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A comparative study on hydrogen bonding ability of thioformohydroxamic acid and formohydroxamic acid

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ABSTRACT

The presence of intra and intermolecular hydrogen bonding interactions has been explored in six tautomeric forms of thioformohydroxamic acid and its 1:1 aggregates with water employing MP2/Aug-cc-pVDZ theoretical level. The intramolecular hydrogen bonding interactions are observed to be present in both the most stable forms of thione and thiol tautomeric forms (1Z and 2Z, respectively). The stabilization energy resulting from aggregation of TFHA with H_2O in 1:1 ratio for all the tautomeric forms has been evaluated for different orientations of H_2O relative to TFHA. The most stable aggregate has orientation similar to the most stable aggregate of FHA with H_2O and the stabilization energy for TFHA is only 0.79 kcal/mol less than the value for FHA at MP2/Aug-cc-pVDZ theoretical level.

1. Introduction

The chemistry to study the guiding principles behind the study of weak interactions is an emergent branch [1,2]. Out of several types of weak interactions, the study of hydrogen bonding has always been a topic of interest for the researchers since it represents the strongest force governing the influence of solvents on molecular structure and reactivity [3]. The conventional hydrogen bond can be described as a typical donor–acceptor interaction where one of the participants is electron rich atom like O, N and other is protic hydrogen, while unconventional hydrogen bond includes interactions involving H attached to some electronegative atom and π electrons; C—H and electronegative atom [4–8]. The structures of polypeptides and double helices of polynucleotides are directed by hydrogen bonding interactions. The role of hydrogen bonding in solvation, diffusion through membranes and adsorption on to the surfaces is well recognized [9–12]. Both inter and intramolecular interactions alter the reactivity and structural properties of the molecules.

The interactions with water are particularly important because of water being universal solvent and its abundance in the biological systems. There is scarce information available on H-bonding involving sulfur atoms. The nature of hydrogen bonds formed by sulfur is quite different from that formed by oxygen atoms and is known further from much familiar examples of H_2O and H_2S. According to electrostatics, sulfur atoms are usually positive and oxygen is negative, so the fundamental nature of hydrogen bonds is different in them. The hydrogen bonds to oxygen are driven by charge–charge interaction while in case of sulfur, the stabilization principally results from the interaction of charge on the acidic hydrogen with the dipoles and quadrupoles of sulfur [13–15]. Though the electronegativity difference between H and S is just 0.38 on the Pauling scale, yet there are reports that the hydrogen bond acceptor ability of thioamide sulfur could surprisingly be equal to or exceed that of amide oxygen [16–18].

The living systems contain a number of sulfur containing molecules including thiopeptides, amino acids e.g. cysteine and methionine etc. Hence understanding biomolecular interactions during protein folding by studying S...H bonding carries prime importance in biochemical research [19]. N—H...S hydrogen bonds are suggested to be present at the active site of various cytochrome P450s [20] and these H-bonds play crucial role in stabilizing the Fe (III) state and protecting the complex against decomposition [21]. The influence of N—H...S interactions in regulation of redox potential of the metal—sulfur proteins and other complexes is well known [22,23]. Since the fundamental building block in thiopurines and thiopyrimidines is S=C—NH— [24] and these are H-bonded in the nucleic acid DNA and RNA, thus TFHA (Thioformohydroxamic acid or *N*-hydroxythioformamide) can serve as a model for studying H-bonds in these systems.

The presence of *N*-methylformothiohydroxamic acid has been recognized in bacterial sources is commonly termed Thioformin [25]. The antibiotic activity of cupric and ferric complexes of *N*-methylthioformohydroxamic acid is also reported [26,27]. Thiohydroxamic acids are important in biological and analytical

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chemistry and are utilized in detection and quantitative determination of metals [28]. Using 'S' and 'O' atoms thiohydroxamic acids coordinate with metal ions like Fe^{+3}, Ni^{+2}, Cu^{+2} forming colored metal complexes and hence find applications in detection and quantitative determination of metals [29,30]. A number of thiohydroxamic acids found applications as biocidal compounds for bacteria, fungi, insects, mites and weeds etc. They are effective as antiperspirant and antihypertensive agents, as enzyme inhibitors, and as drugs for treatment of leukaemia. Thiohydroxamic acids have also been used to counteract the effect of war toxins and to alleviate paralysis [31]. Their other important applications include gravimetric and spectrophotometric determination of metals. Cyclic thiohydroxamic acids such as 1-hydroxy-2(1H)-pyridinethione and 3-hydroxy-4-methyl-2(3H)-thiazolethione find diverse applications as fungicides and alkoxy-radical precursors in synthetic procedures and mechanistic studies [34]. It is used in personal care formulation such as hand lotions, emollient creams or in shampoos etc. Zinc chloride, acetate or oxide complex of this compound gives enhanced microbiological activity [35].

Formohydroxamic acid (FHA) has undergone structural analysis by a number of research groups due to its vast number of applications [32,33]. The intra and intermolecular hydrogen bonding ability of FHA has already analysed by us and reported [46]. In spite of numerous applications of thiohydroxamic acid, very few studies have been carried out to understand the chemistry of these molecules. Thiohydroxamic acid is expected to undergo tautomerism as observed in formohydroxamic acid. The earlier experimental reports based on IR spectral studies suggested that thiohydroxamic acid exists in thione form in solid state [36,37]. However the natural products separated from plants (e.g. mustard) contain sulfated *S*-glucosyl thiohydroxamates that are derivatives of thiol form [31]. The intra and intermolecular hydrogen bonding interactions play key role in the stability of tautomers and in the process of tautomerism if the strength of interactions is magnificent. There are several biomolecules that contain sulfur atom/atoms, understanding of S...H hydrogen bond is important to infer their behavior.

The present study explores the hydrogen bonding ability of thiohydroxamic acid in its various tautomeric forms and in 1:1 adduct with H_2O and the comparison with the formohydroxamic acid analogs has been made.

2. Computational details

Gaussian 98 W package [38], the windows version of Gaussian 98 suite of programs is used for performing ab initio molecular orbital calculations [39,40]. Complete optimizations have been performed on the various isomeric forms of TFHA and its water aggregates at MP2/Aug-cc-pVDZ theoretical level without any symmetry constraints. Since these molecules contain several lone pair of electrons, in order to account for electron correlation the inclusion of diffuse functions in the basis sets becomes mandatory. Frequencies are computed analytically to characterize each stationary point as a minimum or transition state and also to determine the zero point vibrational energy (ZPE). ZPE value calculated at HF/Aug-cc-pVDZ level and scaled by a factor of 0.9232 [41] has been used to apply ZPE correction to relative energies, activation and rotational barriers. Ab initio methods have been used to estimate the relative stabilities, the interaction energies of various TFHA–H_2O aggregates and the barriers involved in the interconversion pathway among isomeric forms of TFHA have been estimated employing MP2/Aug-cc-pVDZ level. Natural bond orbital (NBO) analysis [42,43] has been used to determine the second order delocalization energies ($E^{(2)}$ values) and the atomic charges have been determined using natural population analysis (NPA) incorporated within NBO at MP2/Aug-cc-pVDZ level. Basis set superposition error (BSSE) is corrected by counterpoise method of Boys and Bernardi [44]. The distortion energy which estimates the relaxation of monomers on complexation, was computed using Eq. (1)

$$E_{Dis} = (E_a + E_b) - (E_{a,Dis} + E_{b,Dis}) \quad (1)$$

where E_a and E_b are energies of individual monomeric forms in gas phase and $E_{a,Dis}$ and $E_{b,Dis}$ are single point energies obtained for the distorted isolated monomer geometry upon complexation.

3. Results and discussion

3.1. Conformational stability and tautomerism

Keto ↔ enol tautomerism in formohydroxamic acid has been studied by a number of research groups. The replacement of carbonyl oxygen by sulfur can alter the conformational stability, hydrogen bonding ability and the overall reactivity of the molecule. The present study is aimed at understanding the characteristics of thiohydroxamic acids in comparison to formohydroxamic acids. There are two reports on the gas phase intramolecular tautomerism in thioformohydroxamic acid (TFHA) [23,31]. Both the studies concentrate on similar pathways for proton transfer in tautomerization as adopted by formohydroxamic acid (FHA). It has been recognized that hydrogen bonding interactions play important role in stability of tautomers and proton transfer in case of formohydroxamic acid [45]. In thiohydroxamic acid, where sulfur has replaced the oxygen of formohydroxamic acid, hydrogen bonding ability of the molecule can be anticipated to decrease by a significant amount.

To understand the role of H-bonding interactions on conformational stability, seven minima including one zwitter ionic structure have been located employing MP2/Aug-cc-pVDZ theoretical method. All the seven structures and three transition states for intramolecular proton transfer among isomeric forms of TFHA are shown in Fig. 1. Table S1 (Supporting Information) compares geometrical parameters of four most stable isomeric forms of FHA and TFHA. The relative energy differences among these forms at MP2/Aug-cc-pVDZ level are given in Table 1. The gas phase order of stabilities is 1Z > 2Z > 1E > 2E > 2Z2 > 2E2 > Zwitter ion in FHA at MP2/Aug-cc-pVDZ level [46]. The gas phase order of stabilities in TFHA being 2Z > 2Z2 > 1Z > 2E > 2E2 >1E > 3 (Zwitter ion) determined theoretically at MP2/Aug-cc-pVDZ. This order of relative energies for TFHA isomers is the same as determined by R. Kakkar et al. and J.J. Ho et al. [31,23]. The conformation 2Z is the most stable conformation in TFHA while in FHA it was the conformation similar to 1Z.

The comparison of important geometrical parameters of 1Z conformation of TFHA and FHA (Table S1) shows that C—N and O—N bond distances are shorter for the thio analogs (C—N and O—N bond distances are 1.336 Å and 1.379 Å, respectively, in TFHA as compared to 1.368 Å and 1.406 Å in FHA, respectively), thereby suggesting that conjugative interactions in C(=S)—N—O unit of TFHA are stronger than the corresponding interactions in C(=O)—N—O unit of FHA. In spite of enhanced conjugative interactions in 1Z conformer of TFHA, it is 2Z conformation which is more stable than the 1Z. The comparative weaker strength of C=S π bond in comparison to C=N π bond is the rationale behind it. Only 1E conformer shows non planarity in TFHA while both 1Z and 1E conformers of FHA are nonplanar. As thioformamide has planar arrangement of atoms around N, certainly the non planarity in TFHA is the result of presence of hydroxyl group. The repulsive interactions between lone pairs present on oxygen and nitrogen distort the orientation of lone pairs present on nitrogen away from oxygen that favors conjugation with C=S in 1Z while disfavors in