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Formation of Supramolecular Network in Cinnarizinum 5-Chlorosalicylate *Via* Hydrogen Bond Interactions

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Abstract

The title molecule, Cinnarizinum 5-chlorosalicylate was crystallized in the monoclinic crystal system under space group $P2_1/c$ and with unit cell parameters a = 22.605(16) Å, b = 10.698(7) Å, c = 12.293(8) Å, β = 91.3(2)° and Z = 4. The crystal and molecular structure of the molecule was stabilized by N—H···O and C—H···O hydrogen bond interactions, and were visualized through the Hirshfeld surfaceanalysis.

Keywords: Crystallization; molecular structure; hydrogen bond; Hirshfeld surface; molecular contacts.

1. Introduction

Cinnarizine is an antihistamine which is largely used for the control of nausea and vomiting due to motion sickness. Cinnarizine can be used in scuba divers without an augmented risk of central nervous system oxygen toxicity. The crystal structures of few related compounds viz. cinnarizine [1], cinnariziniumdipicrate [2], cinnarizinium picrate [3], cinnarizinium 3,5-dinitrosalicylate [4], cinnariziniumdimaleate [5] and Cinnarizinium fumarate [6] have been reported. In the title molecule, Cinnarizinum 5-chlorosalicylate (Systematic name: 4-Diphenylmethyl-1-[(*E*)-3- phenylprop-2-en-1-yl]piperazin-1-ium 5-chloro-2-hydroxybenzoate), the —OH group was slightly twisted about the mean plane of 5-chlorobenzoate ring. The molecules are chained through strong hydrogen bond interactions, N—H···O as the nitrogen N1 atom piperazin-1-ium ring at (x, y, z) acts as donor to the oxygen O2 atom at (x, 3/2−y, −1/2+z) of the neighbouring molecule.

EXPERIMENTAL SECTION

Synthesis of Cinnarizinum 5-chlorosalicylate

Cinnarizine (3.68 g, 0.01 mol) and 5-chlorosalicylic acid (1.72 g, 0.01 mol) were dissolved separately in methanol. The solutions were mixed and stirred over a heating magnetic stirrer for about an hour at 320

K (Fig. 1). The resulting solution was allowed to cool slowly and kept at ambient temperature without disturbing. X-ray quality crystals of the title salt appeared after three days. (m.p.: 389-391K).

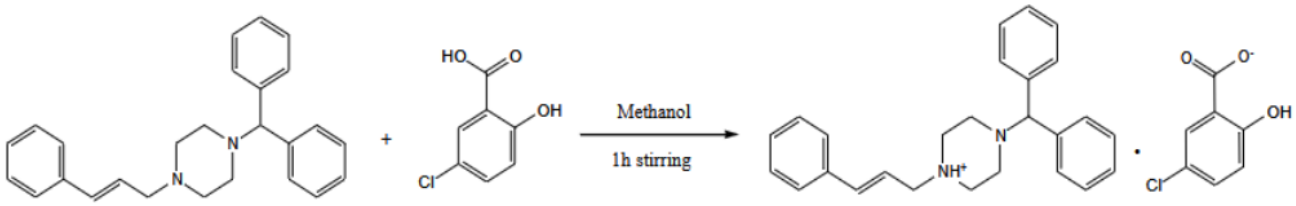

Figure 1: Preparation of the title compound

Data collection and structure refinement

A colourless block shaped single crystal of dimension 0.28 × 0.55 × 0.65 mm of the title compound was selected for X-ray diffraction studies. X-ray intensity data were collected for the title compound at temperature 100 K on Bruker AXS X-ray diffractometer at an operating voltage of 45 kV and current of 10 mA by using MoK$_\alpha$ radiation of wavelength λ = 0.71703 Å. Data were collected with different settings of φ equal to 0° and 90° by keeping the scan width of 0.5°, exposure time of 5 s and the sample to detector distance, 45.10 mm. A complete data set was processed using SAINT [7]. All the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods by full-matrix least squares method on F^2 using SHELX [8]. The geometrical calculations were carried out using PLATON and MERCURY [9, 10]. All hydrogen atoms of 4-Diphenylmethyl-1-[(*E*)-3-phenylprop-2-en-1- yl]piperazin-1-ium 5-chloro-2-hydroxy benzoate were clearly located in the difference Fourier map, positioned geometrically with N—H = 1.01 Å, C—H = 0.95-0.99 Å, O—H = 0.86 Å and were allowed to ride on their parent atoms with U_{iso} (H) = 1.3 U_{eq} (N) and U_{iso} (H) = 1.2 U_{eq} (aromatic C) and U_{iso} (H) = 1.4 U_{eq} (O) respectively. 360 parameters were refined with 6776 unique reflections, zero constraints and restraints which saturated the residuals to $R1$ = 0.0507 at the final cycle ofrefinement.

Hirshfeld surface analysis

The Hirshfeld surface [11] of the title molecule was constructed on the basis of the electron distribution calculated as the sum of spherical atom electron densities [12, 13]. The normalized contact distance d_{norm} based on the distance from a point on the surface to the nearest nucleus outside the surface, d_e and the distance from a point on the surface to the nearest nucleus inside the surface, d_i enables the identification of the regions of particular importance to the intermolecular interactions. The combination of d_e and d_i in the form of two-dimensional fingerprint plot [14, 15] gives the summary of intermolecular contacts in the crystal lattice.

RESULTS AND DISCUSSION

Crystal structure description

X-ray diffraction analysis revealed that the title compound is crystallized in the monoclinic crystal system with the space group $P2_1/c$, and with unit cell parameters a = 22.605(16) Å, b = 10.698(7) Å, c = 12.293(8) Å, β = 91.3(2)° and V = 2972.0(3) Å^3. The *ORTEP* of the molecule with displacement ellipsoids drawn at 50 % probability level is shown in **Figure 2**. The crystal data and the structure refinement details are given in **Table 1.**

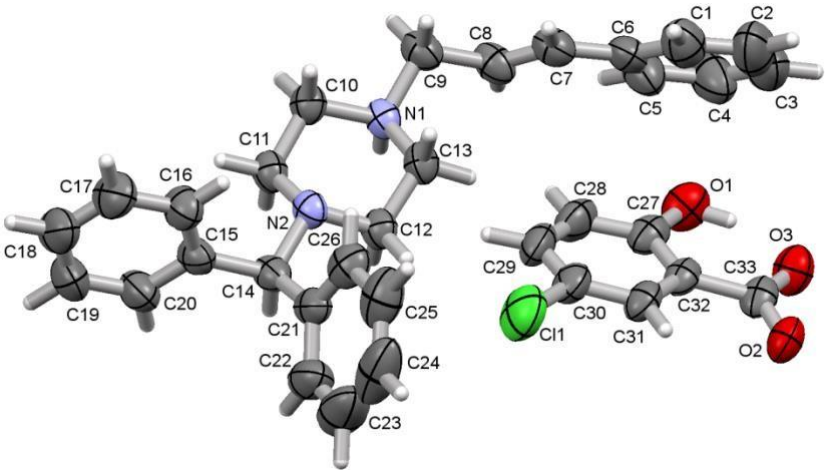

Figure 2: The *ORTEP* of the molecule with numbering scheme for non hydrogen atoms drawn at 50% probability level.

Table 1: Crystal structure data and structure refinement details.

Empirical formula	$C_{26}H_{29}N_2$, $C_7H_4ClO_3$
Formula weight	541.06 g mol^{-1}
Temperature	100 K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P $2_1/c$
Unit cell dimensions	a = 22.605(16) Å
	b = 10.698(7) Å
	c = 12.293(8) Å
	β= 91.3(2)°
Volume	2972.0(3) Å ^{3}
Z, calculated density	4, 1.209 Mg/m^3
Absorption coefficient	0.163 mm^{-1}
F000	1144
Crystal size	0.28×0.55×0.65 mm
Theta ranges for data collection	1.8 to 27.5°

Limiting indices	$-27 \leq h \leq 29$, $-13 \leq k \leq 13$, $-15 \leq l \leq 15$
Reflections collected / unique	26829 / 6776 (Rint = 0.029)
Absorption correction	multi-scan, T_{min} = 0.901 and T_{max} = 0.956
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6776 / 0 / 360
Goodness-of-fit on F^2	1.014
Final R indices [I>2sigma(I)]	$R1$ = 0.0507, $wR2$ = 0.1419
R indices (all data)	$R1$ = 0.0815, $wR2$ = 0.1715
Largest diff. peak and hole	0.50 and -0.22 e. Å^{-3}

In the title compound, Cinnarizinum 5-chlorosalicylate (Systematic name: 4-Diphenylmethyl-1- [(*E*)-3-phenylprop-2-en-1-yl]piperazin-1-ium 5-chloro-2-hydroxybenzoate), the —OH group was slightly twisted about the mean plane of 5-chlorobenzoate ring as indicated by the torsion angles about the segment, C27—C28 (**Table 2**).

Table 2: Selected bond lengths, bond angles and torsion angles (Å,°).

Cl1—C30	1.744 (3)	N1—C10	1.502 (2)
O1—C27	1.356 (3)	N1—C9	1.504 (2)
O2—C33	1.258 (2)	N2—C12	1.461 (2)
O3—C33	1.266 (2)	N2—C11	1.466 (2)
N1—C13	1.485 (2)	N2—C14	1.474 (2)
C13—N1—C10	110.33 (14)	C8—C9—N1	112.24 (17)
C13—N1—C9	112.08 (15)	N1—C10—C11	111.19 (16)
C10—N1—C9	110.72 (15)	N2—C11—C10	110.14 (15)
C12—N2—C11	107.50 (14)	N2—C12—C13	110.27 (15)
C12—N2—C14	110.54 (14)	N2—C14—C21	110.47 (16)
C11—N2—C14	112.85 (15)	N2—C14—C15	111.89 (15)
C7—C8—C9—N1	−113.1 (2)	C11—N2—C14—C15	−53.4 (2)
C13—N1—C9—C8	60.7 (2)	N2—C14—C15—C20	122.6 (2)
C10—N1—C9—C8	−175.59 (16)	C21—C14—C15—C20	−114.7 (2)
C13—N1—C10—C11	−52.2 (2)	N2—C14—C15—C16	−60.5 (3)
C9—N1—C10—C11	−176.88 (16)	C21—C14—C15—C16	62.2 (2)
C12—N2—C11—C10	−62.84 (19)	N2—C14—C21—C22	−147.18 (19)
C14—N2—C11—C10	175.01 (15)	C15—C14—C21—C22	89.3 (2)
N1—C10—C11—N2	57.9 (2)	N2—C14—C21—C26	36.1 (2)
C11—N2—C12—C13	63.94 (19)	C15—C14—C21—C26	−87.4 (2)
C14—N2—C12—C13	−172.49 (15)	O1—C27—C28—C29	−176.7 (2)
C10—N1—C13—C12	52.92 (19)	O1—C27—C32—C31	176.87 (18)
C9—N1—C13—C12	176.80 (15)	O1—C27—C32—C33	−4.7 (3)

N2—C12—C13—N1	−59.96 (19)	C31—C32—C33—O2	4.5 (3)
C12—N2—C14—C21	64.15 (18)	C27—C32—C33—O2	−173.97 (17)
C11—N2—C14—C21	−175.43 (15)	C31—C32—C33—O3	−176.59 (18)
C12—N2—C14—C15	−173.79 (15)	C27—C32—C33—O3	4.9 (3)

The piperazin-1-ium ring adopts a chair conformation with puckering amplitude Q = 0.590 (19) Å, θ = 6.74 (17)°and Phi = 187.1 (16)° similar to the structure 4-(Methylsulfonyl)piperazin-1- ium chloride [16] whose bond lengths and angles are comparable to those of the title molecule (Table 2). The mean planes of phenyl rings; C1/C2/C3/C4/C5/C6 of 3-phenylprop-2-en-1-yl, C15/C16/C17/C18/C19/C20 and C21/C22/C23/C24/C25/C26 of 4-Diphenylmethyl-1-[(E)-3- phenylprop-2-en-1-yl]piperazin-1-ium form dihedral angles of 69.6 (12)°, 81.3 (10)° and 65.6 (12)° respectively with the mean plane of the piperazin-1-ium ring, showing that they lie in the equatorial positions. The mean plane of the 5-chloro-2-hydroxybenzoate ring lies in the axial position with respect to the mean plane of the piperazin-1-ium ring as confirmed by the dihedral angle 25.55(10) °.

The molecules were chained through strong hydrogen bond interactions [17, 18], N—H···O through (1 2 2) and (2 2 1) planes (**Figure 3 and 4)** as the nitrogen N1 atom in the molecule at (*x, y, z*) of 4-diphenylmethyl-1-[(E)-3-phenylprop-2-en-1-yl]piperazin-1-ium acts as donor to the oxygen O2 atom at (*x*, 3/2−*y*, −1/2+*z*) of the neighbouringmolecule.

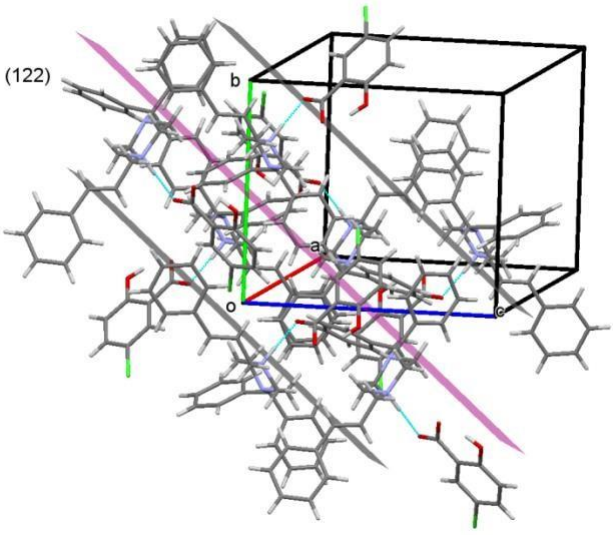

Figure 3: The packing of molecules when viewed down along *a*axis. The dotted lines represent N—H···O hydrogen bond interactions through (122)plane.

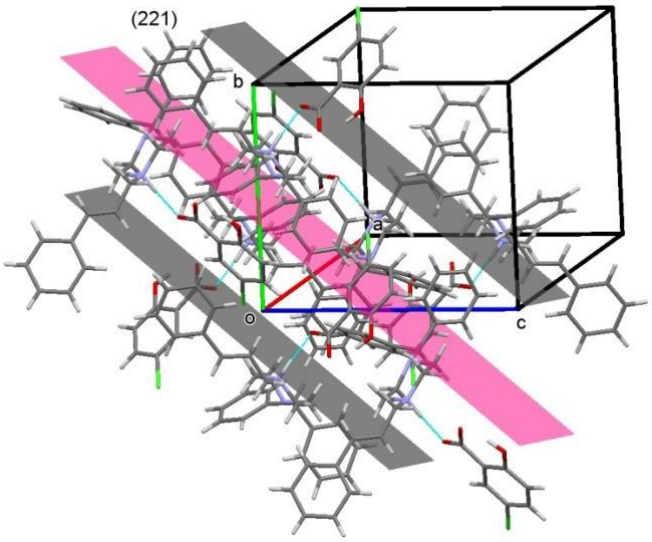

Figure 4: The packing of molecules when viewed down along *a*axis. The dotted lines represent N—H···O hydrogen bond interactions through (221)plane.

Considering that supramolecular construction can be achieved not only with strong hydrogen bond interaction, N—H···O but also with weak C—H···O hydrogen bond interactions, rationalization of the packing observed may be useful for the recognition of supramolecular synthons. In the title molecule, carbon C9 atom of 3-phenylprop-2-en-1-yl at (*x*, *y*, *z*) acts as a donor to O3 atom at (*x*, 3/2−*y*, −1/2 +*z*), the piperazin carbon C10 atom at (*x*, *y*, *z*) acts as a donor to O1 atom at (*x*, 1+*y*, *z*) and carbon C29 atom of 5-chloro-2-hydroxybenzoate at (*x*, *y*, *z*) acts as a donor to O2 atom at (*x*, 3/2−*y*, −1/2 +*z*) to the formation of hydrogen bond interactions (**Figure5**).

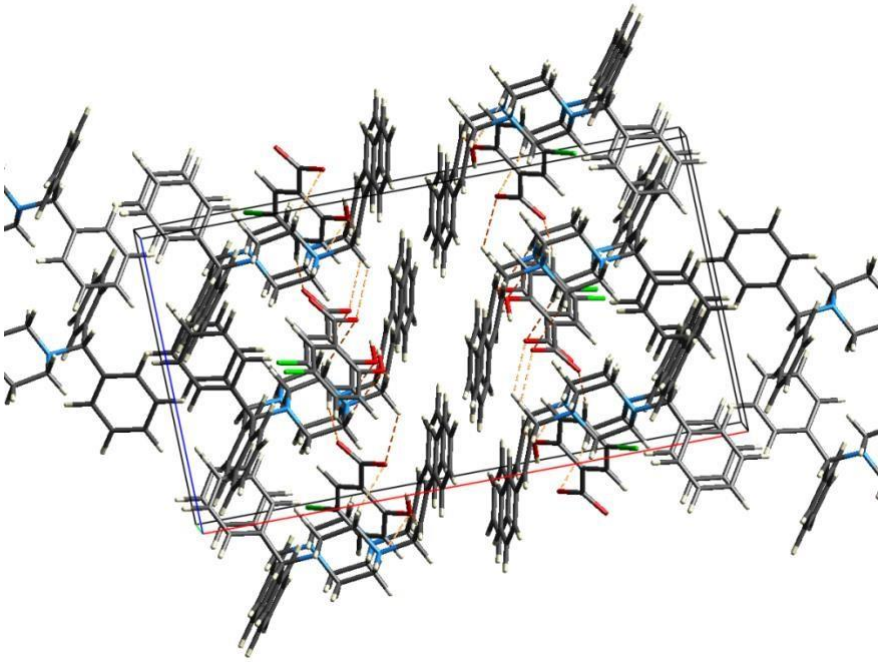

Figure 5: Packing of molecules when viewed down along *b* axis. The orange dotted lines represent C–H···O hydrogen bond interactions.

A combination of these extensive hydrogen bond interactions, listed in **Table 3** result in the formation of a 3D supramolecular network in the crystal.

Table 3: Hydrogen bond geometry (Å, °)

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***	**Symmetry**
N1—H1N1···O2	1.01	1.66	2.658(2)	175	*x*, 3/2−*y*, −1/2 +*z*
C9—H9A···O3	0.99	2.56	3.194(3)	122	*x*, 3/2−*y*, −1/2 +*z*
C29—H29A···O2	0.95	2.37	3.305(3)	168	*x*, 3/2−*y*, −1/2 +*z*
C10—H10B···O1	0.99	2.48	3.410(3)	156	*x*, 1+*y*, *z*

Hirshfeld surface analysis description

The hydrogen bond interactions discussed in X-ray diffraction studies were visualized through the dark red spots obtained on the Hirshfeld surface, delineated in **Figure 6**, as a result of hydrogen bond acceptors of N−H···O [N1−H1N1···O2] and C−H···O[C9−H9A···O3; C10−H10B···O1;C29−H29A···O2].

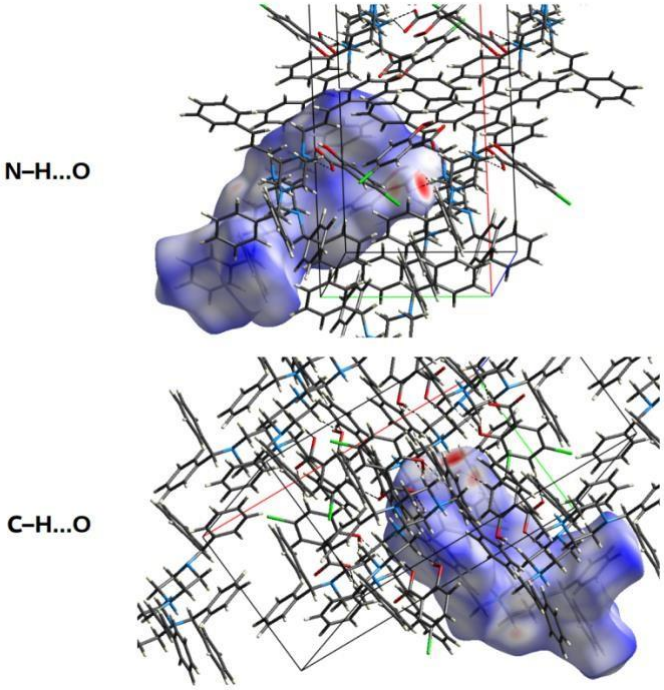

Figure 6: The visualization of N−H···O and C−H···O hydrogen bond interactions through Hirshfeld surface.

The fingerprint plot (**Figure 7**) can be decomposed to highlight the close contacts of a particular pair of atoms. This decomposition enables the separation of contributions from different interaction types which overlap in the full fingerprint.

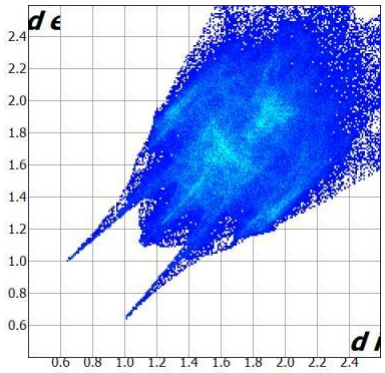

Figure 7: Fingerprint plot of the molecule.

The H···H intermolecular close contacts appear as two sharp spikes of dark blue color, almost overlapped with each other in the region 1.08 Å < (*d*e + *d*i) < 1.10 Å; O···H intermolecular close contacts appear as two very sharp and long spikes in the region 0.66 Å < (*d*e + *d*i) < 1.01 Å and C···H intermolecular close contacts appear as two sharp and wide spikes in the region 1.05 Å < (*d*e + *d*i) < 1.65 Å of the full fingerprint plot. The intermolecular close contacts (at distances shorter than 3.27 Å), H···H (54.7 %), O···H (14.8 %) and C···H (21.3 %), play a vital role in the formation of Hirshfeld surface and stabilization of crystal and molecular structure of 4- Diphenylmethyl-1-[(*E*)-3-phenylprop-2-en-1-yl]piperazin-1-ium 5-chloro-2-hydroxybenzoate.

Conclusions

The structure of the compound, Cinnarizinum 5-chlorosalicylate was confirmed by the single crystal X-ray diffraction studies. The compound crystallizes in the monoclinic crystal system with the space group $P2_1/c$. The crystal and molecular structure of the compound was stabilized due to the strong N—H···O and weak C—H···O hydrogen bond interactions. The Hirshfeld surface analysis was carried out to visualize the N—H···O and C—H···O hydrogenbond interactions and intermolecular close contacts which are responsible for the stabilization of crystal and molecular structure of the title compound wereanalyzed.

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