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Theoretical Studies of Transition State, Equilibrium constants and Molecular descriptors of 2-amino-1, 3-benzothiazole tautomers by Density Functional Theory (DFT)

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ABSTRACT

In the present study, we report a theoretical study on molecular structure, electronic and thermodynamical properties of 2-amino-1,3-benzothiazole tautomers by using density functional theory (DFT) methods employing B3LYP exchange correlation with different basis;6-311,6-311++, and 6-311++G(d,p) basis set. The Synchronous Transit-Guided Quasi-Newton (STQN) method was used to locate the transition structures. The reactants and products were fully optimized at the DFT level of theory using 6-311++G (d,P) basis set in gas phase and the equilibrium constant and rate of reaction were calculated. Global descriptors such as ionization energy (I), electron affinity (EA), molecular hardness (η), chemical potential (μ), electrophilicity (ω), and frontier molecular energy gaps (ΔE_g) were determined and used to identify the differences in the reactivity of reactant and product. The bond lengths of transition state were lie between the reactant and product. From the values of η, μ and ω suggested that product is more energetically stable and less reactive, that reactant is more electronegative than the product and reactant is a good electrophile and product is a good nucleophile.

Introduction

A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Nitrogen, oxygen, and sulphur are the most common heteroatoms. Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring. Benzothiazole ring found to be possessing pharmacological activities such as anti- viral [1] , anti- bacterial [2], anti- microbial [3] and fungicidal activities [4].They are also useful as anti-allergic [5], anti-diabetic [6], antitumor [7], anti- inflammatory [8], anthelmintic , and anti- HIV agents. Benzothiazoles show antitumor activity, the phenyl-substituted Benzothiazoles [9,10] while condensed pyrimido benzothiazoles and benzothiazolo quinazolines show anti-viral activity. Substituted 6- nitro-and 6-aminobenzothiazoles show antimicrobial activity [11]. A number of 2-aminobenzothiazoles have been studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments [12].

The number of 2-aminobenzothiazoles was intensively studied, as the 2- amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [13, 14] and reported cytotoxic on cancer cells. [14] It must be emphasized that combination of 2- amino benzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. The 2-(4-aminophenyl) benzothiazoles are novel class of potent and selective antitumor agents and display characteristic profile of cytotoxic response across the cell lines. In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties. In last few years it was reported that benzothiazole, its bioisosters and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacterias (e.g., Enterobacter, Pseudomonas aeruginosa, E. coli, and Staphylococcus epidermidis etc.) and the yeast (e.g., Candida albicans).

Computational details

The initial structures of benzo[d]thiazol-2-amine (Amine) and their tautomer benzo[d]thiazol-2(3H)-imine (Imine) were optimized in a gas phase by Becke's three parameter hybrid

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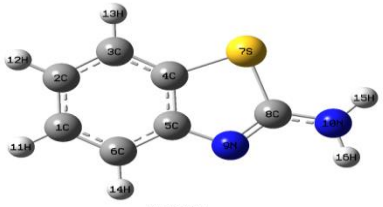
density functional theory method (DFT) [15] using the Lee-Yang-Parr correlation functional (B3LYP) [16] with different basis sets 6-311,6-311++ and 6-311++G(d,p) with the Gaussian 09W program[17]. Following the geometry optimizations, analytical frequency calculations were preceded following the standard procedures, to obtain the thermo chemical properties. The structures of amino and imino tautomers were modeled with Gaussveiw program.

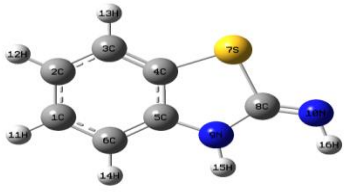
The Synchronous Transit-Guided Quasi-Newton (STQN) method [18] was used to locate the transition structures. The reactants and products were fully optimized at the DFT level of theory using 6-311++G (d,P) basis set in gas phase. It uses a linear synchronous transit or quadratic synchronous transit approach to get closer to the quadratic region around the transition state and then uses a quasi-Newton or eigenvector-following algorithm to complete the optimization. It performs optimizations by default using redundant internal coordinates. This method will converge efficiently to the actual transition structure using an empirical estimate of the Hessian and suitable starting structures. To characterize each stationary point as a minimum or a transition state and to estimate the zero point vibrational energies (ZPE) and vibrational frequencies for all optimized species were computed at all levels. The transition states were further confirmed by vibrational analysis and characterised by only one imaginary vibrational mode.

Results and Discussion

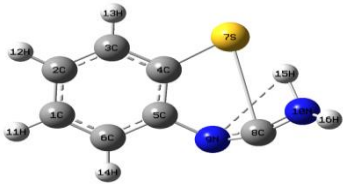
2-amino-1,3-benzothiazole was exiting two tautomers ;one is amine form {(benzo[d]thiazol-2-amine (ABTA)}tautomer and other one is imine form {(benzo[d]thiazol-2(3H)-imine(ABTI) }tautomes. The amine and imine tautomers in whose structures, where in the thiozole ring the amine form has the NH_2 group and one N-H bond while in the imine form that ring contain two N-H and C=N bonds. The geometry of 2-amino-1, 3-benzothiazole tautomers (ABTA& ABTI) were optimized at DFT (B3LYP) levels using different basis sets; 6-311, 6-311++, 6-311++G (d,p) in gas phase. At the optimized geometry for the title molecule no imaginary frequency modes were obtained, so there is a true minimum on the potential energy surface. The optimized molecular structure with symbols and numbering of the title molecule is obtained from Gaussian 09W **[**17**]** and Gauss View programs as shown in the Fig. (1). In addition to locate the transition state (TS), the reactants and products were fully optimized at the DFT level of theory using 6-311++G (d,p) basis set in gas phase as shown in Fig.1. The transition states were further confirmed by vibrational analysis and characterized by only one imaginary vibrational mode.



ABTA



ABTI



TS

Figure 1. Optimized geometrical molecular structures of 2-amino-1,3-benzothiazole tautomers and transition state (TS) structure at DFT/B3LYP/6-311++G (d,p) in gas phase.

The bond lengths of ABTA and ABTI are listed in Table 1., at different level of basis sets and also included the transition state (TS) bond lengths at 6-311++G(d,p) bsis set. Compared the bond lengths from Table 1, all bonds are small difference with different basis sets and all C-C, C-N and C-S bond lengths with 6-311++G (d,p) are less than with other (6-311,6-311++) basis sets bond lengths, but different trend in case of C3-C4 bond length for the two tautomers. Because of the benzene ring C4 atom was attached by the thiozole ring S7 atom. The remaining all C-H and N-H bond lengths are higher values with 6-311++ G (d,p) basis set compared to the other two basis sets. The bond lengths of 2-amino-1,3-benzothiazole transition state was lie between the reactant (ABTA) and product (ABTI).

Energies

The absolute energies were presented from the full geometry optimizations performed on the reactant, transition state and products in gas phase and presented in table 2. Comparison of energies the product is more stable than reactant. As we can see from Table 2, the calculated dipole moments are changed on moving from reactant to product.

The imine tautomer has the largest dipole moment than the amine tautomer, having the largest dipole moment the imine tautomer is expected to have the strongest interaction with polar molecules of water in biological environment. The structure of a tautomer obviously affects the magnitude and orientation of a dipole moment. However, the position of hydrogen attached to nitrogen in the thiozole ring of ABTI has much greater influence on the dipole moment. Not only does it affect the magnitude of the dipole moment but it even changes its orientation. This is indicated by the fact that the orientation of dipole moments.

Thermodynamics Analysis

Thermodynamics Analysis results provided in Tables 3 are for the change of enthalpy (ΔH), the change free energy (ΔG) and the change of entropy (ΔS) for the conversion of amine tautomer to imine tautomer. Gibbs free energy is evaluated under standard condition, i.e. 298.15 K and 1 atmosphere using the aforementioned methods. The ΔH is positive, the reaction is endothermic and the bonds formed in the products are weaker than the bonds broken in the reactants. The equilibrium constant provides a measure of the degree to which reactants or products are favored during the course of a chemical reaction.. Based on the Gibbs free energies of the species provided by Table 3, the equilibrium constant (K) can be readily calculated using equations

$$K = e^{-\Delta G/RT} \quad (1)$$

The equilibrium constant between for the amine tautomer (ABTA) and imine tautomer (ABTI) was calculated by using equation (1), K = 0.985079. The equilibrium constant is nearly one (K ≈1), the concentration of the products and the concentration of the reactants are equal, so the compound existing the mixture of two forms.

Table 1. Optimized geometrical parameters of 2-amino-1,3-benzothiazole tautomers (ABTA&ABTI) and transition state bond length (Å).

Bond length	ABTA			ABTI			TS
	6-311	6-311++	6-311++ G(d,p)	6-311	6-311++	6-311++G(d,p)	6-311++ G(d,p)
C1-C2	1.4025	1.4034	1.4001	1.3984	1.3994	1.3952	1.3911
C1-C6	1.3950	1.3956	1.3911	1.3989	1.3993	1.3957	1.3803
C1-H11	1.0816	1.0819	1.0841	1.0813	1.0816	1.0836	1.0696
C2-C3	1.3994	1.4000	1.3940	1.4013	1.4018	1.3968	1.3826
C2-H12	1.0814	1.0818	1.0837	1.0810	1.0813	1.0833	1.0705
C3-C4	1.3886	1.3897	1.3906	1.3870	1.3882	1.3888	1.395
C3-H13	1.0808	1.0811	1.0835	1.0808	1.0812	1.0835	1.0687
C4-C5	1.4145	1.4142	1.4141	1.4045	1.404	1.4035	1.3995
C4-S7	1.8313	1.8302	1.7639	1.8328	1.8331	1.7706	1.8468
C5-C6	1.3984	1.3986	1.3983	1.3956	1.3959	1.3915	1.3839
C5-N9	1.4027	1.4034	1.3861	1.4008	1.4013	1.3914	1.4368
C6-H14	1.0803	1.0808	1.0833	1.0821	1.0825	1.0843	1.0693
S7-C8	1.8742	1.8687	1.7888	1.8666	1.8627	1.7982	3.0126
C8-N9	1.2969	1.2967	1.2920	1.3977	1.3952	1.3898	1.1755
C8-N10	1.3568	1.3589	1.3586	1.2720	1.2741	1.2695	1.2561
N10-H15	1.0015	1.0024	1.0036	------	------	-------	1.2472
N9-H15	------	------	------	1.0069	1.0073	1.0086	2.6714
N10-H16	1.0047	1.0057	1.0066	1.0223	1.0226	1.0189	0.9935

Table 2. Gas phase absolute electronic energies, in atomic units (Hartrees) of reactant (ABTA), Product (ABTI) and transition state (TS) and dipole moment (μ) with different basis sets.

	ABTA	ABTI	TS	μ(ABTA)	μ(ABTI)	μ(TS)
6-311	-778.038193	-778.021535	-----	1.9215	4.3884	-----
6-311++	-778.048294	-778.032394	------	1.7890	4.4760	------
6-311++g(d,p)	-778.192632	-778.178433	-774.791119	2.2240	3.9277	5.5542

Table 3. The change of enthalpy (ΔH), the change free energy (ΔG) and the change of entropy (ΔS) for the conversion of amine tautomer to imine tautomer and equilibrium constant(K) and activation energies of transition sate and the rate constant(k).

	Thermodynamic data			
Basis set	ΔH(kcal/mol)	ΔG(kcal/mol)	ΔS(cal/mol)	K
6-311	9.986814	10.108551	-0.41	0.983082
6-311++	9.706317	9.929710	-0.748	0.983379
6-311++G(d,p)	9.329184	8.906242	1.419	0.985079
TS				
	$\Delta H^{\neq}$	$\Delta G^{\neq}$	$\Delta S^{\neq}$	k
6-311++G(d,p)	2037.741092	2037.850279	-229.040967	0.000

Table 4. The theoretical electronic properties (HOMO, LUMO) and energy gap (E_g) and reactive descriptors ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (s), chemical potential (μ), softness (S), electrophilicity index (ω), charge transfer (ΔN_{max}), nucleofugality (ΔE_n) and electrofugality (ΔE_e) of cyanuric acid tautomers calculated by DFT/with different basis set in gas phase.

descriptors	ABTA			ABTI			TS
	6-311	6-311++	6-311++ G(d,p)	6-311	6-311++	6-311++ G(d,p)	6-311
HOMO	-0.21983	-0.22456	-0.21986	-0.21689	-0.22125	-0.21752	-0.29006
LUMO	-0.02032	-0.02697	-0.02420	-0.02264	-0.02998	-0.03176	-0.06033
I	5.98188	6.11059	5.98269	5.90188	6.02052	5.91902	7.89294
ΔE_g	-5.42895	-5.37670	-5.32418	-5.28581	-5.20472	-5.05479	-6.25127
A	0.55293	0.73389	0.65851	0.61606	0.81579	0.86423	1.64166
χ	3.26740	3.42224	3.32060	3.25897	3.41816	3.39162	4.76730
η	2.71447	2.68835	2.66209	2.64291	2.60236	2.52739	3.12564
μ	-3.26741	-3.42224	-3.32061	-3.25897	-3.41816	-3.39163	-4.76730
ω	0.67861	0.67208	0.66552	0.66072	0.65059	0.63184	0.78141
S	0.18419	0.18598	0.18782	0.18918	0.19213	0.19783	0.15997
ΔN_{max}	1.20370	1.27299	1.24737	1.23310	1.31348	1.34195	1.52523
ΔE_n	0.12568	-0.06180	0.00700	0.04466	-0.16521	-0.23239	-0.86025
ΔE_e	6.66050	6.78260	6.64820	6.56260	6.67110	6.55080	8.67435

Reaction Energies

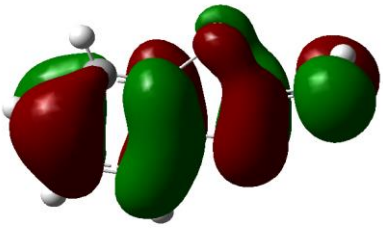
Geometries of reactant, product and transition state are fully optimized at the DFT/B3LYP/6- 311++G(d,p) level and the character of the stationary points is confirmed by frequency calculations performed at the same level. Frequency calculations were carried out for both ground and transition state geometries, with the latter having one imaginary frequency corresponding to the reaction coordinate [19]. All the reported transition states present one, and only one imaginary frequency corresponding to the expected transition vector. The first order coefficient K(T) was calculated using transition State theory (TST) assuming that the transition coefficient is unity as shown in the following equation [20]:

$$k(T) = \frac{k_B T}{h} e^{-\Delta G^{\neq}/RT} \quad (2)$$

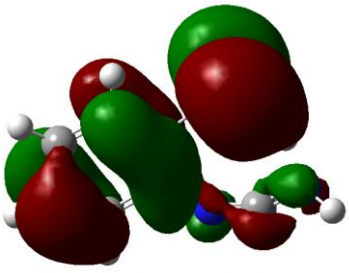
Where $\Delta G^{\neq}$ is the Gibbs free energy change between the reactant and the transition state and k_B and h are the Boltzmann and Planck's constants respectively. By using equation (2), the rate constant is zero. That means the title compound is always the mixture of two tautomers.

HOMO-LUMO energies

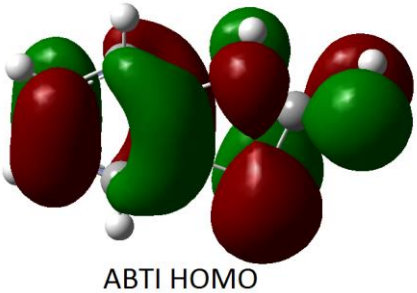
The calculated HOMO level, LUMO level, and HOMO-LUMO energy gap (ΔEg) are summarized in Table 4 in gas phase for amine (ABTA) and imine (ABTI) and transition sate (TS). In fact, it is important to study of the HOMO and LUMO energies and to test how these will affect the quantities that are related to these frontier orbitals and, accordingly, the chemical reactivity. The HOMO and LUMO orbital's for tautomers in ground state and the transition sate shown in the Fig 2.



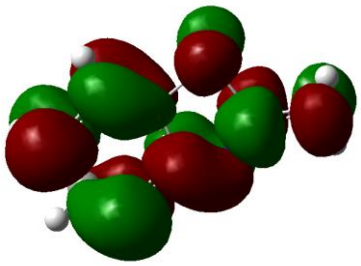
ABTA HOMO



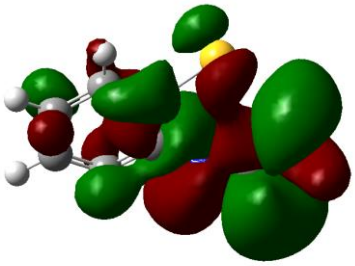
TS HOMO



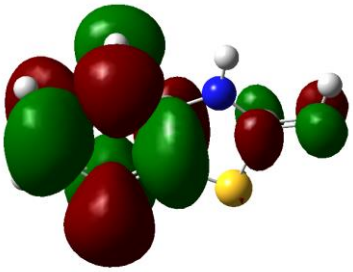
ABTI HOMO



ABTA LUMO



TS LUMO



ABTI LUMO

Figure 2. The HOMO and LUMO frontier molecular orbitals of two tautomers and transition sate at at DFT/6-311++G (d,p) level in gas phase. In surface box, grey= available; Red= displayed.

Global descriptors

There is a large interest in the study of reactivity indices such as electronegativity [21], hardness [22], electrophilicity [23], nucleophilicity [24] and nucleofugality [25] with great importance for classifying organic and inorganic molecules. In this, the important quantities to be obtained are the frontier orbitals (the highest occupied and the lowest unoccupied, HOMO and LUMO, respectively). From the energies of these orbitals and using the frozen orbital [26] approximation, one can calculate the chemical potential (μ) [21, 27], global hardness (η) [28], electrophilicity (ω)[29,30], nucleophilicity [31], nucleofugality [32] and local reactivity indices, such as local softness[33]. These quantities have been calculated and were used to understand the chemical reactivity of molecular systems. Chemical potential, (μ), global chemical hardness (η), electronegativity (χ) are defined as follows:

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(\vec{r})} \quad \text{and} \quad \mu = \left(\frac{\partial E}{\partial N}\right)_{V(\vec{r})} \quad (3)$$

Softness [34] is a property of molecules that measures the extent of chemical reactivity. It is the reciprocal of hardness and electronegativity has been defined as the negative of the electronic chemical potential in Mulliken sense.

$$S = \frac{1}{\eta} \quad \text{and} \quad \chi = -\mu = \left(\frac{\partial E}{\partial N}\right)_{V(\vec{r})} \tag{4}$$

Using Koopmans theorem for closed-shell molecules, η, μ and χ can be redefined as:

$$\eta \approx \frac{1}{2}\left(IP - EA\right) \approx \frac{1}{2}\left(\varepsilon_{LUMO} - \varepsilon_{HUMO}\right) \tag{5}$$

$$\mu \approx \frac{1}{2}\left(IP + EA\right) \approx \frac{1}{2}\left(\varepsilon_{HUMO} - \varepsilon_{LUMO}\right) \tag{6}$$

$$\chi = \frac{I + A}{2} \tag{7}$$

The concept of electrophilicity viewed as a reactivity index was introduced by Parr et al.[35 It is based on a second order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. This index, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, is defined by the following simple and more familiar form [36] in terms of the electronic chemical potential (μ) and the chemical hardness(η). Electrophilicity is a useful structural depictor of reactivity and is frequently used in the analysis of the chemical reactivity of molecules.

$$\omega = \frac{\mu^2}{2\eta} \tag{8}$$

On the other hand, the maximum amount of electronic charge that an electrophile system may accept is given by [37]

$$\Delta N_{\max} = -\frac{\mu}{\eta} \tag{9}$$

The maximum charge transfer ΔNmax towards the electrophile was evaluated using Eq. (9).Thus, while the quantity defined by Eq. (9) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (9) describes the charge capacity of the molecule. Very recently, Ayers and co-workers [38, 39] have proposed two new reactivity indices to quantify nucleophilic and electrophilic capabilities of a leaving group, nucleofugality (ΔEn) and electrofugality (ΔEe), defined as follows

$$\Delta E_n = EA + \omega = \frac{(\mu + \eta)^2}{2\eta} \tag{10}$$

$$\Delta E_e = IP + \omega = \frac{(\mu - \eta)^2}{2\eta} \tag{11}$$

Naturally, earlier studies have analyzed isolated molecules corresponding to the gas phase situation. However, most of the chemical reactivity occurs in solution. As the presence of the solvent may lead to significant differences in the chemical behavior, it is very important to understand its effects. Hence, the study of reactivity indices in solution is the natural next step and has indeed been of interest.

The theoretical electronic properties (HOMO, LUMO) and energy gap (E_g) and reactive descriptors ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (s), chemical potential (μ), softness (S), electrophilicity index (ω), charge transfer (ΔNmax), nucleofugality (ΔEn) and electrofugality (ΔEe) of cyanuric acid tautomers calculated by DFT/with different basis set in gas phase are presented in Table.4.

HOMO-LUMO gap as a characteristic of reactivity shows that imine tautomer is expected to be more reactive than amine tautomer i.e. the product is more reactive than reactant. So for more energetically stable and less reactive is product. A higher HOMO energy and lower LUMO energy corresponds for molecular reactions with electrophiles and nucleophiles respectively.

The hardness corresponds to the gap between these two orbitals in the molecule, and it measures the resistance of a molecule to a change in their electron distribution and hardness corresponds to higher stability and lower reactivity for particular aromatic systems. From the table 3, values show that the product has low hardness (η) value, so for more energetically stable and less reactive product .The chemical potential measures the escaping tendency of an electron and is minus the Mulliken electro negativity. Also, note that μ is lower value for reactant comparison to the product. This behavior indicates that reactant is more electronegative than the product. According to this definition ω measures the susceptibility of chemical species to accept electrons. Thus, low values of ω suggest a good nucleophile while higher values indicate the presence of a good electrophile. Therefore reactant is a good electrophile and product is a good nucleophile.

Conclusion

A theoretical study of the reactivity was carried out at the density functional theory (DFT) calculation level for the structures of 2-amino-1,3-benzothiazole tautomers. The converts of two structures were studied by transition state theory (TST) by using DFT/B3LYP level and 6-311++G (d,p) basis set in gas phase. From the equilibrium constant the reaction lies equilibrium and the rate constant is 0.0 s^{-1}. Therefore the reaction is always equilibrium and the two tautomers exiting equal. HOMOLUMO energy gap indicate the product is more reactive than reactant. From the values of η, μ and ω suggested that product is more energetically stable and less reactive, that reactant is more electronegative than the product and reactant is a good electrophile and product is a good nucleophile.

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