Journal of Molecular Structure 1130 (2017) 623–632

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Investigation of two *o*-hydroxy Schiff bases in terms of prototropy and radical scavenging activity

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ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form
5 November 2016
Accepted 6 November 2016
Available online 9 November 2016

Keywords:
Schiff base
Tautomerism
Phenol-imine
Keto-amine
X-ray
NMR
Scavenging activity

ABSTRACT

Two Schiff bases, namely (*E*)-4,6-dibromo-3-methoxy-2-[(phenylimino)methyl]phenol (**1**) and (*Z*)-2,4-dibromo-6-[(4-buthylphenylamino)methylene]-5-methoxycyclohexa-2,4-dienone (**2**), have been investigated by considering solvent, substituent and temperature dependence of prototropy, and scavenging activities. Experimental (X-ray diffraction, UV–vis and NMR) and computational (DFT) techniques have been used to obtain key data on prototropy and other properties of interest. X-ray and UV–vis results underline the variability in the structural preferences of the compounds with respect to the phase and solvent media conditions. This kind of tautomeric behavior has been elaborated by ^{1}H NMR and ^{13}C NMR experiments performed at room and low temperatures. Radical scavenging properties of two compounds have been probed for their usage potentials as therapeutic agent and ingredient in medicinal and food industries, respectively. For this purpose, three different test methods (DPPH, ABTS$^{\bullet+}$ and DMPD$^{\bullet+}$) have been used. It has been found from *in vivo* and *in vitro* studies that the compound **2** could be interesting as an active component in pharmaceutical industry or as an additive in food industry when its antiradical activity is considered.

1. Introduction

Schiff bases were first reported by Hugo Schiff in 1864 [1]. Since then, Schiff bases have been an indispensable research subject for the scientists from various fields with the organic chemistry being in the forefront. A number of reasons for this popularity can be summarized as follows: Schiff bases can be used in industrial [2–4], pharmaceutical [5–7], biological [8–13] and chemical applications [14–18], depending on their structural properties. For example, those with photochromic and thermochromic properties may have potential applications in information storage, electronic display systems, optical switching devices, ophthalmic glasses, and so on [19–22]. These properties are closely related to the factors such as proton tautomerism [23], molecular geometry (planarity) and the way of crystal packing [24]. Detailed investigation of these three factors in Schiff bases with different substituents and solvent media has been constituted the main objective of our studies so far [25–32]. In this study, we have selected two Schiff bases with different tautomeric forms in order to investigate which differences occur depending on the prototropy in the family of Schiff basis. Two compounds have been probed experimentally by XRD in solid state and by NMR and UV–vis in solvent media. Two compounds have been also investigated in terms of radical scavenging activity in order to see their usage potentials as therapeutic agent and ingredient in medicinal and food industries.

2. Experimental and computational methods

2.1. Synthesis

Compounds **1** and **2** have been synthesized using the same method that we used in our previous studies [25–32], this time

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http://dx.doi.org/10.1016/j.molstruc.2016.11.023

using 3,5-dibromo-2-hydroxy-6-methoxybenzaldehyde, aniline and 4-buthylaniline as reactants. Single crystals of both compounds have been obtained by slow evaporation of ethanol at ambient temperature. For 1, yield = 82%, m.p. = 417–419 K while yield = 78%, m.p. = 347–349 K for 2.

2.2. Spectroscopic, crystallographic and computational methods

The following instruments have been used for spectroscopic measurements: StuartMP30 for melting points, Thermo scientific BioGenesis spectrometer for UV–vis spectra, 400 MHz Bruker spectrometer for NMR spectra at room and low temperatures (RT and LT) and STOE IPDS II diffractometer for XRD data. Experimental conditions and other details are given in crystallographic information file (CIF). The crystal structure has been solved by direct methods using SHELXS-97 [33]. All non-hydrogen atoms have been refined anisotropically by full matrix least-squares methods [33]. All H atoms except for H1 have been located geometrically and refined by a riding model with $U_{iso}(H) = 1.2U_{eq}(C)$ and $U_{iso}(H_{methyl}) = 1.5U_{eq}(C)$. H1 atom has been located from difference Fourier map since its position identifies the tautomeric form the compounds. Coordinates of H1 and $U_{iso}(H)$ values were refined freely. WinGX [34] and ORTEP-3 [35] softwares have been used for plotting figures and other materials related to the molecular structures.

Gaussian 03W [36] and GaussView programs [37] have been used for computational studies. Gas phase geometry optimizations have been carried out at DFT/B3LYP level [38] using 6-311G(d,p) basis set [39,40]. TD-DFT method [41–44] has been applied for electronic excitations of **1** and **2**.

2.3. Radical scavenging activity measurements

Scavenging activity measurements have been carried out using similar methods to those reported in previous studies [45–47]. Experimental results were given as mean ± S.D. of the three parallel measurements. Analysis of variance was performed by ANOVA procedures. Significant differences between means were determined by Duncan's Multiple Range tests. *P* values of <0.05 were regarded as significant. Both operations were done with SPSS (version 15.0.0, SPSS Inc., Chicago, IL, USA) for windows.

3. Results and discussion

3.1. Molecular structures of *1* and *2*

It is generally mentioned about two structural forms in *o*-Hydroxy Schiff bases regarding the prototropic tautomerism. These forms are called *phenol-imine* and *keto-amine* structures (Fig. S1). One or both of these structural forms can be seen in a solid state compound of a Schiff basis [48–50]. These forms are geometrically identified by two data from the crystallographic point of view: (i) the position of tautomeric hydrogen atom (H1) and (ii) the characters of C1–O1 and C7–N1 bonds and of those in the aromatic ring. In crystal structures of both compounds (Figs. 1 and 2), the tautomeric protons are shown to be located on different atoms. In **1**, H1 atom is bonded to the oxygen atom (O1) with a bond distance of 0.791 Å, indicating the preference of phenol imine form by the compound **1**. On the other hand, it is located on nitrogen atom (N1) in **2**, resulting in a keto-amine structure with a bond distance of 0.778 Å for N1–H1. Moreover, C1–O1 and C7–N1 bond distances in **1** are 1.327(5) Å and 1.283(5) Å, respectively. It is seen that the C7–N1 bond distance has a double bond character, being compatible with the tautomeric form described as phenol-imine structure. In the molecular structure of **2**, the tautomeric proton is bonded to the nitrogen atom (N1), and the bond distance for C1–O1 (1.310(7) Å) is shorter than that of a single bond. However, C7–N1 bond distance is 1.289(8) Å. Characteristic bond distances and angles related to tautomeric forms of the compounds are given in Table 1. When C1/C6 rings of the compounds are compared, it is seen that **2** has shorter C2–C3 bond and longer C3–C4, C5–C6 and C6–C1 bonds than **1**. In this sense, the C1/C6 ring in **2** is considered

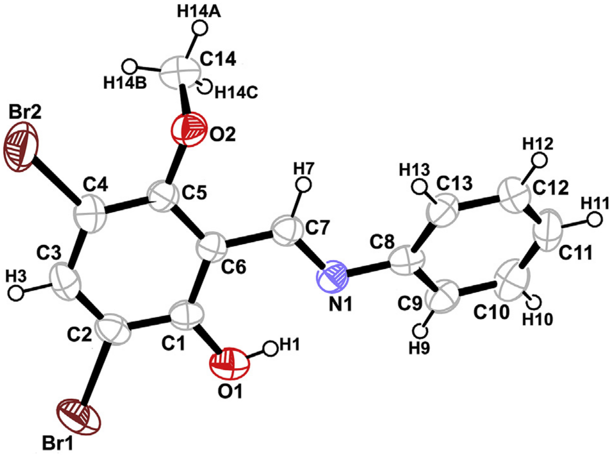

Fig. 1. Molecular structure of **1**.

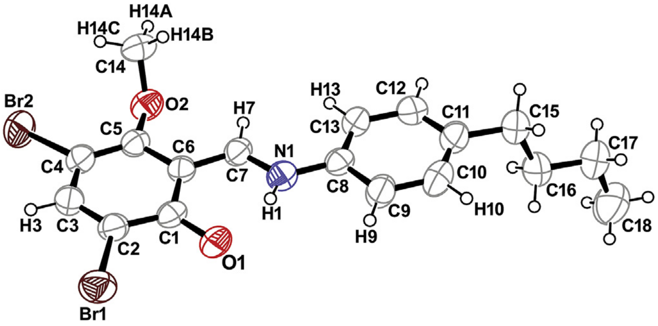

Fig. 2. Molecular structure of **2**.

Table 1
Selected bond lengths (Å), angles (°) and torsion angles (°) obtained from XRD method for phenol-imine and keto-amine structures of the compounds.

	(1)	(2)
Bond length		
C1–O1	1.327(5)	1.310(7)
N1–C7	1.283(5)	1.289(8)
C6–C7	1.435(5)	1.424(9)
C1–C2	1.393(6)	1.400(10)
C2–C3	1.359(6)	1.346(9)
C3–C4	1.388(6)	1.404(9)
C4–C5	1.374(6)	1.370(10)
C1–C6	1.412(5)	1.433(8)
C5–C6	1.397(6)	1.411(9)
C2–Br1	1.886(5)	1.894(6)
C4–Br2	1.898(4)	1.891(7)
C8–N1	1.425(5)	1.402(9)
Bond angle		
C7–N1–C8	121.6(4)	127.5(7)
N1–C7–C6	121.9(4)	121.4(6)
O1–C1–C6	122.1(4)	120.7(6)
Torsion angle		
C8–N1–C7–C6	−179.5(3)	−177.4(6)
O1–C1–C6–C7	−0.4(5)	−3.7(9)