



Conformational study, Rotation Barrier and Solvent Effect of bi-1,2,3-triazole compounds using DFT calculations

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Abstract

The conformational analysis of the bi-1,2,3-triazole molecule has been studied using Density Functional Theory (DFT) at B3LYP/6-311++G(d,p) level of theory. The potential energy surface (PES) scan of eight configurational isomers for bi-1,2,3-triazole has been studied and fourteen conformers with energy minima have been found. Various electronic and thermodynamic parameters have been evaluated to obtain the most favorable conformer among all. The geometry of the most favorable conformers for each configurational isomer was optimized using Polarizable Continuum Model (PCM) model of solvent. The gas phase electronic energy for most favorable conformers were compared with the electronic energy in cyclohexane, chloroform, methanol and water solvents. Vibrational spectroscopic analysis has been performed for the most stable conformer in the gas phase and selected solvents.

Keywords: Conformational analysis; bi-1,2,3-triazole; solution phase; DFT calculations.

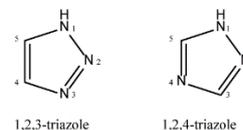
1. Introduction

The conformational preference of heterocyclic compounds has recently been the subject of several experimental and theoretical studies [1]. Heterocyclic compounds have an excessive diversity of physical, chemistry, and biological properties which provide them a wide range of useful application. Such these compounds are largely used in the pharmaceutical industry not only in commercial products but also in research and development. More recently, they are gaining attention in researches for the development of new anticorrosive compounds [2].

Nitrogen-containing heterocycles are one of the important compounds found in organic chemistry as well as in the pharmaceutical industry. Among these, 1,2,3-triazoles have drawn considerable attention in the chemical community. The application of triazoles has emerged in each corner of pharmaceutical research including derivatives with anticancer, antibacterial, antiviral, and antifungal properties. In addition to the pharmaceutical applications, they have also been

proposed for industrial applications such as lubricants, photo-stabilizers, and dyes [3].

Triazole is an important class of heterocyclic compounds exhibiting a wide range of pharmacological activities. It is also known as pyrotriazoles, and is a five-membered, diunsaturated ring system containing three nitrogen atoms in a heterocyclic core and occurs in two possible isomeric forms, 1,2,3 triazoles and 1,2,4 triazoles Scheme 1.



Scheme 1: 1,2,3-triazole and 1,2,4-triazole.

Compounds containing the 1,2,3-triazole moiety can be synthesized through click-chemistry, which is rapid reactions with good yields allowing the synthesis of a great derivatives diversity by making minor changes in the reagents. Compounds containing the 1,2,3-triazole moiety can be synthesized through click-

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chemistry, which is rapid reactions with good yields allowing the synthesis of a great derivatives diversity by making minor changes in the reagents. The copper-catalyzed 1,3-dipolar cycloaddition reaction between an azide and an alkyne is widely used for the synthesis of compounds with the 1,2,3-triazole ring with substituents in position 4 [4].

1,2,3-triazole are attractive constructs of target molecules due to their wide range of biological properties, such as antimicrobial [5], antitubercular, antimalarial, antibiotic, anticancer, cyto-toxic agents, and antioxidant [6, 7]. Meanwhile, some evidences had roved that triazole-functionalized derivatives of poly saccharide showed obviously enhanced biological activities incomparison to raw poly saccharide. Several therapeutically active compounds containing 1,2,3-triazole moiety have been reported as antimicrobials, anti-HIV agents and kinase inhibitors [8].

The number of works about the synthesis of bi-1,2,3-triazoles have increased considerably in recent years; however, there are few reports which describe structural and other physical characteristics [9, 10].

Bi-1,2,3-triazole structure is similar to other biaryl compounds such as binaphthyls, bipyridines, biimidazoles, bipyrazoles, and 4,4'-bi-1,2,4-triazoles [10]. This characteristic converts bi-1,2,3-triazoles in potential useful ligands for catalysis with others. Hence, structural studies in bi-1,2,3-triazoles are important in order to describe properties such as possible coordination sites and stable conformations, especially those which are related to the aromatic rings linked by a single bond forming the biaryl part of the molecule.

The synthetic approaches for the preparation of biand bistriazoles are discussed in detail and their application is discussed briefly in each section. Accordingly, the following three types of bi- and bistriazoles will be primarily presented: (1) The 4,4'-linked symmetric or unsymmetrical bitriazoles, (2) The 5,5'-linked symmetric bitriazoles, and (3) The bistriazoles formed through spacers from the dialkyne or diazide substrates [11].

In the past years, bis-triazoles with dialkyne spacers have gained significant attention for their potential application in supramolecular chemistry, pharmaceutical chemistry, biological chemistry and organometallic chemistry. "The construction of bistriazoles from dialkynes is now well-developed, and three main methods are reported: (1) the one-pot CuAAC reactions of the terminal dialkynes with two equiv of the organic azides, providing the corresponding bistriazoles, which is the most popular method for the synthesis of bistriazoles with dialkyne spacers. (2) The second protocol is the sequential CuAAC-deprotection-CuAAC reaction for the construction of the bistriazoles. In general, the trialkylsilyl group was used as a temporary masking

group for one of two alkyne moieties. Thus, this method provides the possibility of one molecule bearing two alkynes reacted with two different organic azides. (3) The third method involves the utilization of the substrate bearing two alkyne moieties with different reactivity in the successive Huisgen cycloaddition reactions: Huisgen reaction of the activated alkyne with the first azide and the CuAAC reaction of the nonactivated alkyne with another azide, leading to the corresponding bistriazoles [12]".

Some bis-triazole-based commercial drugs are also available in the market, for example Fluconazole, Itraconazole and Posaconazole were used as antifungal drugs and Vorozole as antineoplastic drug. Fluconazole was the first-line bis-triazole-antifungal drug recommended by World Health Organization (WHO) [13]. The application of bitriazoles as chelating N- heterocyclic carbene ligands for ruthenium(II), palladium(II), and rhodium and their applications in catalytic organic synthesis have also been reported.[14, 15]. Some of the bis-triazole products showed noteworthy activity against B16 melanoma included in the range 1-20 μM [8].

To the best of our knowledge, the detail information about the conformational analysis of bi-1,2,3-triazole have not yet been obtain previously. Therefore, the aim of the present theoretical research is to study the conformational analysis of bi-1,2,3-triazole in the gas as well as in different solvents.

2. Methods and calculations

All calculations are performed using the Gaussian 09 program package using default optimization criteria [16]. The DFT method with B3LYP functional is employed in this study (Khabashesku, Kudin & Margrave 2001; Lemal 2017; Parr & Weitao 1989). B3LYP (Becke's three-parameter hybrid exchange functional and the Lee-Yang-Parr correlation functional) is used throughout in combination with the 6-311++G(d,p) basis set [17, 18]. All energies and thermodynamic parameters reported in this paper were obtained from the frequency calculations at the same level of theory. The enthalpies, Gibbs free energies and entropies in gas phase were deduced with the standard statistical thermodynamics at 298.15 K and 1 atm.

The conformer geometries are optimized in the potential energy surface using same level of theory. The effect of various solvents were included with the integral equation formalism-polarizable continuum model (IEF-PCM) of solvation [19, 20]. The IR spectra for the most stable conformers at different solvents are obtained using optimized geometry. All frequencies are found to be positive to ensure the geometry corresponding to true minimum in the potential energy surface.

3. Results and Discussion

The conformational analysis of different configurational isomers of bi-1,2,3-triazole were studied theoretically using DFT method at B3LYP/6-311++G(d,p) level of theory. The configurational isomers were **I1** - **I8** as shown in Scheme 2.

In order to verify whether the optimized bi-1,2,3-triazole structures belong to the global maxima or global minima of molecular potential energy surface, we have considered the rotation of the N-N or C-C bond of bi-1,2,3-triazole, which results in the change in dihedral angles. Therefore, the potential energy surfaces for each configurational isomer have scanned along the dihedral angle and the scan curve are plotted in Figure 1. The conformers for configurational isomers were also labeled in potential energy surface (PES) curves. All possible conformers are shown in Figure 2.

The PES curves were performed on driving the dihedral angle from 0° to 180°. The results showed that twenty seven conformers, of which fourteen were energy minima and thirteen transition states, were significant in the description of the conformational properties of bi-1,2,3-triazole. **Figure 1-I1** shows the PES scan curve of **I1** and it clearly reveals that **I1b** and its corresponding optimized structure in **Figure 2-I1b** indeed corresponds to global minimum. The thermodynamic parameters, relative energies and imaginary frequency values for all conformers are listed in **Table 1**. The dihedral of **I1b** is approximately 112° and its relative energy is 44.68 kcal/mol relative to the lowest conformer **I3c**. The global and local maxima were found at 0° (**I1a**) and 180° (**I1c**) at energy levels of 8.36 and 0.97 kcal/mol, respectively, relative to the lowest **I1b** of the configurational isomer **I1**. The energy maxima **I1a** and **I1c** have an imaginary frequency of -109.28 cm⁻¹ and -51.08 cm⁻¹, respectively.

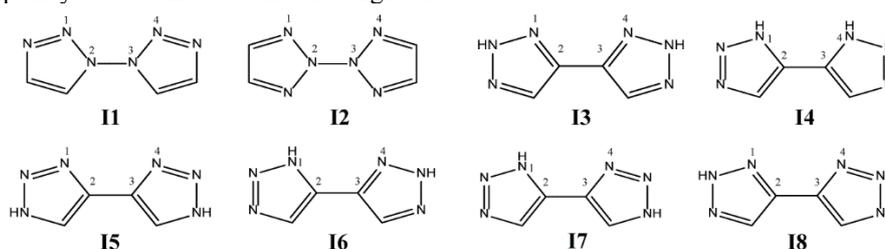
Conformational search of **I2** gave one energy minimum structure **I2b**, when dihedral angle is 90°, having lower energy than **I1b**. We also found two transition state structures **I2a** and **I2c** having only an imaginary frequency, which are less stable than **I2b** by 5.46 kcal/mol. The PES scan curve **I3** exhibits two minima **I3a** and **I3c** at a dihedral angles corresponding to 0° and 180°, respectively. The PES curve, see **Figure 1-I3**, displays one global maxima **I3b** with an imaginary frequency -60.33 cm⁻¹ at a dihedral angle of

90°. The **I3c** conformer is more favorable conformer than **I3a** by about 3.0 kcal/mol. The PES scan for configurational isomer **I4** gave two minima **I4b** and **I4d** at dihedral angles 38° and 145°, respectively, and three maxima **I4a**, **I4c** and **I4e** at dihedral angles 0°, 84° and 180° having an imaginary frequency -62.33, -43.52 and -42.54 cm⁻¹, respectively. The configurational isomer **I5** has two conformers **I5b** and **I5d** as minima at dihedral angles 45° and 180°, respectively. These two conformers are very far in energy by 5.78 kcal/mol, see **Figure 1-I5**, with very low energy barrier of only 0.21 kcal/mol.

Configurational isomers **I6**, **I7** and **I8** have two optimized conformers as minima at dihedral angles 0° and 180°. The PES scan curve shows that **I6** and **I7** have global minima at a dihedral angle of 0°, while **I8** has global minima at a dihedral angle 180°. The isomers **I6**, **I7** and **I8** have global maxima at dihedral angles corresponding to 90°, 100° and 80°, respectively, each with a single imaginary frequency. It worth to notice that these configurational isomers have very close energy barriers approximately 4.26, 4.80 and 4.84 kcal/mol for isomers **I6**, **I7** and **I8**, respectively.

The DFT results for all possible conformers of all configurational isomers of bi-1,2,3-triazole in gas phase have been compared and tabulated in Table 1. It is worth to note that configurational isomer **I3** has more favorable conformers as compared to the others. Particularly, the conformer **I3c** has the lowest electronic energy with an energy barrier of only 1.67 kcal/mol. The **I8c** conformer is considered as a second most favorable conformer with an energy 3.50 kcal/mol relative to the most stable **I3c** conformer.

The geometry of the most favorable conformers for each configurational isomer were optimized using IEPCM model of solvent. The electronic energy in gas phase was compared with different solvents (cyclohexane, chloroform, methanol and water). The relative energies (ΔE) for more favorable conformers were listed in Table 2. The energies are given relative to the most stable conformers, **I3c**. Based on the ΔE results given in Table 2, the stability of conformers increases as the dielectric constant of the solvent increased. It is worth to note that the conformer exhibits the higher obtained dipole moment is favored in the conformational distribution for water and methanol as polar solvents, see Table 3.



Scheme 2: Configurational isomers for bi-1,2,3-triazole.

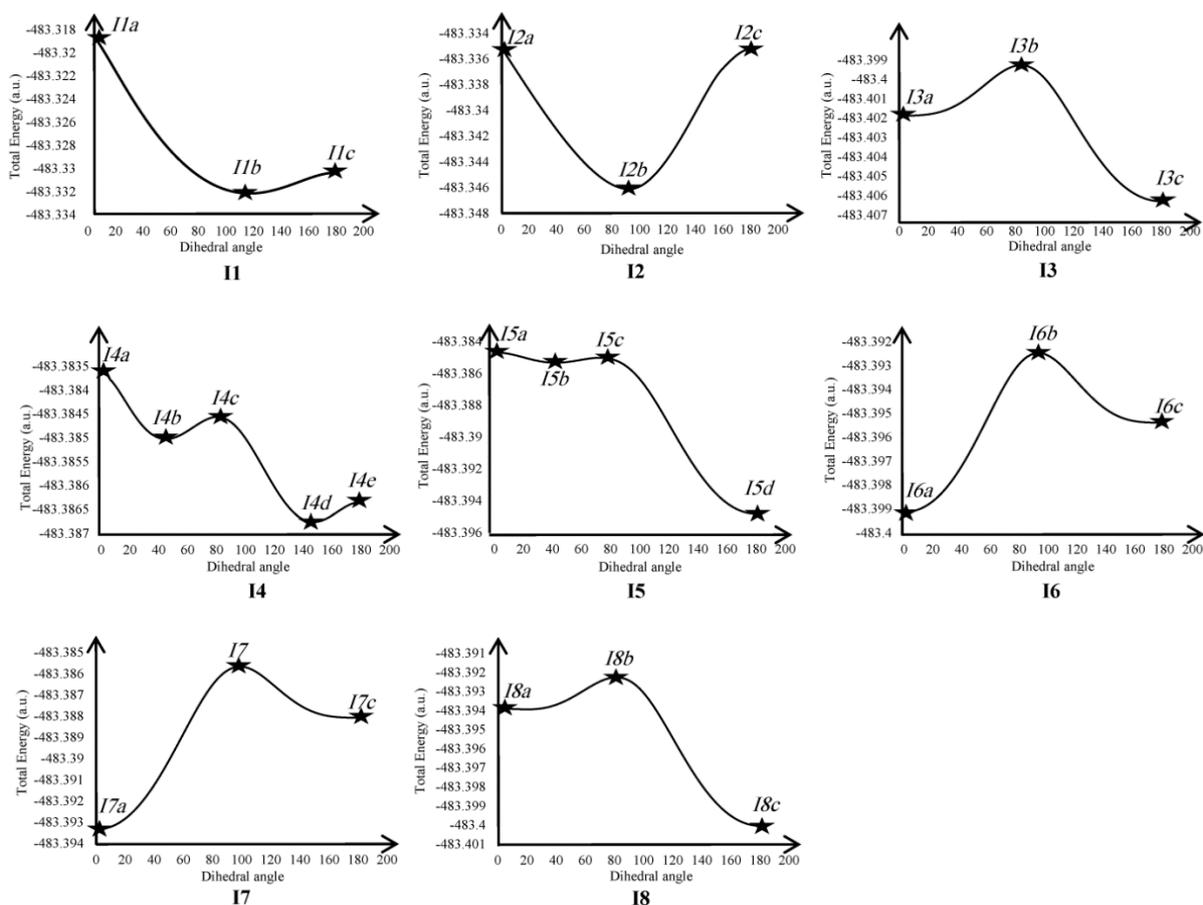
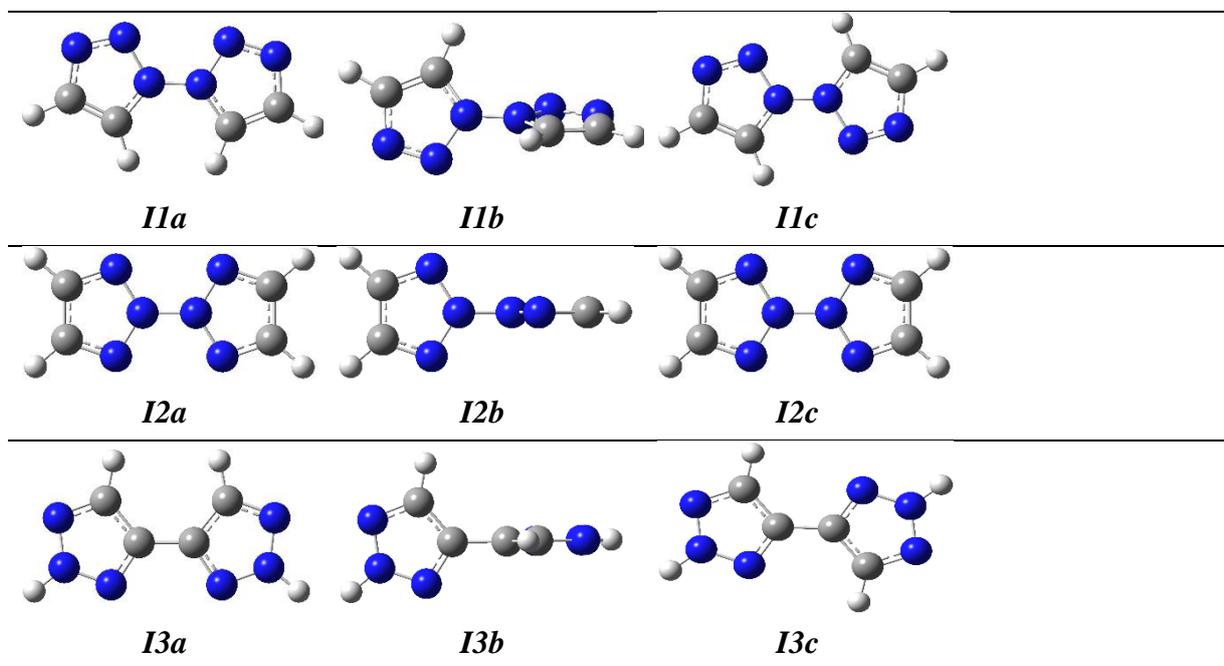


Figure 1: Potential energy surface scan of the calculated energies against dihedral angles at B3LYP/6-311++G(d,p) level of theory for configurational isomers of bi-1,2,3-triazole in gas phase.



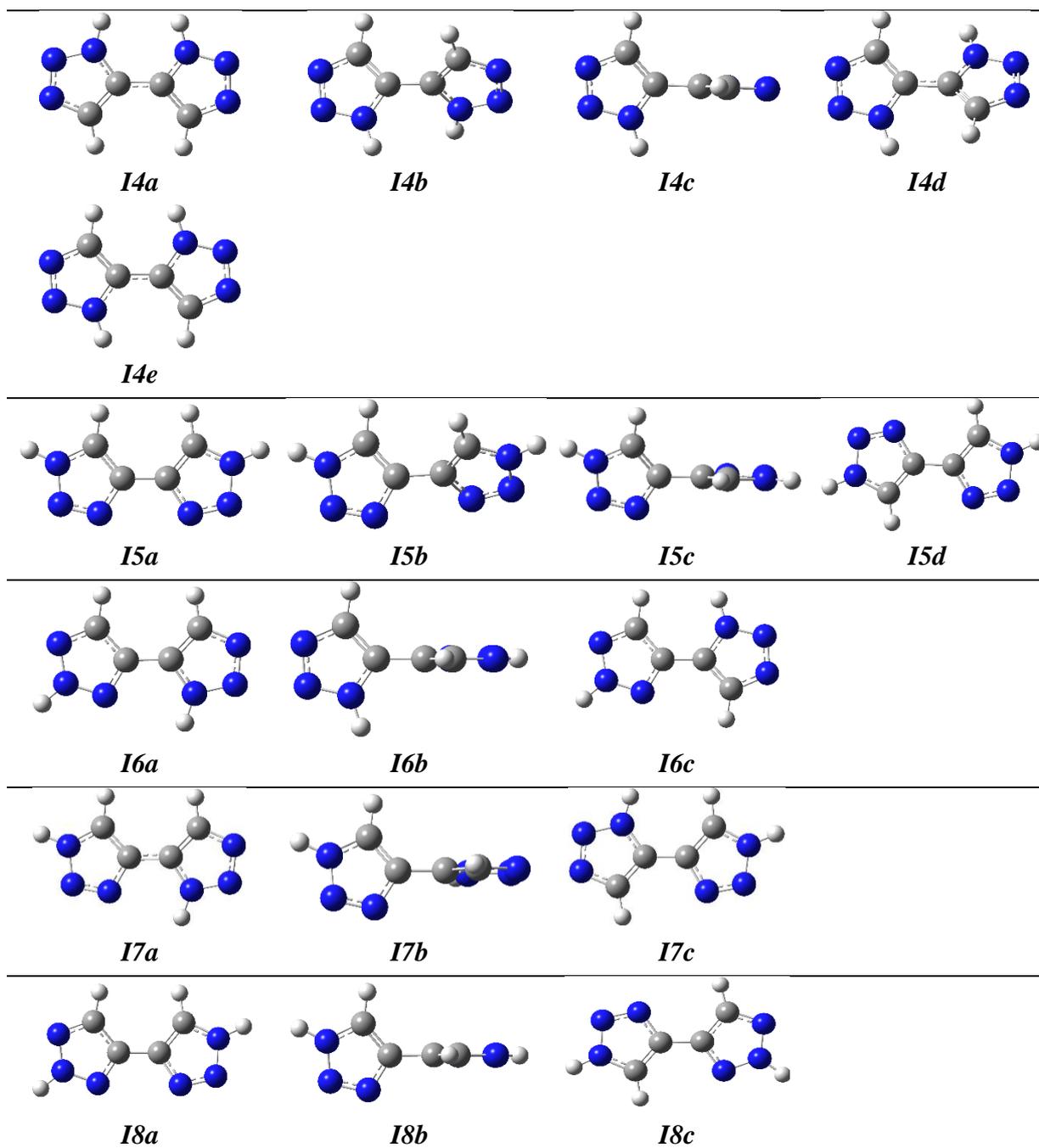


Figure 2: Optimized structures of all conformations for different configurational isomers of bi-1,2,3-triazole

 Table 1: Relative energies (ΔE), the relative enthalpies (ΔH) and relative Gibbs free energies (ΔG) in kcal/mol of all possible conformers. The results are given relative to the most stable conformer of each bi-1,2,3-triazol.

Configurational isomers	Conformer	Dihedral angle	ΔE_i	ΔE	ΔH	ΔG	i^*
I1	<i>I1a</i>	0	8.36	53.04	7.98	9.28	1
	<i>I1b</i>	112	0.00	44.68	0.00	0.00	0
	<i>I1c</i>	180	0.97	45.65	0.47	2.02	1
I2	<i>I2a</i>	0	5.46	42.48	5.00	6.81	1
	<i>I2b</i>	90	0.00	37.02	0.00	0.00	0
	<i>I2c</i>	180	5.46	42.48	5.00	6.81	1
I3	<i>I3a</i>	0	2.72	2.72	2.74	2.18	0

	I3b	90	4.39	4.39	3.85	5.22	1
	I3c	180	0.00	0.00	0.00	0.00	0
	I4a	0	1.59	12.93	1.14	2.95	1
	I4b	38	1.11	12.45	1.11	1.08	0
I4	I4c	84	1.47	12.81	0.92	2.40	1
	I4d	145	0.00	11.34	0.00	0.00	0
	I4e	180	0.05	11.34	0.04	0.96	1
	I5a	0	6.00	12.42	5.51	6.82	1
I5	I5b	45	5.78	12.20	5.81	5.53	0
	I5c	80	5.99	12.41	5.48	6.74	1
	I5d	180	0.00	6.42	0.00	0.00	0
	I6a	0	0.00	4.02	0.00	0.00	0
I6	I6b	90	4.26	8.29	3.71	5.13	1
	I6c	180	2.22	6.24	2.28	1.42	0
	I7a	0	0.00	7.31	0.00	0.00	1
I7	I7b	100	4.80	12.11	4.27	5.60	0
	I7c	180	3.02	10.33	3.13	2.28	1
	I8a	0	3.73	7.23	3.76	3.36	1
I8	I8b	80	4.84	8.34	4.30	5.65	0
	I8c	180	0.00	3.50	0.00	0.00	1

i = number of imaginary frequency

Table 2: The effect of solvents on the relative electronic energies (ΔE) of the most favorable conformers obtained at B3LYP/6-311++G(d,p) level of theory.

Conformer	Dihedral angle	ΔE (kcal/mol)				
		Gas phase	Cyclohexane	Chloroform	methanol	water
I1b	112	44.68	44.38	43.79	42.96	42.85
I2b	90	37.02	37.83	38.25	38.52	38.53
I3c	180	0.00	0.00	0.00	0.00	0.00
I4d	145	11.34	9.40	7.49	5.57	5.33
I5d	180	6.42	4.72	3.11	1.68	1.51
I6a	0	4.02	3.23	2.48	1.74	1.65
I7a	0	7.31	5.45	3.65	2.30	2.15
I8c	180	3.50	2.59	1.66	0.84	0.75

Table 3: Dipole moments (Debye) calculated at the B3LYP/6-311++G(d,p) level for most favorable conformers as a function of solvent dielectric constant (in parentheses).

Conformer	Dipole (Debye)				
	Gas phase (1)	Cyclohexane (2.02)	Chloroform (4.9)	Methanol (24.55)	Water (78.39)
I1b	4.08	4.94	5.85	6.76	6.89
I2b	0.024	0.02	0.01	0.023	0.033
I3c	0.00	0.105	0.175	0.26	0.27
I4d	0.62	0.62	0.63	0.68	0.73
I5d	0.0001	0.0004	0.0016	0.0022	0.0025
I6a	4.68	5.22	5.65	6.01	6.05
I7a	6.55	7.29	7.91	8.44	8.51
I8c	4.36	4.99	5.49	5.97	6.03

The predicted IR spectra of the most stable conformer, **13c**, in the selected solvents were obtained at B3LYP/6-311++G(d,p) level of theory using IEFPCM model of solvent. The IR spectra calculated in different solvents are shown in **Figure 3**. It is worth to note that the presence of a dielectric media has a strong influence on the calculated vibrational frequencies. There are significant changes in the obtained frequencies of **13c** conformer on going from the gas phase through non-polar to polar media. Important changes in frequencies are observed in polar solvents and large frequency shifts (more than 50 cm^{-1}) are observed. There are also striking changes in the calculated frequency and increased in polar solvents. These significant changes are partly due to the presence of the reaction field of the solvents.

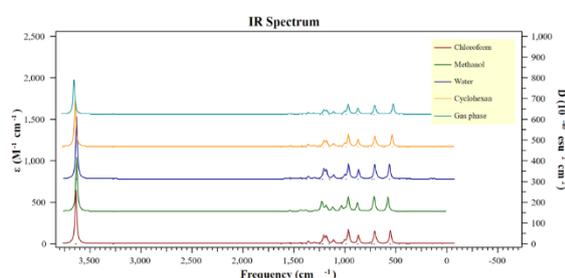


Figure 3: IR spectrum of **13c** obtained in gas phase and different solvents at B3LYP-6-311++G(d,p) level of theory.

4. Conclusions

The conformational analysis of the bi-1,2,3-triazole molecule has been studied at B3LYP/6-311++G(d,p) level of theory. Various configurational isomers of bi-1,2,3-triazole were obtained and the PES scan of these configurational isomers has been performed. Fourteen conformers with energy minima have been found using PES scan. A number of electronic and thermodynamic parameters have been obtained to find the most favorable conformer. The PCM model of solvation was used for selected conformers in order to compare the gas phase electronic energy with the electronic energy in cyclohexane, chloroform, methanol and water solvents. The analysis of results indicate that the stability of conformers increases as the dielectric constant of the solvent increased. The predicted IR spectra of the most stable conformer in the selected solvents were obtained and significant changes in frequencies are observed in polar solvents and large frequency shifts are also observed.

5. Compliance with Ethical Standards

Funding: This study has no fund.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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