



# Theoretical study of the molecular structure and intramolecular proton transfer in benzohydroxamic acid



Richa Arora, Upasana Issar, Rita Kakkar\*

Computational Chemistry Group, Department of Chemistry, University of Delhi, Delhi 110007, India

## ARTICLE INFO

### Article history:

Received 23 January 2017

Received in revised form 13 February 2017

Accepted 14 February 2017

Available online 16 February 2017

### Keywords:

Benzohydroxamic acid

DFT

Tautomerism

Aqueous solvation

Hydrogen bonding

## ABSTRACT

Benzohydroxamic acid (BHA), an important member of the hydroxamic acid family (R-CO-NH-OH), has been investigated in detail in the gas and aqueous phase using density functional methods. Like the other members, it displays amide/imide tautomerism. Each tautomer may also exist as **Z** or **E** conformer. The **Z** amide conformer is found to be the most stable in both phases. The electronic properties of benzohydroxamic acid, along with its NBO analysis, suggest that the molecule is hard (stable). It is found that **Z** amide can be converted to **Z** imide via two paths, having almost equal activation energies. An explanation of their acid character, which had been eluding scientists, has emerged from this work. The relative stabilities of the anions suggest that BHA behaves as an N-acid, i.e. deprotonation of the N-H group occurs from the **1Z** tautomer. It can also be considered as an O-acid formed by deprotonation from the **2Z** tautomer. On consideration of the charge distribution of the anion, it is concluded that the latter description is more apt, and it is an O-acid formed by deprotonation of the iminol tautomer. Furthermore, the probable protonation sites of benzohydroxamic acid have been studied and the carbonyl oxygen is found to be the preferred site for protonation.

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## 1. Introduction

Hydroxamic acids, R-CO-NH-OH, are a group of weak organic acids that are constituted from two simple functional groups - an amide group and a hydroxyl group [1]. They have varied applications in fields like analytical chemistry, biology, agriculture, pest control, nuclear fuel processing and corrosion inhibition [2,3]. Hydroxamic acids are also important, as they contain the smallest fragment of the protein structure, HNC=O, that winds the secondary structure of DNA and RNA protein into an  $\alpha$ -helix skeleton [4].

The focus of this work is benzohydroxamic acid (BHA), a unique member of the hydroxamic acid family. Over the years, a lot of work has been done to elucidate its structure. The unique property of BHA is that it exhibits varied conformations depending upon the concentration, temperature and nature of the solvent [5]. Benzohydroxamic acid can adopt either the **Z** (*cis*) or **E** (*trans*) conformation, resulting from free rotation about the C–N bond and can also exhibit amide/imide tautomerism. Further, each tautomer has many possible rotamers arising from the different orientations of the hydroxyl groups. According to *ab initio* calculations [6,7] and

kinetic measurements, the **Z**-amide form is the most stable one in the gas phase and aqueous solution owing to intramolecular (in the gas phase) and intermolecular (in aqueous solution) hydrogen bonding. On the other hand, in acetone, according to NMR measurements the **E**-amide form is favored [7].

Another point of controversy arises from the acid-base behavior of BHA, since its deprotonation site depends upon the medium [7]. Various studies were conducted in different solvents to deduce the exact deprotonation site of BHA. It was found to behave as an O-acid in NaNO<sub>3</sub> and DMSO solution [8,9]. Later on, it was suggested that deprotonation at both N- and O-sites contributes to the experimental  $pK_a$  value of 8–9 [7,8,10–12]. Gas phase theoretical calculations on BHA suggested deprotonation at the N-site [7,13,14], whereas NMR studies concluded that deprotonation occurs at both the N- and O-sites [7]. For the aqueous phase, theoretical calculations at the HF/6-31G(d)/CPCM and HF/6-31 + G(d)/CPCM levels [6], as well as kinetic experiments [7], favor deprotonation of the O-site, either directly or by transformation of the N-ion to the O-ion via proton transfer from oxygen to nitrogen. However, the deprotonation site of BHA still remains a mystery.

To obtain more clarity about the above-mentioned facts, we carried out Density Functional Theory (DFT) studies on the various possible conformers of BHA in the gas and solution phases. BHA is known to form stable chelates in its anionic form [15]. Therefore,

\* Corresponding author.

E-mail address: [rkakkar@chemistry.du.ac.in](mailto:rkakkar@chemistry.du.ac.in) (R. Kakkar).

we also studied the deprotonation site of BHA in the gas phase and in aqueous solution. We further carried out a brief analysis of the possible protonation sites of BHA.

## 2. Computational details

DFT calculations were performed at the B3LYP/6-311++G(d,p) level [16–19] using Gaussian 09W [20]. Full geometry optimizations were followed by harmonic frequency calculations at the same level to confirm the nature of the stationary points and to account for zero-point energy corrections, as well as the entropy contributions to the Gibbs energies [21].

Natural bond orbital (NBO) analysis was performed to identify the best resonance structure using the NBO program [22–26] incorporated in the Gaussian suite. The partial charges reported here are based on NBO charges. Bond orders reported are Wiberg bond orders.

The influence of the solvent (water) on the relative stability of the various conformers was investigated at two levels: taking discrete water molecules and bulk solvent using the continuum model. The influence of bulk solvent was studied using the universal implicit solvent model, SMD (steered molecular dynamics) [27] with the dielectric constant ( $\epsilon$ ) taken as 78.39 for water at 298.15 K. SMD is reported to give better solvation Gibbs energies for neutral as well as ionic species [28] than the other solvation methods. The gas and solution phase basicities and  $pK_a$  values were calculated by the procedure outlined in our earlier work [29].

## 3. Results and discussion

### 3.1. Gas phase studies of BHA

#### 3.1.1. Relative Gibbs energies and properties

We performed geometry optimizations on all the possible conformers (Fig. 1). The optimized structures are given in Fig. S1, Supplementary Information. The nomenclature follows our previous work on thioformohydroxamic acid [30]. The three possible tautomers are labeled **1** (amide), **2** (imide) and **3** (zwitterion). The calculated relative energies for the tautomers and conformers with respect to the most stable **1Z** conformer are given in Table 1. The order of stabilities is **1Z** > **2Z** > **1E** > **2E** > **3**, where each term represents the most stable conformer of each tautomer, i.e., **1Zc**, **2Ztc**, **1Et**, **2Etc** and **3tc**, respectively. The **Z-amide** form (**1Z**) is found to be the most stable one in the gas as well as in the aqueous phase, in agreement with previous theoretical results [7,31,32]. This result is also in agreement with those for formohydroxamic and thioformohydroxamic acids [30,33]. The **1Z** conformer has an O...H–O kind of hydrogen bond, whereas **2Z** possesses a hydrogen bond of the H...O–H kind.

The tautomeric equilibrium constants,  $K_T$ , were also calculated (Table 1) at 298.15 K using the equation  $\Delta G = -RT \ln K_T$  to determine the molar concentrations of various tautomers in both

phases. We found that conformer **1Z** is present to the extent of 79.6%, **2Z** to the extent of 15.9%, along with small amounts of **1E** (4.2%) and **2E** (0.1%) in the gas phase. In the aqueous phase also, the **1Z** conformer is the dominating one (75.8%), followed by **1E** (20.3%) and **2Ztc** (3.0%), with small amounts of **2Ztt** (0.5%). Therefore, we have considered only the **1Z** conformer for our further studies on BHA.

The **Z-amide** (**1Z**) form of BHA (Scheme 1) is found to be non-planar. Its calculated optimized geometrical parameters and bond order values are given in Tables S1 and S2 (SI). The C<sub>12</sub>–O<sub>13</sub> bond order (1.614) indicates weakening of this C=O bond. The C<sub>12</sub>–N<sub>14</sub> bond order value is 1.179, which indicates that the bond has partial double bond character, implying the involvement of the lone pair of N<sub>14</sub> in resonance with the keto C<sub>12</sub>–O<sub>13</sub> bond. The C<sub>12</sub>–N<sub>14</sub>–O<sub>16</sub>–H<sub>17</sub> dihedral angle (3.5°) and the orientation of O<sub>16</sub>–H<sub>17</sub> with respect to C<sub>12</sub>–O<sub>13</sub> are both favorable for intramolecular hydrogen bonding. The low value of the Wiberg bond order of the O<sub>16</sub>–H<sub>17</sub> bond (0.721) suggests its weakening due to the presence of an intramolecular hydrogen bond between O<sub>13</sub> and H<sub>17</sub>, which is also responsible for the stability of the **1Z** conformer of BHA. This is further supported by the non-bonded distance between H<sub>17</sub> and O<sub>13</sub> of 1.963 Å, which is less than the sum of the van der Waals radii of hydrogen and oxygen (2.68 Å) [34]. The negative charge on O<sub>13</sub> (–0.639) and positive charge on H<sub>17</sub> (0.482) also confirm the existence of a hydrogen bond between them, as suggested by their short non-bonded distance. The values of the dihedral angles (Tables S2, SI) agree well with the values obtained by other workers [31]. Even though an intramolecular hydrogen bond is present in the **1Z** amide isomer, it is not planar because of the mutual repulsion between the lone pairs of the oxygen atoms (O<sub>13</sub> and O<sub>16</sub>) present on the same side of the C<sub>12</sub>–N<sub>14</sub> bond.

It is found that the carbon of the CO–NH moiety acquires a significant positive charge (0.627), whereas the nitrogen and oxygen atoms are negatively charged (–0.314 and –0.639, respectively). This suggests resonance involving the CO–NH group.

The highest occupied molecular orbital (HOMO) of BHA is delocalized over the CO–NH–OH moiety, suggesting some interaction between the oxygen of the carbonyl group and the hydrogen of the hydroxyl group (Fig. 2). The overlap of molecular orbitals further supports the presence of intramolecular hydrogen bonding in BHA. In the HOMO, there is a nodal plane in the benzene ring (Fig. 2). The negative energy of the lowest unoccupied molecular orbital (LUMO) suggests that the molecule is electron-deficient, and the large HOMO–LUMO gap (5.20 eV) implies that BHA is a kinetically stable molecule. The LUMO represents a  $\pi^*$  orbital, as evident from the presence of nodes in the benzene ring, as well as in the C–O and C–N bonds (Fig. 2).

We also calculated various global reactivity indices, like the chemical potential ( $\mu$ ), chemical hardness ( $\eta$ ), electrophilicity ( $\omega$ ) and nucleophilicity (N) for the most stable **1Z** conformer. All these parameters can be calculated using vertical ionization potentials (IP) and electron affinities (EA), whose values were obtained from

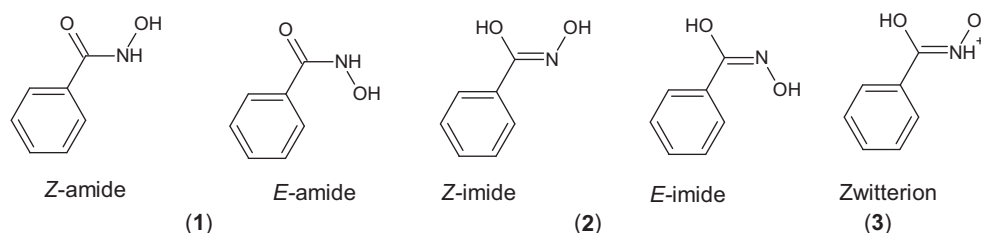


Fig. 1. Tautomers and conformers of benzohydroxamic acid.

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