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Crystal and molecular structure studies of cinnarizinium dimaleate

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ABSTRACT

The title salt {systematic name: 1-diphenylmethyl-4-[(2E)-3-phenylprop-2-en-1-yl]piperazine-1,4-dium bis (hydrogen maleate)}, crystallizes in the monoclinic space group $P2_1$, with $a = 9.940$ (2) Å, $b = 27.115$ (6) Å, $c = 11.802$ (3) Å, $\beta = 98.403$ (3)°, $V = 3146.8$ (12) Å³ and $Z = 2$. The piperazine ring is protonated at both the N atoms and adopts a distorted chair conformation. The sum of the bond angles around the piperazine N atoms N1 and N2 indicates that they are sp^3 hybridized. The structure exhibits both intra- and intermolecular hydrogen bonds of the type $O-H\cdots O$ and $N-H\cdots O$.

Keywords: molecular structure, crystal packing, maleic acid, dihedral angles, hydrogen bonds.

INTRODUCTION

Piperazines are among the most important building blocks in today's drug discovery. Cinnarizine (Stugeron, Stunarone) is an antihistamine which is mainly used for the control of nausea and vomiting due to motion sickness. Cinnarizine could be also viewed as a nootropic drug because of its vasorelaxating abilities (due to calcium channel blockage) and as a labyrinthine sedative [1]. A clinical evaluation of cinnarizine in various allergic disorders has been reported earlier [2]. Cinnarizine can be used in scuba divers without an increased risk of central nervous system oxygen toxicity. The crystal structures of some related compounds viz., cinnarizine [3] and cyclizine hydrochloride [4] have been reported. A review on the current pharmacological and toxicological information for piperazine derivatives is described [5]. In view of these, and as a part of our studies on the salts of the piperazines [6-9], we report herein the crystal and molecular structure of the title salt.

MATERIALS AND METHODS

Cinnarizine (3.68 g, 0.01 mol) and maleic acid (2.32 g, 0.02 mol) were dissolved separately in methanol. Both the solutions were mixed together and stirred for half an hour at 333K. The solution was allowed to cool to room temperature. Good quality single crystals were obtained by slow evaporation of methanol. (M.P.: 391--393 K).

X-ray crystallographic analysis

Crystal of the title salt (I) with dimensions of 0.14 mm × 0.13 mm × 0.02 mm was selected and mounted on a Bruker APEX-II [10] CCD diffractometer with a fine-focus sealed tube graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) using φ and ω scans at 296 K in the range of $2.6 \leq \theta \leq 16.9^\circ$. A total of 16448 reflections were collected, of which 9360 were independent and 4660 reflections with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 [11] program and the empirical absorption corrections were applied. The hydrogen atoms were determined by placing the H atoms at idealized positions and allowed to ride on their parent atoms with C—H distances in the range 0.92–0.98 \AA and N—H = 0.86 \AA ; Uiso(H) values were set equal to xUeq(carrier atom), where x = 1.2 for all H atoms. The final full-matrix least squares refinement gave R = 0.069 and wR = 0.150 ($w = 1/[\sigma^2(F_o^2) + (0.0371P)2]$ where $P = (F_o^2 + 2F_c^2)/3$), S = 0.97 (Δ/σ)max < 0.001, $\Delta\rho$ max = 0.21 e \AA^{-3} and $\Delta\rho$ min = -0.18 e \AA^{-3} . A summary of Crystal data and refinement details are given in Table 1.

Table 1. Crystal data and parameters for structure refinement of (I)

Compound	(I)
CCDC	918233
Molecular formula	C ₆₈ H ₇₂ N ₄ O ₁₆
Molecular weight	1201.30
Crystal system	Monoclinic
Space group	$P2_1$
a/ \AA	9.940 (2)
b/ \AA	27.115 (6)
c/ \AA	11.802 (3)
$\alpha/^\circ$	90
$\beta/^\circ$	98.403 (3)
$\gamma/^\circ$	90
V/ \AA^3	3146.8 (12)
Z	2
Dcalc (Mg cm ⁻³)	1.268
Crystal Dimensions (mm)	0.14 × 0.13 × 0.02
μ/mm^{-1}	0.09
Radiation λ (\AA)	0.71073
Tmin/Tmax	0.987/0.998
Reflections measured	16448
Ranges/ indices (h, k, l)	-11, 11; -30, 32; -12, 14
θ limit ($^\circ$)	2.6–16.9
Unique reflections	9360
Observed reflections ($I > 2\sigma(I)$)	4660
Parameters	814
Goodness of fit on F2	0.97
R1, wR2 [$I \geq 2\sigma(I)$]	0.069, 0.150

RESULTS AND DISCUSSION

The asymmetric unit consists of two molecules. The molecular structure and atom numbering scheme of (I) are shown in Fig 1. In the title salt, the piperazine group is protonated at both the N atoms and adopts a slightly distorted chair conformation with the puckering parameters Q, θ and ϕ having values of 0.574(6)⁰, 3.2(6)⁰ and 265(9)⁰, respectively. These values significantly differ from those reported earlier for cinnarizinium dipicrate [6]. For an ideal chair conformation, θ has a value of 0 or 180⁰. The bond lengths [12] and bond angles are in good agreement with the standard values. The sum of the bond angles around the piperazine N atoms N1 and N2 are 331.59⁰ and 331.30⁰, respectively, indicating that they are sp^3 hybridized. The bonds N1-C9 and N2-C14 connecting the diphenylmethyl and the phenyl-but-2-ene groups make an angle of 71.7(3)⁰ and 70.0(4)⁰, respectively, with the Cremer and Pople [13] plane of the piperazine ring and thus are in the equatorial plane. The dihedral angle between the piperazine ring and the phenyl ring (C1–C6) bridged by the but-2-ene group is 13.8(4)⁰ whereas the dihedral angles between the piperazine ring and the diphenyl methyl rings (C15–C20) and (C21–C26) are 66.7(4)⁰ and 73.0(3)⁰, respectively. The crystal structure is stabilized by both intra- and intermolecular hydrogen bonds of the type O—H•••O and N—H•••O (Table 2). The packing of the molecules when viewed down along the *b* axis indicate that the molecules are interlinked by these hydrogen bonds to form a chain like structure. The crystal packing is mainly stabilized by van der Waals interactions.

Figure 1. The molecular structure and atom numbering scheme of the title compound (I)

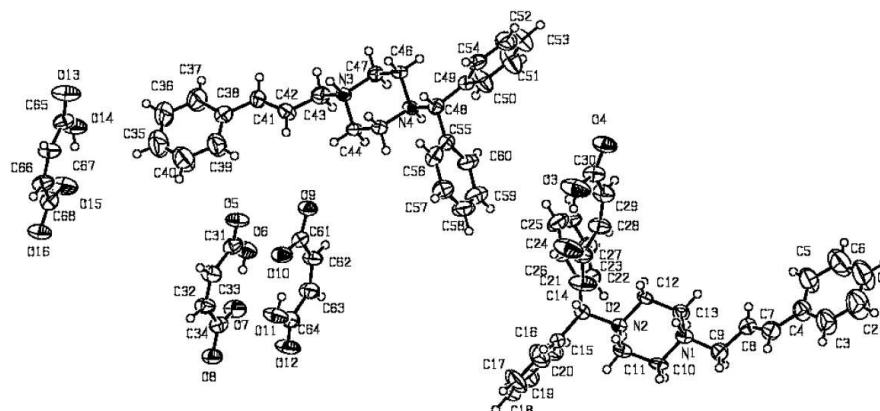
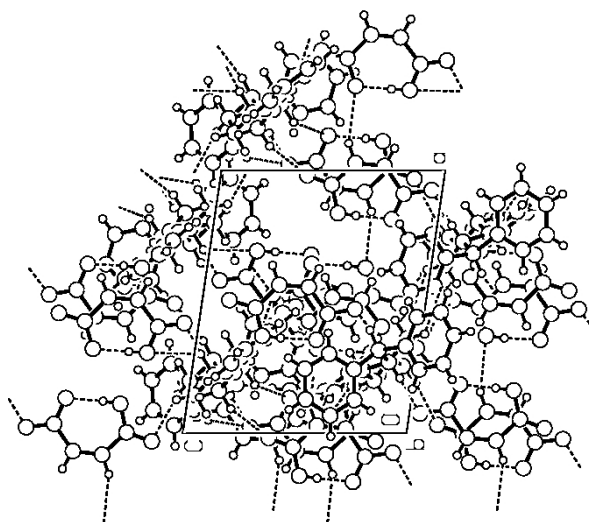
Figure 2. Packing diagram of (I) viewed along *b* axis. Hydrogen bonds are shown in dashed lines

Table 2. Hydrogen bond geometries for compound (1)

<i>D</i> — <i>H</i> ··· <i>A</i>	<i>d</i> (<i>D</i> — <i>H</i>) (Å)	<i>d</i> (<i>H</i> ··· <i>A</i>) (Å)	<i>d</i> (<i>D</i> ··· <i>A</i>) (Å)	Angle (<i>D</i> — <i>H</i> ··· <i>A</i>) (°)
O6—H6A···O7	0.82	1.63	2.446 (6)	178
O11—H11···O10	0.82	1.66	2.450 (6)	160
O14—H14A···O15	0.82	1.64	2.433 (6)	161
N3—H3B···O4 ⁱ	1.11 (6)	1.56 (6)	2.671 (7)	175 (5)
N3—H3B···O3 ⁱ	1.11 (6)	2.47 (6)	3.231 (7)	124 (4)
N4—H4A···O9 ⁱⁱ	1.08 (6)	1.65 (6)	2.731 (6)	176 (5)
N1—H1A···O16 ⁱⁱⁱ	1.01 (6)	1.67 (6)	2.672 (7)	172 (5)
N2—H2A···O8 ^{iv}	0.89 (6)	1.81 (6)	2.691 (7)	171 (6)

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

CONCLUSION

The title salt was prepared, crystal and molecular structure is discussed in detail. The crystal packing is stabilized by both inter and intra molecular hydrogen bonds in addition to Van der Waals forces.

Supplementary Material

Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. CCDC No: 918233 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

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