro} hydrogen-bonding interaction. The same H-atom donor has a second but geometrically less favoured contact with respect to hydrogen bonding, with the second nitro O atom (N12—H122···O51*A*; see Table 1). The second and third aminium H donors also give associations with both carboxyl and phenolate O-atom acceptors, resulting in a two-dimensional sheet structure. Undulating one-dimensional chain substructures [graph set *C*(8); Etter *et al.*, 1990], comprising head-to-tail linked DNSA anions formed through carboxyl–nitro O—H···O hydrogen bonds, extend along the *b* cell direction (Fig. 2). The aminium groups of the cations are incorporated within these chains, closing a cyclic $R_3^3(8)$ hydrogen-bonding interaction incorporating the previously mentioned cation–anion N—H···O_{nitro} hydrogen bond and an unusual carboxyl–nitro O—H···O interaction (Fig. 3 and Table 1). The aromatic body of the BDF cation folds back under the DNSA benzene rings, layering down the *a* direction in the unit cell (Figs. 3 and 4). This gives cation–anion π–π interactions [minimum centroid separation for rings C1–C6 to C1*A*–C6*A* = 3.566 (2) Å; inter-ring dihedral angle = 5.13 (1)°]. The two-dimensional sheet structure is generated through single aminium–carboxyl N—H···O *C*(8) extensions along the *c* axial direction. The O atoms of the second nitro group of the anion (at C3*A*) are unassociated, as are the O atoms of the furan 'wings' of the cation. The primary DNSA anion–aminium group interactive

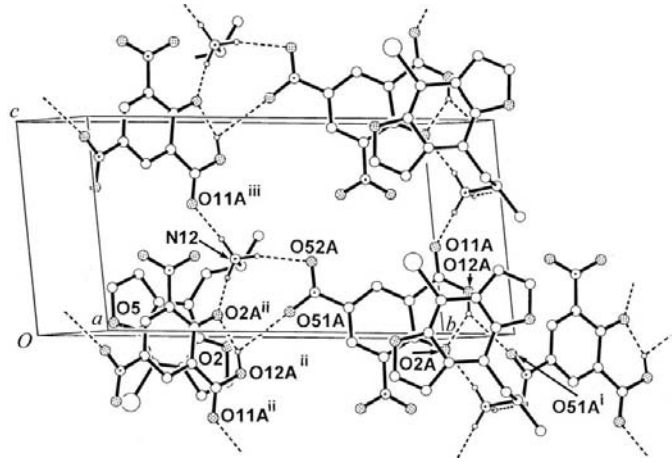


Figure 3
A perspective view of the unit cell in a similar direction to Fig. 2 but with the BDF cations included. Cation–anion interactions are shown (dashed lines), including the cyclic $R_3^3(8)$ cation–anion hydrogen-bonding association and the *c*-axis extensions in the two-dimensional structure. For symmetry codes, see Table 1.

pattern found in (I) has been categorized previously (Smith *et al.*, 2007); the primary N^+—H···O carboxyl association is Type 1 [linear *C*(*n*)], found in a large number of DNSA proton-transfer compounds. However, the secondary structure-extending interaction mode is unusual for DNSA, particularly with respect to the cyclic proximal group $R_3^3(8)$ association formed, along with the linear *C*(8) interchain association.

Because of the layered structural features found in (I), the aminium group of the BDF cation lies approximately normal to the plane of the BDF ring system [torsion angles C2—C1—C11—C12 = −72.2 (5)° and C1—C11—C12—N12 = −60.8 (4)°]. The DNSA anions have the expected short intramolecular hydrogen bond between the carboxyl and phenolate groups [O···O = 2.477 (4) Å], with the H atom localized on the carboxylate O atom rather than on the phenol O atom. This is the case for *ca* 80% of the DNSA anions in the

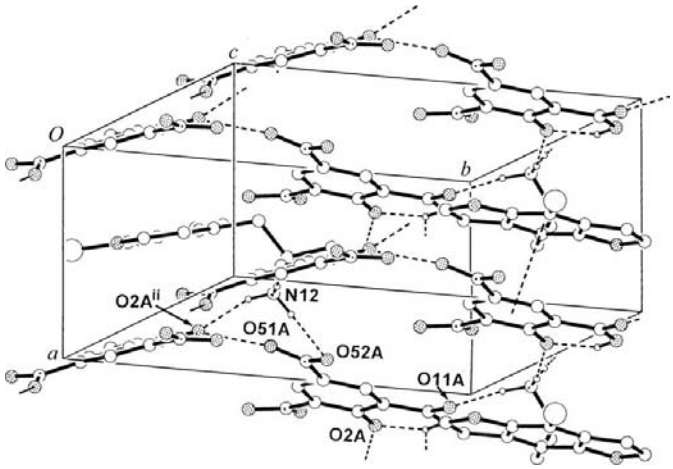


Figure 4
The layering in the unit cell of (I), viewed down the *c* axis, showing the undulating anion chains and and cation–anion π–π aromatic ring interactions. Dashed lines indicate hydrogen bonds and a π–π interaction. For symmetry codes, see Table 1.

structures of over 60 proton-transfer compounds of the acid (Smith *et al.*, 2007). This hydrogen bond results in the carboxyl group being essentially coplanar with the benzene ring [C2*A*—C1*A*—C11*A*—O11*A* = −176.5 (4)°]. Both nitro groups are rotated slightly out of the benzene plane [C2*A*—C3*A*—N3*A*—O32*A* = 163.5 (4)° and C4*A*—C5*A*—N5*A*—O52*A* = 172.1 (4)°].

The structure of (I) reported here is the first of any form of this bis(furan)-substituted hallucinogenically potent amphetamine, which has in the past presented problems with respect to crystal structure analysis because of its lack of crystallinity, both in the parent compound and in its salts with a number of organic acids. However, with (I), obtained from the reaction with 3,5-dinitrosalicylic acid in ethanol–water, the crystals are particularly well formed and chemically stable. The crystal structure determination not only provides a key to the stability of the crystal in the hydrogen-bonded two-dimensional network structure, but also confirms that this compound is the enantiopure (*R*) configurational isomer, which is known to be the more hallucinogenically active form.

Experimental

Compound (I) was synthesized by heating together under reflux BDF (0.29 g, 1 mmol) and DNSA (0.23 g, 1 mmol) in 50% ethanol–water (50 ml) for 10 min. After concentration to *ca* 30 ml, partial room-temperature evaporation of the hot-filtered solution gave well-formed pale-yellow crystal prisms of (I) (m.p. 493–495 K). The original BDF was solvent extracted from samples of speciality paint products (Cotton *et al.*, 2008), the purified BDF being used for the preparation of the DNSA salt. ^{1}H NMR (400 MHz, d_6-DMSO, 298 K): δ 17.12 (1H, *br s*, COOH), 8.36 (3H, *br s*, NH_3^+), 8.16 (1H, *d*, *J* = 2.3 Hz, ArH21), 8.13 (1H, *d*, *J* = 2.3 Hz, ArH51), 7.46 (1H, *d*, *J* = 2.3 Hz, ArH52), 7.01 (1H, *d*, *J* = 2.3 Hz, ArH22), 3.52 (2H, *m*, H2, H11), 3.303 (1H, *dd*, *J* = 12.9 and 8.5 Hz, H12), 1.14 (3H, *d*, *J* = 6.4 Hz, H13); ^{13}C{1H} NMR (100 MHz, d_6-DMSO, 298 K): δ 149.7 (C2), 148.4 (C5), 147.7 (C21), 147.2 (C51), 126.3 (C6), 125.9 (C3), 111.4 (C1), 106.8 (C52), 106.5 (C22), 92.0 (C4), 47.0 (C12), 31.7 (C11), 17.9 (C13). The assignments obtained are comparable with those obtained for BDF hydrochloride (Chambers *et al.*, 2001; Cotton *et al.*, 2008).

Crystal data

$C_{13}H_{13}BrNO_2^+\cdot C_7H_3N_2O_7^-$
M_r = 522.28
Monoclinic, $P2_1$
a = 6.9596 (3) Å
b = 17.2201 (9) Å
c = 8.7147 (4) Å
β = 103.315 (4)°
V = 1016.34 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 2.08 mm^{-1}
T = 297 K
0.50 × 0.30 × 0.25 mm

Data collection

Oxford Gemini-S Ultra CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.410, T_{max} = 0.590
10418 measured reflections
4450 independent reflections
3733 reflections with $I > 2\sigma(I)$
R_{int} = 0.053

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.112
S = 1.01
4450 reflections
315 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.82 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}
Absolute structure: Flack (1983), with 2047 Friedel pairs
Flack parameter: 0.038 (9)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O12*A*—H12*A*···O2*A*	0.88 (5)	1.69 (5)	2.477 (4)	147 (5)
O12*A*—H12*A*···O51*A*^{i}	0.88 (5)	2.58 (5)	3.120 (5)	120 (4)
N12—H121···O2*A*^{ii}	0.87 (4)	1.99 (4)	2.826 (4)	160 (3)
N12—H122···O51*A*	0.92 (5)	2.58 (4)	3.059 (5)	114 (3)
N12—H122···O52*A*	0.92 (5)	2.21 (5)	3.101 (5)	165 (4)
N12—H123···O11*A*^{iii}	0.96 (5)	1.81 (5)	2.763 (4)	172 (4)

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

H atoms involved in hydrogen-bonding interactions were located by difference methods and their positional and isotropic displacement parameters were refined. Other H atoms were positioned geometrically and treated as riding, with aromatic C—H = 0.93 Å and aliphatic C—H = 0.96–0.98 Å, and with $U_{iso} = 1.2U_{eq}$(C). The C2 (*R*) absolute configuration was confirmed with statistically valid certainty (Flack & Bernardinelli, 2008). The absence of a small number of reflections (16) of the 1909 possible below $2\theta_{min}$ is ascribed to instrumental collection limitations.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; 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*.

The authors acknowledge financial support from the Australian Research Council, the Faculty of Science and Technology of the Queensland University of Technology, the School of Biomolecular and Physical Sciences, Griffith University, and the Queensland Department of Health.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3145). Services for accessing these data are described at the back of the journal.

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