Very Short Intramolecular Hydrogen Bonds in the Crystal Structure of 1-[Bis(4-Fluorophenyl)methyl]Piperazinediium Dimaleate

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Abstract The crystal structure of 1-[bis(4-fluorophenyl)methyl]piperazine-1,4-diium dimaleate has been determined at 130(1) K in order to analyze the short intramolecular hydrogen bonds in maleate anions. The salt crystallizes in the orthorhombic *Pbca* space group with unit-cell parameters: *a* = 9.7143(3) Å, *b* = 18.2668(3) Å, *c* = 27.2219(8) Å. The two anions display different kinds of very short intramolecular hydrogen bonds (O...O distance is 2.4184(12) and 2.4414(13) Å). In one of the anions the hydrogen atom is located asymmetrically, much closer to one of the oxygen atoms than to the other, while in the other anion the hydrogen atom is almost in the middle between two oxygen atoms. These positions were confirmed by the analysis of the difference Fourier maps. The dication is protonated on both nitrogen atoms of piperazine ring (which is in quite regular chair conformation), and all three N–H groups of the cation are involved in short and linear hydrogen bonds with oxygen atoms of the anions, not involved in intramolecular hydrogen bonds. These hydrogen bonds connect cations and anions into ribbons expanding along *b*-axis. Much weaker C–H...F, C–H...O and C–H... π interactions take part, along with the electrostatic and van der Waals interactions, in the determination of the crystal packing.

Keywords Flunarizine derivatives · Maleate, short hydrogen bonds · Conformation · Crystal packing

Results and Discussion

1-[bis(4-fluorophenyl)methyl]piperazine (**1**) is an intermediate for the preparation of flunarizine, 1-[bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine, which is a calcium channel blocker [1, 2] and has been used for treatment of migraine and seems to be a little less effective than propranolol [3].

The crystal structures of some mono-salts of **1** (always protonated at N34 nitrogen atom) have been reported: 2-(2-phenylethyl)benzoate [4] and picrate [5], as well as the structures of the unsubstituted free base, 1-benzhydrylpiperazine [6] and some of its derivatives' di-salts, e.g. 1-benzhydryl-4-(2-benzoyl-ethyl)piperazinium tetrachlorocuprate(ii) hydrate [7] or 1-diphenylmethyl-4-ethylpiperazine-1,4-diium dichloride [8]. Here we present the first crystal structure that contains the dication of **1**, namely 1-[bis(4-fluorophenyl)methyl]piperazine-1,4-diium dimaleate (**1dim**, Scheme 1). No phase transition has been observed between room temperature and 100 K.

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Molecular Structure

The asymmetric part of the unit cell of **1dim** contains one dication and two maleate anions (Fig. 1). The cation is protonated at both nitrogen atoms of piperazine ring, the positions of appropriate hydrogen atoms were found in the difference Fourier maps and successfully refined without constraints. The piperazinium ring is in the chair conformation, and the small values of asymmetry parameters

Scheme 1 Molecular formula of the salt **1dim**

Fig. 1 Anisotropic ellipsoid representation of the molecular complex of **1dim_100**, together with atom labeling scheme [14]. The ellipsoids are drawn at 50 % probability level, hydrogen atoms are depicted as spheres with arbitrary radii, hydrogen bonds are shown as dashed lines

(which measure the deviations from the ideal symmetry of a given conformation [9]) show that the distortions are relatively unimportant. Table 1 lists some relevant geometrical parameters. The hydrogen atom at N31 is in an axial position (C33–C32–N31–H31 torsion angle is $-62.6(11)^\circ$ and C35–C36–N31–H31 $61.4(11)^\circ$).

In both maleate anions strong intramolecular hydrogen bonds are observed (O...O distances of 2.4184(12) and 2.4414(13) Å). Such bonds, enforced by *cis* conformation of the double bond (C–C=C–C torsion angles are $1.0(2)^\circ$ and $0.7(2)^\circ$ in anions A and B respectively) were also observed in other maleates. For instance, the imidazolium hydrogen maleate and calcium di(hydrogen maleate) were studied by the difference X–N (X-ray vs. neutron) method [10]. Figure 2 shows the distribution of the O...O distances and O–H...O angles for 169 hits found in the Cambridge Structural Database [11]; ver.5.33 of Nov. 2011, updated Feb. 2012; search criteria: organic, $R < 0.075$, absolute

Table 1 Selected geometrical parameters (Å, °) with s.u.'s in parentheses

C1–C11	1.5179(15)
C1–C21	1.5151(15)
C1–N31	1.5219(13)
N31–C32	1.5004(14)
N31–C36	1.4999(14)
N34–C33	1.4887(15)
N34–C35	1.4892(15)
C1A–O11A	1.2400(14)
C1A–O12A	1.2836(14)
C1A–C2A	1.4984(16)
C2A–C3A	1.3364(17)
C3A–C4A	1.5004(16)
C4A–O41A	1.2330(14)
C4A–O42A	1.2922(15)
C1B–O11B	1.2181(16)
C1B–O12B	1.2990(17)
C1B–C2B	1.4958(18)
C2B–C3B	1.3357(17)
C3B–C4B	1.4969(16)
C4B–O41B	1.2615(16)
C4B–O42B	1.2523(15)
C1A–C2A–C3A	130.70(11)
C2A–C3A–C4A	130.33(11)
C1B–C2B–C3B	131.01(12)
C2B–C3B–C4B	129.06(12)
N31–C32–C33–N34	$-54.42(13)$
C32–C33–N34–C35	55.77(12)
C33–N34–C35–C36	$-58.53(12)$
N34–C35–C36–N31	59.72(12)
C35–C36–N31–C32	$-56.38(12)$
C36–N31–C32–C33	53.88(12)
C35–C36–N31–C1	$-176.85(9)$
C33–C32–N31–C1	174.70(9)
C1A–C2A–C3A–C4A	1.0(2)
O11A–C1A–C2A–C3A	178.01(12)
O12A–C1A–C2A–C3A	$-1.08(19)$
C2A–C3A–C4A–O41A	176.96(12)
C2A–C3A–C4A–O42A	$-2.87(19)$
C1B–C2B–C3B–C4B	0.7(2)
O11B–C1B–C2B–C3B	169.89(15)
O12B–C1B–C2B–C3B	$-9.4(2)$
C2B–C3B–C4B–O41B	12.0(2)
C2B–C3B–C4B–O42B	$-167.72(14)$

value of the C–C–C–C torsion angle less than 30° , O...O contact less than 3 Å).

In the structure of **1dim** the details of intramolecular hydrogen bonds in two symmetry-independent molecules are different, as far as the standard X-ray diffraction can

Fig. 2 The distribution of O...O distances (*left*) and O-H...O angles (*right*) in maleate anions found in the Cambridge Structural Database

determine this. The hydrogen bond in the anion A is almost symmetrical (O-H and H...O distances are 1.15(2) and 1.27(2) Å while in the anion B it is better localized near one of the O atoms (appropriate distances are 0.99(2) and 1.45(2) Å). The reasonability of these results is somehow confirmed by the difference electron density plots, calculated after removing the hydrogen atom (Fig. 3a, b), where the results for additional data collection at room temperature (CCDC-870693) are also shown for comparison.

Interestingly, these differences seem to be correlated with the geometrical features of both anions. Anion A (with more “symmetrical” hydrogen bond) is almost ideally planar, maximum deviation from the mean plane calculated for all non-hydrogen atoms is only 0.0373(8) Å and the COO groups make the dihedral angles of 2.43(18)° and 1.44(20)° with perfectly planar (within 0.0035(8) Å) C=C-C-C fragment. In contrast, anion B is significantly twisted: the dihedral angles between COO groups and planar (0.0024(9) Å) carbon skeleton are as large as 9.4(2)° and 12.54(15)°.

Crystal Packing

In the crystal, the “building block” consists of a dication and two anions connected by the strong, linear hydrogen bonds (cf. Fig. 1; Table 2) that involve two N-H groups of cation (different nitrogen atoms) and two oxygen atoms from two anions, not involved in intramolecular hydrogen bonding. These blocks are connected by means of another

N-H...O hydrogen bond and quite strong C-H...O bond into the infinite chains along *y* direction (Fig. 4; Table 2).

This figure shows that the anion A connects two cations by means of N-H...O hydrogen bonds, while anion B by one N-H...O and one C-H...O interactions. These chains are then connected by weaker contacts (C-H...O, C-H... π and C-H...F) into three-dimensional crystal structure (Fig. 5; Table 2).

Experimental

4,4'-Difluorobenzhydryl piperazine (2.88 g, 0.01 mol) in 10 ml of benzene was mixed with maleic acid (1.16 g, 0.01 mol) in 10 ml of toluene. Both the solutions were mixed and stirred in a beaker at 333 K for 30 min. The mixture was kept aside for a day at room temperature. The formed salt was filtered and dried in a vacuum desiccator over phosphorous pentoxide. The compound was recrystallized from a mixture of (1:1) ethanol and acetonitrile by slow evaporation (m.p.: 395–398 K).

X-ray diffraction data were collected at 130(1) K by the ω -scan technique, on an Agilent Technologies four-circle SuperNova diffractometer equipped with Atlas detector [12] equipped with Nova microfocus Cu K $_{\alpha}$ radiation source ($\lambda = 1.54178$ Å). The temperature was controlled with an Oxford Instruments Cryosystem device. The data were corrected for Lorentz-polarization effects as well as for absorption (multiscan) [12]. Accurate unit-cell parameters were determined by a least-squares fit of and 9393

Fig. 3 The plot of the residual electron density across the O...O direction of the anions A (*left*) and B (*right*) at room temperature (*top*) and at 100 K (*bottom*). The hydrogen atoms were removed, the

contours are drawn every $0.1\text{e}\text{\AA}^{-3}$. Maximum and minimum values of the electron density are 0.53 and $-0.19\text{e}\text{\AA}^{-3}$

reflections of highest intensity, chosen from the whole experiment. The calculations were mainly performed within the WinGX program system [13]. The structures were solved with SIR92 [14] and refined with the full-matrix least-squares procedure on F^2 by SHELXL97 [15]. Scattering factors incorporated in SHELXL97 were used. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2 + (0.0411 \cdot P)^2 + 1.544 \cdot P]$, where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$. All non-hydrogen atoms were refined

anisotropically; all hydrogen atoms were found in difference Fourier maps and isotropically refined. Relevant crystal data are listed in Table 3, together with refinement details.

Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, No. 870694. Additionally, data for room temperature structure have been also deposited as CCDC 870693. Copies of this

Table 2 Short contact data (Å, °); CgA denotes the midpoint of the ring C11...C16, and CgB – of the ring C21...C26

D	H	A	D–H	H...A	D...A	D–H...A
O12A	H42A	O42A	1.27(2)	1.15(2)	2.4184(12)	174(2)
O12B	H12B	O42B	0.99(2)	1.45(2)	2.4414(13)	173(2)
N31	H31	O41B	0.981(18)	1.719(18)	2.6921(12)	170.7(16)
N34	H34A	O11A	0.980(18)	1.799(18)	2.7553(13)	164.5(15)
N34	H34B	O41A ⁱ	0.921(19)	1.943(19)	2.8208(13)	158.7(16)
C1	H1	O11A ⁱⁱ	0.972(14)	2.383(14)	3.3224(13)	162.6(11)
C23	H23	F14 ⁱⁱⁱ	0.963(18)	2.521(17)	3.2810(15)	135.8(14)
C33	H33B	O42B	0.987(15)	2.526(14)	3.1869(15)	124.2(10)
C36	H36B	O42B ⁱ	0.969(16)	2.396(15)	3.0621(15)	125.5(12)
C25	H25	CgA ^{iv}	0.944(18)	2.931(17)	3.5538(16)	124.7(12)
C2B	H2B	CgB ^v	0.973(17)	2.747(17)	3.6734(17)	159.4(12)

Symmetry codes: ⁱ $1/2 - x$, $1/2 + y$, z ; ⁱⁱ $1/2 + x$, $1/2 - y$, $1 - z$; ⁱⁱⁱ $3/2 - x$, $1/2 + y$, z ; ^{iv} $-1/2 + x$, y , $1/2 - z$; ^v $1/2 - x$, $-1/2 + y$, z

Fig. 4 A ribbon of the cations and anions as seen approximately along x direction (y across, z down) [14]; hydrogen bonds are shown as dashed lines

Fig. 5 Crystal packing of **1dim** as seen along x -direction; hydrogen bonds and weak interactions (see text) are shown as dashed lines [14]

Table 3 Crystallographic data and refinement details

Formula	$\text{C}_{17}\text{H}_{20}\text{F}_2\text{N}_2^{2+} \bullet 2(\text{C}_4\text{H}_3\text{O}_4)^-$
Formula weight	520.48
Crystal system	Orthorhombic
Space group	Pbca
a(Å)	9.7143(3)
b(Å)	18.2668(3)
c(Å)	27.2219(8)
V(Å ³)	4830.5(2)
Z	8
D _x (g cm ⁻³)	1.43
F(000)	2176
μ(mm ⁻¹)	1.00
Crystal size (mm)	0.3 × 0.2 × 0.15
Θ range (°)	3.25–73.75
hkl range	–11 ≤ h ≤ 4 –22 ≤ k ≤ 22 –33 ≤ l ≤ 32
Reflections	
Collected	12162
Unique (R _{int})	4749 (0.014)
With I > 2σ(I)	4548
Number of parameters	438
R(F) [I > 2σ(I)]	0.033
wR(F ²) [I > 2σ(I)]	0.083
R(F) [all data]	0.034
wR(F ²) [all data]	0.083
Goodness of fit	1.08
max/min Δρ (e Å ⁻³)	0.26/–0.23

information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk, or www: www.ccdc.cam.ac.uk.

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