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Synthesis and intermolecular interactions of *N*-benzylidenetyramines

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ABSTRACT

In this paper, the synthesis and intermolecular interactions between *N*-benzylidenetyramine molecules were investigated. The crystal structure of *N*-(4-nitrobenzylidene)tyramine shows a molecular organization in zigzag chains with intermolecular O-H···N hydrogen bonds between the azomethine and phenolic hydroxyl groups. Those chains are held together by C-H···O hydrogen bonds to generate layers, which are connected by C-H···O, π···π and NO_2···π interactions.

1. Introduction

Tyramine (**1**) is a biologically important biogenic phenethylamine due to its sympathomimetic activity, which has allowed its use in studies aimed towards the comprehension of the physiological and pathophysiological behaviors of the sympathetic nervous system and its influence on the cardiovascular system. Tyramine (**1**) and *N*-benzyltyramine derivatives (**2**) were recently used in the synthesis of a new family of azacyclophanes (**3**,**4**) through a Mannich-type aromatic double condensation with formaldehyde in a basic medium (Scheme 1) [1–3].

It has been demonstrated that both tyramine (**1**) and *N*-benzyltyramines (**2**) form cyclic dimer arrangements through hydrogen bonds in solution [1–3]. These dimer arrangements are stable due to the presence of two O-H···N hydrogen bonds between the phenolic hydroxyl group of one unit and the amino group of another unit, this molecular pre-organization favors their macrocyclization when they react with formaldehyde (Scheme 1).

In the solid state, the tyramine molecules also interact through intermolecular hydrogen bonds leading to double chains which are stabilized by "head-to-tail" interactions [4]. The dimer motif can be found in those double chains, whereas complementary hydrogen bonding interactions allow an arrangement in double layers. A disposition in double chains are also established in the packing of the tyramine hemihydrate [5], but the chains are composed by "head-to-head" and "tail-to-tail" interactions, and the presence of water prevents the dimeric associations.

On the other hand, some phenolic Schiff bases have drawn attention due to their great versatility and ability to coordinate metals and form liquid crystals. The formation of metal complexes, the stability of liquid crystals and the photophysical properties of phenolic imines in the solid state are consequences of hydrogen bonds or proton transfer between phenolic hydroxyls and iminic nitrogens [6,7]. Continuing with our studies related to the chemical and structural behavior of phenylethylamines and some of their derivatives, the synthesis and structure of *N*-benzylidenetyramine Schiff bases are presented in this article. The results show that in the solid state, *N*-benzylidenetyramine units are held together by intermolecular hydrogen bonds between the phenolic hydroxyl group and the imine nitrogen atom of adjacent molecules leading to zigzag chains.

2. Experimental section

2.1. Materials

The reagents tyramine and aldehydes were purchased from Aldrich and used as received. The solvents, methanol and ethanol (Merck, analytical grade), were used without further purification. Infrared (IR) analysis was performed with a Nicolet iS10

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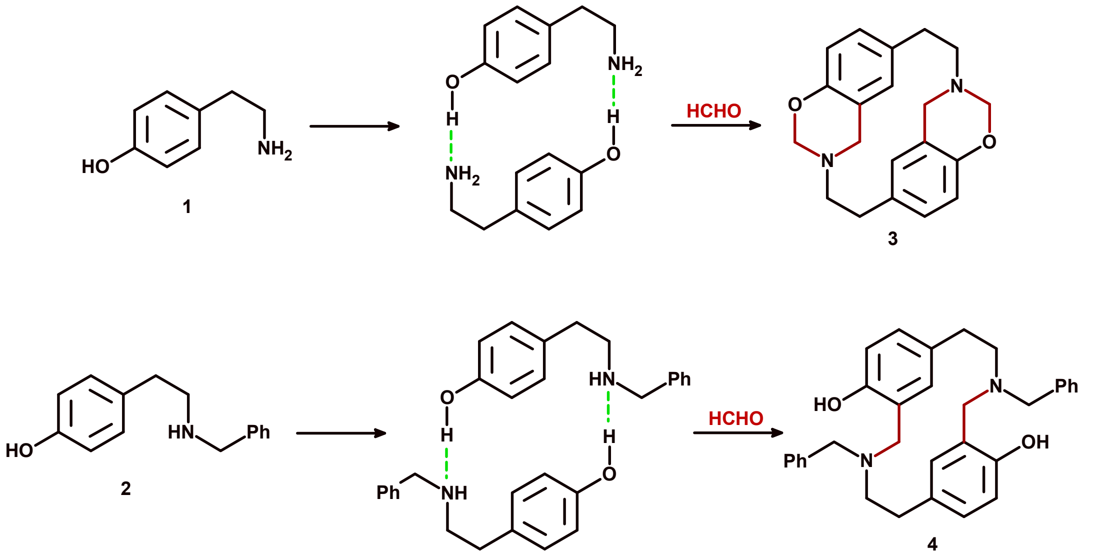

Scheme 1. Molecular pre-organization and reaction between tyramine derivatives with formaldehyde.

spectrometer (Thermo Fisher Scientific, 4000–400 cm^{-1}) using KBr disks. Mass spectra were recorded on a Shimadzu LCMS-IT-TOF liquid chromatograph mass spectrometer using electrospray ionization (ESI). The ESI probe was operated in the positive mode using the following parameters: CDL temperature, 200 °C; heating block, 200 °C; flow gas (N_2), 1.5 L/min; detector voltage, 1.69 kV; and scan range, *m/z* 100–350. The LCMS Solution software was used for data collection and analysis. Nuclear magnetic resonance spectra were collected on a Bruker Avance 400 spectrometer with a direct probe (5 mm BBO BB-1H/2H) operating at 400.130 MHz for ^{1}H and 100.634 MHz for ^{13}C. The deuterated solvents were acquired from Merck.

2.2. Crystallization and X-ray diffraction

Single crystals of **6a** were grown from an ethanolic solution of *N*-(4-nitrobenzyliden)tyramine by slow evaporation at room temperature. A suitable crystal was selected with the aid of a microscope, mounted on a cryoloop, and placed in the low temperature nitrogen stream of the diffractometer. The intensity data sets were collected on a Bruker-Nonius KappaCCD diffractometer equipped with an Oxford Cryostream 700 unit. The molybdenum radiation was used, graphite monochromated, and enhanced with a MIRACOL collimator. Crystallographic data are presented in Table 1.

The structure was solved, using the WINGX package [8], by direct methods (SHELXS-2013) [9], and refined by least-squares against F^2 (SHELXL-2014/7) [10]. All non-hydrogen atoms were anisotropically refined. The hydrogen atoms were positioned geometrically and refined by using a riding model, except the hydroxyl hydrogen atom which was isotropically refined.

2.3. Synthesis of N-benzylidenetyramines (*6a-d*)

An equimolar amount of the respective aldehyde (**5a-d**) was added to a solution of tyramine (**1**) in 96% ethanol (the liquid aldehydes were added directly, while the solid aldehydes were added into a 96% ethanol solution). The reaction mixture was heated to reflux for 24 h; subsequently, the solvent was removed under reduced pressure. The solid residue obtained was filtered, washed with 96% ethanol and dried at room temperature [11,12].

Table 1
Crystal data for *N*-(4-nitrobenzylidene)tyramine (**6a**).

	6a
Empirical formula	$C_{15}H_{14}N_2O_3$
Formula weight	270.28
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.682(1) Å
	b = 12.569(1) Å
	c = 13.699(1) Å
Volume	1322.8(2) $Å^3$
Z	4
D_{cal}	1.357 g cm^{-3}
Absorption coefficient	0.096 mm^{-1}
F(000)	568
Crystal size	0.25 × 0.22 × 0.22 mm^3
θ range for data collection	3.04 to 27.50°
Index ranges (h, k, l)	−9 to 9
	−16 to 16
	−17 to 17
Reflections collected	16310
Unique data	3034, R(int) = 0.059
Observed data [I > 2σ(I)]	2484
Goodness-of-fit on F^2	1.061
Final R^a indices [I > 2σ(I)]	R1 = 0.041, w*R*2 = 0.091
R^a indices (all data)	R1 = 0.058, w*R*2 = 0.101
Largest diff. peak and hole	0.162 and −0.152 e.$Å^{-3}$

[a] $R1 = \sum||F_0| - |F_c||/[\sum|F_0|]$ $wR2 = \{\sum(F_0^2 - F_c^2)^2/[\sum w(F_0^2)^2]\}^{1/2}$.

2.3.1. N-(4-nitrobenzyliden)tyramine (*6a*) ($C_{15}H_{14}N_2O_3$)

Yellow solid, yield: 80%, m.p. 148–149 °C, FT-IR (KBr) (cm^{-1}): 3300–2200, 1641, 1604, 1526, 1345, 1230, 851, 829, 743. ^{1}H NMR (DMSO-d_6) (ppm): 8.37 (1H, s), 8.28 (2H, d, J = 8.8 Hz), 7.96 (2H, d, J = 8.8 Hz), 7.02 (2H, d, J = 8.4 Hz), 6.65 (2H, d, J = 8.4 Hz), 3.81 (2H, t, J = 7.3 Hz), 2.83 (2H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6) (ppm): 159.6, 155.6, 148.6, 141.8, 129.8, 129.7, 128.9, 124.0, 115.1; 62.5, 35.9. ESI-HRMS: *m/z* 271.1028 ($[M+H]^+$, Calcd 271.1077) [12].

2.3.2. N-(3-nitrobenzyliden)tyramine (*6b*) ($C_{15}H_{14}N_2O_3$)

Orange solid, yield: 98%, m.p. 119–120 °C, FT-IR (KBr) (cm^{-1}):): 3300–2200, 1644, 1612, 1534, 1512, 1353, 1245, 834, 734, 675. ^{1}H NMR (DMSO-d_6) (ppm): 8.49 (1H, t, J = 1.8 Hz), 8.37 (1H, s), 8.27