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A theoretical study on the structure of 2-amino-1,3,4-thiadiazole and its 5-substituted derivatives in the gas phase, water, THF and DMSO solutions

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ABSTRACT

The results of a detailed DFT (B3LYP) and ab initio (HF and MP2) investigation on one of the amino–imino tautomers and its derivatives are presented here. The energy, geometrical parameters and vibrational frequencies of 2-amino-1,3,4-thiadiazole tautomerization in the gas phase, water, THF and DMSO solutions were calculated using 6-311++G(d,p), 6-311G(d) and 6-31+G(d,p) basis sets. The solvent effect was explored using the PCM method and the related conformers have been fully optimized at the B3LYP/6-311++G** level of theory. For the investigated molecule, proton-transfer from N to N and from N to C occurred, which leads to three tautomers: 2-amino-1,3,4-thiadiazole (**A**), 2(3H)-imino-1,3,4-thiadiazole (**B**) and 2(5H)-imino-1,3,4-thiadiazole (**C**). For **B** and **C**, geometrical isomerism (*E* and *Z*) was also considered. This leads to five isomers: **A**, $\mathbf{B_1}$, $\mathbf{B_2}$, $\mathbf{C_1}$ and $\mathbf{C_2}$ for each derivative. However, all calculations evidently show that isomer **A** strongly or solely dominates and dictates the structure of 2-amino-1,3,4-thiadiazoles. Substituents and solvents have no effect on the tautomeric preferences.

1. Introduction

The 1,3,4-thiadiazole derivatives were synthesized with the aim of new antituberculosis drug's development. The family of heterocyclic compounds, containing both nitrogen and sulfur atoms is considered as an important class of compounds in medicinal chemistry because of their interesting and diversified biological applications. The 1,3,4-thiadiazole and amino-thiazole groups are associated with various biological activities, probably due to the presence of a toxophoric (−N = C−S−) group [1–4]. The importance of the sulfur atom in drugs as sulfide or disulfide linkages provides great stability for the three-dimensional structure within the molecule [5]. 2-Amino-1,3,4-thiadiazole and certain structurally related compounds have been known for 50 years to have antitumor activity [6]. Compounds of this class are uricogenic agents in man [7]. Both the antitumor and the uricogenic activities can be prevented or reversed by nicotinamide [8,9]. Due to the structural properties of 2-amino-1,3,4-thiadiazoles, they can also participate in several chemical reactions, and they are found to have significant use as intermediate for the synthesis of nitrogen atom containing heterocyclic compounds. To elucidate the reaction mechanisms and reactivity correctly, it is important to obtain information about the tautomeric structures of these compounds [10]. The tautomerism in the title compound is a type of prototropic tautomerism. This phenomenon exists in structures having more than one position to which the mobile proton can be bound. Due to this property one molecule may have more than one structure. It is noteworthy that solvents and substituents have a considerable effect on prototropy.

In this work, the three levels of calculations; HF, MP2 and B3LYP, will be applied to study various tautomerizations of 2-amino-1,3,4-thiadiazole with the specific aim to:

(1) Study the conformational preference of different 2-amino-1,3,4-thiadiazole tautomers.
(2) Investigate the energetics of their tautomers and their relative stabilities in the gas phase and solutions.
(3) Compare the different tautomers with respect to their structure and tautomerization ability.
(4) Explore the effect of substituent type on the structure of 2-amino-1,3,4-thiadiazole tautomers.
(5) Investigate the Cartesian coordinates obtained from the optimized geometry.

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2. Computational methods

The outcomes of the geometry optimizations are presented in Section 3. The total energies are given in hartrees; the relative energies and stabilization energies are given in kcal mol^{-1}; using the conversion factor: 1 hartree = 627.5095 kcal mol^{-1}.

The ab initio (HF [11] and MP2 [12]) and DFT [13] calculations using 6-311++G(d,p), 6-311G(d) and 6-31 + G(d,p) basis sets, full geometry optimizations and harmonic vibrational frequency calculations were performed using the Gaussian 03 program [14]. Density functional theory (DFT) calculations were employed in order to properly account for the electron correlation effects. The actual calculations were performed for three solvents (THF, DMSO and water), which were modeled using the polarizable continuum model (PCM) [15].

B3LYP and HF/6-311++G(d,p) calculations have been carried out to simulate the influence of substitutions in position R of various tautomers of 2-amino-1,3,4-thiadiazole. The following substituents are taken into consideration: CN, NO_2, NO, Cl, F and CH_3.

HOMA which is a geometrical indicator of a local aromaticity [16,17] can be expressed by the following equation:

$$\mathrm{HOMA} = 1 - \frac{1}{n}\sum_{j=1}^{n} \alpha_i \left(R_{\mathrm{opt},i} - R_j\right)^2$$

where n represents the total number of bonds in the molecule and α_i is normalization constant. Using CN and NN bonds: $R_{opt,CN}$ = 1.331 Å, $R_{opt,NN}$ = 1.299 Å, α_{CN} = 97.2, and α_{NN} = 107.5 (all of the values were calculated in this work) gives HOMA = 0 for a model non-aromatic system and HOMA = 1 for a system with all bonds equal to the optimal value $R_{opt,i}$, assuming fully aromatic systems [18]. The higher the HOMA value, the more "aromatic" the ring in question is and, hence, the more delocalized the π-electrons in the system are.

3. Results and discussion

3.1. Tautomerism of 2-amino-1,3,4-thiadiazole

3.1.1. Geometries

Tables of the optimized structural parameters of the studied molecules are given in Table 1, in accordance with the atom-numbering scheme given in Fig. 1.

Calculated geometrical parameters in the gas phase, water, THF and DMSO solutions for all species were very similar. In tautomer **A**, going from the gas phase to polar solvents, the C_2-N_7 bond length decreases and the C_2-N_3 bond length increases, and in tautomer **B**, the C_2-N_3 bond length decreases and the C_2-N_7 bond length increases. These changes show that the charges on N_7 in tautomer **A** and N_3 in tautomer **B** are more delocalized with increasing solvent polarity. Bond angles do not change with increases in the polarity of the solvents. The tautomerization causes significant changes in bond lengths, in the range of about 0.005 to 0.186 Å, except for CH and NH that are about 0.001 to 0.013 Å. Molecular geometries can be specified in terms of bond lengths, bond angles and torsional angles. It can be inferred that for a bond to be stronger, the overlap should be greater, which in turn would shorten the distance between the nuclei, i.e., bond length. A stronger bond has, therefore, a shorter bond length. For **A**, $\mathbf{B_1}$, $\mathbf{B_2}$, $\mathbf{C_1}$ and $\mathbf{C_2}$ species, the strongest bond is formed between N_7-H_8 and the weakest bond is between $S-C_2$. Our calculations show that 2-amino-1,3,4-thiadiazole tautomers are planar structures. The theoretical calculations also show that the difference between two C═N bonds is about 0.08 Å in tautomer **A** which increases to about 0.014 Å in tautomer **B**. It should be mentioned that the equalization of the corresponding bonds is the direct geometrical consequence of more electron delocalization. Regarding the geometry-based aromaticity criterion, HOMA, the results of theoretical calculations indicate that HOMA values are 0.739, 0.711 and 0.658 for **A**, $\mathbf{B_1}$ and $\mathbf{B_2}$, respectively. Higher HOMA values correspond to more electron delocalization. Therefore, greater stability of tautomer **A** can be attributed to more electron delocalization. On the other hand, HOMA values for $\mathbf{C_1}$ and $\mathbf{C_2}$ are negative. Indeed, negative HOMA values are probably not as meaningful as positive values since it is considered that HOMA = 0 corresponds to a typical conjugated non-aromatic species such as 1,3-butadiene [19]. It is worth mentioning, a similar situation is observed in solution.

All of the tautomeric structures of 2-amino-1,3,4-thiadiazole are local minimum with no imaginary frequencies. The depth of the minimum on the potential energy surface (PES) are unknown, however, these result demonstrates that any of these tautomers could be stable, and potentially observable, under ideal conditions.

3.1.2. Energies

Thermodynamic parameters such as relative energies, enthalpies, Gibbs free energies and dipole moment of the various tautomers of 2-amino-1,3,4-thiadiazole were calculated by HF, MP2 and B3LYP methods using 6-31 + G** and 6-311++G** basis sets at 298.15 K and 1 atm pressure and are listed in Table 2. ΔE, ΔG and ΔH of each tautomer are defined as the difference between its total energy or Gibbs free energy or enthalpy with respect to the most stable tautomer **A**.

At all computational levels, the stability order (ΔE in kJmol^{-1}) of 2-amino-1,3,4-thiadiazole tautomers are $\mathbf{A} > \mathbf{B_1} > \mathbf{B_2} > \mathbf{C_1} > \mathbf{C_2}$. The first conspicuous fact of Table 2 is that the **A** tautomer is about 4–19 kcal/mol more stable than the other tautomers ($\mathbf{B_1}$–$\mathbf{C_2}$); that is, the structures containing $-NH_2$ and two C═N bonds are systematically more stable than those containing = N – H and one C═N bond, instead. The positive ΔH demonstrates that tautomerization of the system 2-amino-1,3,4-thiadiazole process is endothermic. The calculated ΔG and ΔH values for $\mathbf{A} \rightarrow \mathbf{C_2}$ are higher than those values for the other tautomerization of the 2-amino-1,3,4-thiadiazole process. The ΔG and ΔH discrepancy between the two processes is responsible for change in activation energies. For any highly endothermic reaction, the transition state is located closer to the product. So, the energy barrier diminishes significantly. The large positive ΔG values indicate that the PT process is quite disfavored, i.e., it is nonspontaneous. Such large positive ΔG value implies that this reaction in gas phase and solutions is thermodynamically and kinetically unfavored, meaning that the reverse reaction is both thermodynamically and kinetically favored.

The dipole moment reflects the molecular charge distribution and is given as a vector in three dimensions. Therefore, it can be used as a descriptor to depict the charge movement across the molecule. The direction of the dipole moment vector in a molecule depends on the centers of positive and negative charges. Dipole moments are strictly determined for neutral molecules. For charged systems, its value depends on the choice of origin and molecular orientation. The dipole moment of all species increases in solvents and it has maximum value in water i.e. stabilized in more polar medium (water) than in less polar solvent (CCl_4) whereas the smallest one was observed for compounds in gas phase (data are available upon request as supplementary Tables).

The total energy of 2-amino-1,3,4-thiadiazole tautomers calculated at B3LYP/6-311++G** level of theory in gas phase, water, THF and DMSO solutions (data are available upon request as supplementary Tables) shows that all tautomers in the polar solvents are more stable than gas phase.

The stability order of the investigated tautomers in all of the solvents is as follows:

$$\mathbf{A} > \mathbf{B_1} > \mathbf{B_2} > \mathbf{C_2} > \mathbf{C_1}.$$

3.1.3. Vibrational frequencies

The most relevant vibrational frequencies for various tautomers of 2-amino-1,3,4-thiadiazole are available upon request as Supplementary