Journal of Molecular Structure 1051 (2013) 132–136

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Tautomeric and ionisation forms of dopamine and tyramine in the solid state

Laura Cruickshank [a], Alan R. Kennedy [a,*], Norman Shankland [b]

[a] WestCHEM Department of Pure & Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland, United Kingdom
[b] Crystallografx Ltd, 2 Stewart Street, Milngavie, Glasgow G62 6BW, Scotland, United Kingdom

HIGHLIGHTS

- Dopamine exists as the 3-phenoxide Zwitterionic form in the crystalline state.
- Tyramine exists as four co-crystalline species in the crystalline state.
- Tyramine is shown to have dynamic proton behaviour in the solid.
- Distribution of microspecies in solution is not predictive of the solid state.

ARTICLE INFO

Article history:
Received 25 June 2013
Received in revised form 1 August 2013
Accepted 1 August 2013
Available online 11 August 2013

Keywords:
Tautomerism
Microspeciation
Neurotransmitter
Dopamine
Tyramine
Zwitterion

ABSTRACT

Crystallisation of the phenylethylamine neurotransmitter dopamine from basic aqueous solution yielded the 3-phenoxide Zwitterionic tautomer, despite this being a minority form in the solution state. In the crystal structure, dopamine has a dimeric $[OCCOH]_2$ hydrogen bonded catechol motif that expands through N—H···O interactions to give a 2-dimensional sheet of classical hydrogen bonds. These sheets are further interconnected by N—H···π interactions. The structurally related base tyramine crystallises under similar conditions as a hemihydrate with all four possible species of tyramine present (cationic, anionic, Zwitterionic and neutral) in the crystal structure. Single crystal X-ray diffraction studies at 121 and 293 K showed dynamic hydrogen atom disorder for the phenol/phenoxide group, suggesting that the tyramine speciation observed arises from a solid-state process.

1. Introduction

Dopamine and tyramine are structurally closely related bases of the phenylethylamine family. They are of importance due to their role as neurotransmitters in general, [1] and due to their role in the occurrence and treatment of Parkinson's disease in particular [2]. Recently, high quality work measuring and predicting which of the possible tautomeric and ionic forms of the two bases are actually present in the gaseous-, aqueous- and solid-states has been presented [3]. The driving force behind this prior work is biological, namely understanding how (de)protonation and tautomerism affects drug delivery mechanisms and the interaction of small molecules with bio-receptors [4]. Molecules that undergo facile protonation and tautomerisation in solution are also of interest to the crystal growth community, although here the challenge is generally to identify the minimum range of crystallisation conditions required to obtain each solution species in the crystalline form.

Despite the importance of dopamine and widespread interest in modelling both its structure and its structural receptors within biomolecules [4], to date only crystal structures of salts of dopamine have been published – no crystal structure of dopamine itself has been reported. This may be related to its ready oxidation by molecular oxygen, a reaction which is rapid under mildly basic conditions or when dopamine is in contact with a variety of other oxidation inducing species [5]. The crystal structure of tyramine as a hemihydrate has been reported [6]. However, this is a relatively early (1977), room temperature study which reports some uncertainty in determining the hydrogen atom (H-atom) positions. Indeed the H-atoms needed to determine which tautomeric form is present have been removed from the Cambridge Structural Database [7] entry (refcodeTYRAMH) due to doubts about their unusual geometry. Herein we report the crystal structures of both dopamine and tyramine hemihydrate as isolated from aqueous solution,

* Corresponding author. Tel.: +44 141 548 2016.
E-mail address: a.r.kennedy@strath.ac.uk (A.R. Kennedy).

0022-2860/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2013.08.002

Table 1
Selected crystallographic and refinement parameters.

Compound	Dopamine	Tyramine hemihydrate (low Temp)	Tyramine hemihydrate (room Temp)
Formula	$C_8H_{11}NO_2$	$C_8H_{12}NO_{1.5}$	$C_8H_{12}NO_{1.5}$
Formula weight	153.18	146.19	146.19
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/n$	$Pbc2_1$	$Pbc2_1$
λ Å	0.71073	1.5418	1.5418
a Å	5.8528(3)	18.247(2)	18.2063(6)
b Å	8.8263(5)	10.2941(11)	10.4139(4)
c Å	14.6185(7)	8.1430(7)	8.2160(3)
β°	96.420(5)		
Volume Å^3	750.44(7)	1529.6(3)	1557.74(10)
Temp. K	123(2)	121(2)	293(2)
Z	4	8	8
Refls. Collected	3779	5207	5846
Refls. Unique	1862	1976	2371
Refls. Obs.	1543	1676	2254
Rint	0.0168	0.0408	0.0265
Goodness of fit	1.024	1.139	1.078
$R[I>2\sigma(I)]$, F	0.0422	0.0402	0.0386
Rw, F^2	0.1025	0.1349	0.1077

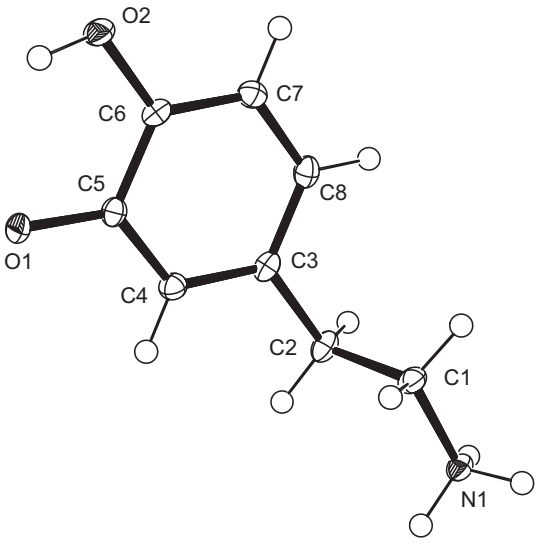

Fig. 1. The molecular structure of dopamine with non-H atoms shown as 50% probability ellipsoids. The conformation matches 'Zwitterion trans 4OH' donor in Scheme 3 of Ref. [3b].

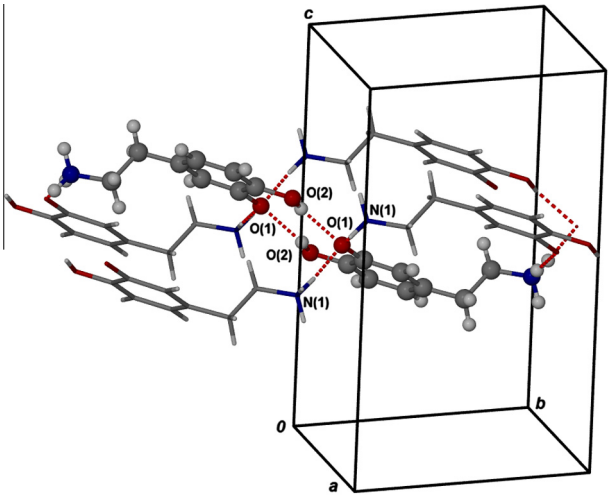

Fig. 2. Part of the 2-dimensional hydrogen-bonded motif in the structure of dopamine. The molecules of the catechol-based dimeric structure is shown as a ball and stick representation and other hydrogen-bonded molecules as capped sticks.

together with a full description of the tautomeric and ionic forms they adopt in the solid-state.

2. Experimental

Crystallographic measurements were made with Oxford Diffraction Xcalibur E and Gemini S instruments. Solution and refinement were performed with the SHELX suite of programs [8]. H-atoms bound to carbon were placed in idealised positions and refined in riding modes, but those bound to nitrogen or oxygen were placed as found in difference syntheses and refined isotropically. The only restraint imposed was on the O–H distances of the disordered hydroxyl proton of tyramine (O–H = 0.90(2) Å). Both the low and room temperature measurements of tyramine hemihydrate were made with the same crystal. Selected details are given in Table 1 and full data has been deposited in cif format. CCDC 942079 (dopamine), 942080 (tyramine LT) and 942081 (tyramine RT) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

A suitably calibrated Oakton Acorn series pH meter was used to measure pH.

Crystals of both dopamine and tyramine were grown by first preparing near-saturated aqueous solutions of their HCl salts. Aliquots (approx. 1 cm^3) were added to narrow (approx. 5 mm) glass tubes and then carefully over-layered with 35% ammonia solution. The tubes were then sealed with parafilm. Over a period of 12 to 24 h, at room temperature, colourless crystals grew at the bottom of the tubes. In the case of dopamine, the upper layers of the solution (ca. 2/3 of the volume) were highly discoloured and contained black material from the oxidisation of dopamine.

3. Results and discussion

In aqueous solution, dopamine is prone to rapid oxidation at higher pH values. Simple attempts at recrystallisation from aqueous solutions of dopamine by evaporation or cooling resulted in