

Theoretical Study of the Substituent and Solvent Effects on Azide-Tetrazole Equilibrium of 2-Azido-1,3-benzothiazoles

Walid M. I. Hassan, Sabry El-Taher, and Mahmoud A. Noamaan

Abstract—Quantum chemical calculations at the *Ab initio* Density Functional Theory have been performed to investigate the azide-tetrazole equilibrium of 2-azido-1,3-benzothiazoles. All geometries were fully optimized at the B3LYP/6-311+G(d,p) level. The electron correlation energy corrections were introduced by carrying out single-point calculations at the second-order Møller-Plesset perturbation theory and the coupled-cluster theory (CCSD(T)) using basis sets of different sizes. The solvent effect on the relative stabilities of azide and tetrazole isomers has been analyzed within the scope of self-consistent field theory using the polarizable continuum model. It was found that the electron donating groups enhance the stability of the tetrazole isomer while the electron-withdrawing groups favor the azide isomer. The study confirmed that the relative stability of the tetrazole species can be maximized to a great extent by increasing the polarity of the solvent, and vice versa for the azide isomer.

Keywords— Azide-tetrazole equilibrium, 1,3-benzothiazole, solvent effect, substituent effect.

I. INTRODUCTION

TWO classes of synthetic nitrogen based molecules have been continuously studied over time: azides [1, 2] and tetrazoles [3–5]. These compounds are widely spread among distinct areas of research and development. Azides constitute one of the most versatile classes of building blocks in organic and heterocyclic syntheses [6-9]. Aryl azides are found to be among the most effective photoaffinity labeling agents and have been used to study the intramolecular interactions such as ligand-receptor and substrate-enzyme interactions [10]. Most azide-containing drugs are approved as active drug ingredients [11], and they are produced from synthesis rather than from natural products.

The chemistry of the tetrazole ring is gaining increasing attention due to its importance in a variety of synthetic and industrial processes [12]. Tetrazoles are widely used for both their biological function and their energetic characteristics.

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Several antihypertensive, anti-allergic and antibiotic activity drugs include the tetrazole ring in its composition [13].

Heterocyclic azides are known to spontaneously cyclize to give the fused tetrazole form or more generally exist as an equilibrium mixture. A variety of heterocyclic tetrazoles have been reported to exhibit the tetrazole-azide isomerization [14]. The gas-phase interconversion of azide and tetrazole forms of thiazole[3,2-d]tetrazole has been theoretically investigated [15, 16]. The tetrazole-azide isomerization is found to be governed by the electron donating capacity of the heterocycle to which the tetrazole ring is fused as well as the polarity of the solvent used. In the current study we study the effect of both substituent and solvent on the azide-tetrazole equilibrium in a series of substituted 2-azidobenzothiazoles. We aim to investigate the extent of these effects when the azide and the tetrazole moieties are attached to a relatively large moiety such as the benzothiazole ring.

II. COMPUTATIONAL METHODS

The density-functional theory (DFT) [17], using the hybrid B3LYP functional, and the second order Møller-Plesset (MP2) perturbation theory [18] were employed to optimize the geometries of the studied species using different Pople [19] basis sets as implemented in Gaussian 09W package [20]. Transition states were determined by varying the N3-N12 distance and optimizing the remaining structural parameters for each choice of the N3-N12 distance. The structure at the saddle point on this graph, the “calculate transition states” option was switched on to optimize the TS structure. The effect of solvent on the azide-tetrazole equilibrium is considered within the scope of the Self Consistent Reaction Field (SCRF) theory, using the Polarizable Continuum Model (PCM) [21]. Geometries of all species have been fully optimized at the B3LYP/6-311+G(d,p) level in each of the four solvents.

Single-point calculations were performed at the CCSD(T)/6-311++G(d,p) and MP2/6-311++G(3df,2p) levels using the B3LYP/6-311+G(d,p) geometries of the different species in gas-phase as well as in different solvents. Vibrational frequencies were calculated at the B3LYP/6-311+G(d,p) level to confirm the nature of all stationary points in gas-phase as well as in solution.

III. RESULTS AND DISCUSSION

A. Molecular Structures

The B3LYP/6-311+G(d,p) optimized molecular structures of azide, transition state, tetrazole species of the 2-azido-1,3-benzothiazole (ABT) are depicted in Fig. 1. Selected bond lengths and angles of the B3LYP/6-311+G(d,p) optimized geometries of the cis-azide, trans-azide, transition-state, and tetrazole species of ABT are given in Table I.

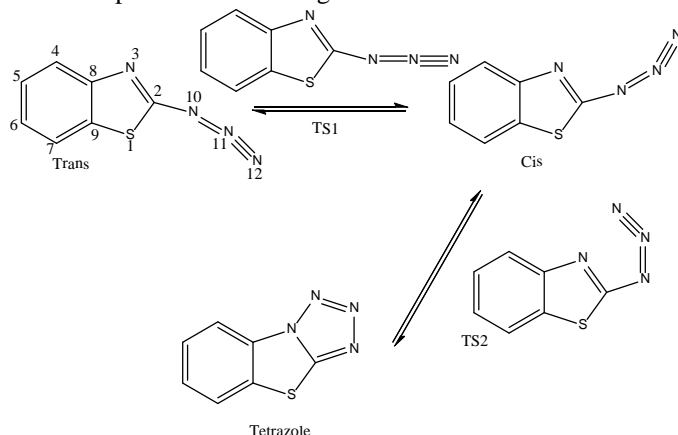


Fig. 1 Schematic molecular structures of azide, transition state, and tetrazole species of ABT. The numbering system is given.

TABLE I
SELECTED GEOMETRICAL PARAMETERS OPTIMIZED AT THE B3LYP/6-311+G(d,p) LEVEL FOR THE CIS-AZIDO, TRANS-AZIDO, TRANSITION STATE (TS), AND TETRAZOLE SPECIES OF ABT.

	cis-azido	trans-azido	TS2	Tetrazole
Bond lengths, Å				
r(N12-N11)	1.126	1.131	1.177	1.295
r(N11-N10)	1.243	1.237	1.322	1.367
r(N10-C2)	1.393	1.394	1.368	1.313
r(C2-N3)	1.290	1.286	1.305	1.355
r(N3-N12)	3.478		1.966	1.354
r(C2-S1)	1.767	1.791	1.747	1.748
r(N3-C8)	1.386	1.383	1.388	1.397
Bond Angles, °				
∠(N12-N11-N10)	172.40	171.63	130.60	112.62
∠(N11-N10-C2)	115.94	118.95	103.10	104.52
∠(N10-C2-N3)	126.47	120.89	120.11	109.36
∠(N3-N12-N11)	39.42		92.05	105.25
∠(N10-C2-S1)	116.26	122.73	124.96	138.37
∠(C2-N3-C8)	110.37	110.94	113.78	116.51
∠(N3-C8-C9)	115.33	115.70	112.68	109.64
Dihedral Angle, °				
∠(N12-N11-N10-C2)	179.96	179.99	0.04	0.00
∠(N11-N10-C2-N3)	0.02	180.00	0.00	0.00
∠(N10-C2-N3-C8)	179.99	180.00	180.00	179.99

Inspection of the data shows insignificant changes in geometry on going from cis to trans conformers, except for an increase in C2-S1 bond length by 0.023 Å, the increase in N10-C2-S1 angle by 6°, and the decrease in N10-C2-N3 angle by 5°, which may be due to the fact that Sulfur atom is larger than Nitrogen atom.

In cis-azides, the N12-N11-N10 angle is on average of 172.4°, showing that the azido group deviates from linearity by about 8°, which is in excellent agreement with an X-ray value of 171.9° reported for 4-phenyl-3(5)azidopyrazole [22].

The dihedral angles N12-N11-N10-C2, N11-N10-C2-N3, and N11-N10-C2-S1 are always 180.0°, 0.0°, and 180.0°, respectively. This means that the azido group keeps on the coplanarity with the benzothiazole ring. The azide bond lengths are almost identical across the studied azides. For example, the N10-N11 bond length lies in the vicinity of 1.244 Å, which is almost the same as the bond length of 1.24 Å in an isolated N=N double bond [23]. On the other hand, a triple bond character is observed for the terminal N11-N12 bond with a bond length of 1.126 Å, compared to an experimental value of 1.14 Å [21] suggesting that azide may have an apparently pentavalent central nitrogen atom as previously reported [24, 25]. The N10-C2 bond (1.393 Å) is significantly shorter by 0.08 Å than normal C-N (1.471 Å) [26], and both C2-S1 (1.767 Å) and S1-C9 (1.758 Å) bonds are shorter than the typical C-S of 1.811 Å [27]. The double bond character between N3 and C2 (1.290 Å) is confirmed and shows the relative conjugation effects this bond has with N3-C8 (1.386 Å) and N10-C2 (1.393 Å) bonds. All these indicate that a considerable π -delocalization over the azide moiety (resonance) and the benzothiazole ring is formed in which the N10 atom is sp² hybridized, which also explains the coplanarity of the azide and benzothiazole moieties.

The cyclization process involves two steps: the conversions from cis-azide to TS, and from TS to tetrazole. The cis-azide → TS conversion starts with the bending of the N12-N11-N10 angle accompanied with an elongation of the N11-N10 bond and a shortening in the N10-C2 bond, while the TS → tetrazole conversion, involves the formation of the new N3-N12 bond which varies from 1.96 to 1.355 Å with associated elongation in the N12-N11 and C2-N3 bonds by 0.17 and 0.05 Å, respectively (Table I).

Fig. 2 reveals the plot of Hammett-constants (σ) of substituents of various electron-donating and electron-withdrawing strengths, which have been used as a measure of the electronic effect [28], against the rN3-N12 bond lengths of the corresponding TS structures of the studied azide-tetrazole isomerization.

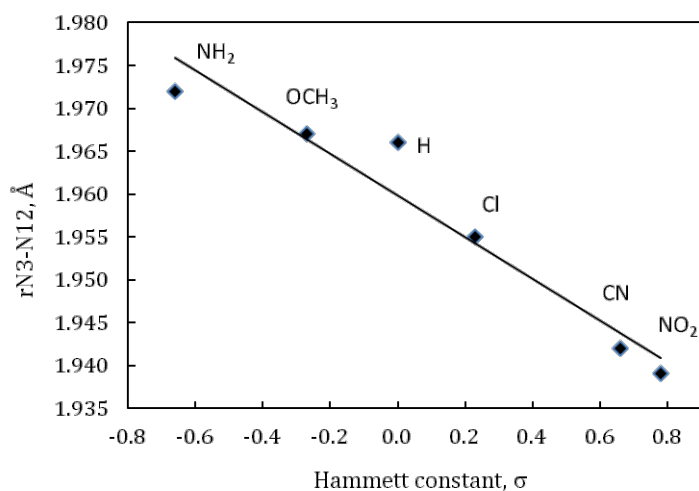


Fig. 2 A plot of Hammett constant (σ) versus the length of the N3-N12 forming bond.

It is obvious that the rN3-N12 bond lengths depend on the nature of the corresponding substituents in the 6-position and linearly correlate with their σ_p . An average of 0.03 Å shortening in the N3-N12 bond is indicated on going from the electron-donating NH₂ group (1.972 Å) to the electron-withdrawing NO₂ group (1.939 Å). Beside the C-6 position, the influence of the substitution of NH₂ and NO₂ on the azide-tetrazole equilibrium of 2-azidobenzothiazole at positions C-4, C-5, and C-7 of the benzene ring was investigated. The results show insignificant influence on the geometries of cis-azide and tetrazole species. This may be due to the well known fact that one of the unique properties of the azide group is the weak interaction between the azide group and a substituent through an aromatic ring [29], which indicates an extremely weak interaction between the π -systems of the benzothiazole ring and the azide group. This also means that there is no specific position at which the substitution becomes more or less effective on the azide-tetrazole equilibrium. This may be explained in terms of the fact that the benzothiazole moiety represents a delocalized system with the negative charge in the heterocyclic part and the positive charge in the benzene part of the moiety. Therefore, the influence of substitution is expected to be better transmitted from the heterocycle to the benzene part than in the opposite direction (that is from the benzene ring to the thiazole ring as in our case).

B. Energetics

The results reported in Table II reveal that the relative energies of trans-azido isomers are slightly affected on going from B3LYP level to either MP2 or CCSD(T) level, which means that the inclusion of relatively higher-order electron correlation has insignificant effect on the relative stability of trans-azideo isomer. However, the results show that the tetrazole isomers are greatly stabilized on going from B3LYP/6-311+G(d,p) to MP2/6-311++(3df,2p) level, where the corresponding ΔE_0 and ΔG_{298} values are decreased by more than 50% which is consistent with the significant redistribution of the electron density accompanied the azide-tetrazole isomerism. In addition, the ΔE_0 and ΔG_{298} values of tetrazole isomers computed at the CCSD(T) level for 6-H-, 6-Cl-, 6-NO₂-, and 6-NH₂-ABT are slightly decreased with regard to the MP2 values, which indicates that the performance of the MP2/6-311++(3df,2p) single-point energy calculations is comparable with that of the CCSD(T) level for improving the B3LYP results.

C. Substituent Effect

The results in Table III also show that the substitution at the 6-position of benzothiazole ring with substituents of various electron-donating and electron-withdrawing strengths causes small influence on the relative stability of tetrazole isomers with regard to the cis-azide ones. Fig. 3 shows a plot of the Hammett-constant (σ) values of these substituents (R = H, Cl, CH₃O, NO₂, CN, and NH₂) against the ΔG_{298} values of the corresponding tetrazole isomers calculated at the MP2/6-311++(3df,2p) level.

TABLE II
RELATIVE ENERGIES (ΔE_0) AND FREE ENERGY DIFFERENCES (ΔG_{298}) (KCAL/MOL) OF TRANS-AZIDO, TRANSITION STATE (TS), AND TETRAZOLE SPECIES OF SUBSTITUTED 2-AZIDO-BENZO THIAZOLES IN VACUUM WITH REGARD TO CIS-AZIDO ISOMER. ZERO-POINT ENERGIES AND THERMAL CORRECTIONS ARE INCLUDED.

	B3LYP/ 6-311+G(d,p)		MP2/ 6-311++G(3df,2p)		CCSD(T)/ 6-311++G(d,p)	
	ΔE_0	ΔG_{298}	ΔE_0	ΔG_{298}	ΔE_0	ΔG_{298}
6-H-ABT						
trans-azido	3.08	2.80	2.35	2.07	3.88	3.60
TS	23.32	23.69	28.35	28.72	21.57	21.88
Tetrazole	5.65	7.67	2.45	4.46	1.49	3.51
6-Cl-ABT						
trans-azido	2.92	2.85	2.2	2.10	3.74	3.66
TS	23.29	24.20	27.64	29.16	21.39	22.31
Tetrazole	7.69	8.70	3.782	5.41	3.41	4.41
6-NO₂-ABT						
trans-azido	3.12	3.037	2.38	2.28	3.93	3.84
TS	23.85	24.72	28.29	29.79	21.94	22.82
Tetrazole	9.44	10.37	5.289	6.86	5.08	6.01
6-NH₂-ABT						
trans-azido	2.70	2.64	2.12	2.02	3.57	3.51
TS	22.75	23.68	26.70	28.50	20.92	21.84
Tetrazole	6.01	7.05	2.07	3.72	2.09	3.13
6-Br-ABT						
trans-azido	2.98	2.87	2.26	2.13		
TS	23.29	24.21	27.66	29.18		
Tetrazole	7.69	8.74	3.89	5.52		
6-CN-ABT						
trans-azido	3.06	2.99	2.37	2.25		
TS	23.73	24.60	28.14	29.63		
Tetrazole	9.09	9.96	5.07	6.65		
6-CH₃-ABT						
trans-azido	2.85	2.82	2.207	2.13		
TS	22.71	23.47	27.13	28.47		
Tetrazole	6.34	5.66	2.58	2.48		
6-CH₃O-ABT						
trans-azido	2.82	2.77	2.19	2.11		
TS	22.87	23.81	27.20	28.74		
Tetrazole	6.46	7.48	2.60	4.25		
6-OH-ABT						
trans-azido	2.78	2.71	2.17	2.04		
TS	23.26	24.19	27.35	28.90		
Tetrazole	7.00	8.04	2.918	4.60		

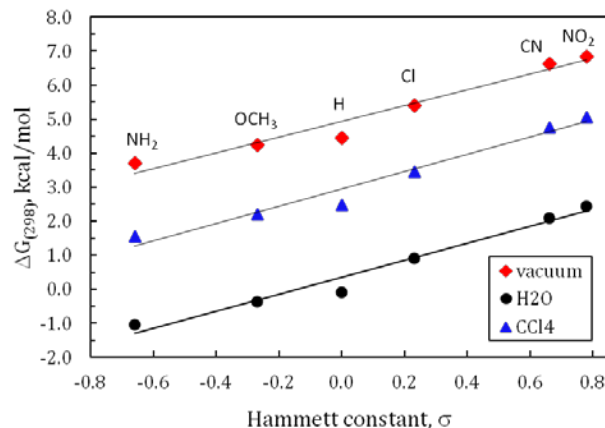


Fig. 3 A plot of Hammett constant (σ) versus the relative free energy differences (ΔG_{298}) of tetrazole isomers of 6-R-ABT (R = H, Cl, OCH₃, NH₂, CN, NO₂) Calculated at MP2/6-311++G(3df,2p) in vacuum, H₂O, and CCl₄.

It is obvious that the free energy difference is linearly correlates with Hammett-constant (σ) values of these substituents. The data show that both NO₂ and NH₂ impose the largest effects on the azide-tetrazole equilibrium.

TABLE III

TOTAL ELECTRONIC ENERGIES (IN A.U.), RELATIVE ENERGIES (ΔE_0), AND FREE ENERGY (ΔG_{298}) DIFFERENCES FOR THE CIS-AZIDO, TRANS-AZIDO, TRANSITION STATE (TS), AND TETRAZOLE SPECIES OF 2-AZIDO-BENZOTHAZOLE IN H₂O, CHCl₃, CCl₄, AND DMSO. ZERO-POINT ENERGIES AND THERMAL CORRECTIONS ARE INCLUDED.

	B3LYP/ 6-311+G(d,p)	ΔE_0	ΔG_{298}	MP2/ 6-311++G(3df,2p)	ΔE_0	ΔG_{298}
Gas-phase						
trans-azido	-886.43779	3.08	2.80	-884.87973	2.35	2.07
cis-azido	-886.44270	0	0	-884.88348	0	0
TS	-886.40554	23.32	23.69	-884.83830	28.35	28.72
Tetrazole	-886.43369	5.65	7.67	-884.87957	2.45	4.46
H₂O						
trans-azido	-886.44549	1.49	1.34	-884.88630	1.05	0.90
cis-azido	-886.44808	0	0	-884.88817	0	0
TS	-886.41177	22.28	23.21	-884.84355	27.50	28.43
Tetrazole	-886.44668	2.13	3.19	-884.89200	-1.14	-0.08
CHCl₃						
trans-azido	-886.44292	1.98	1.68	-884.88418	1.37	1.07
cis-azido	-886.44639	0	0	-884.88668	0	0
TS	-886.40992	22.37	23.29	-884.84198	27.54	28.46
Tetrazole	-886.44280	3.45	4.49	-884.88830	0.18	1.22
CCl₄						
trans-azido	-886.44081	2.38	2.16	-884.88230	1.75	1.53
cis-azido	-886.44493	0	0	-884.88541	0	0
TS	-886.40824	22.50	23.42	-884.84057	27.62	28.53
Tetrazole	-886.43927	4.68	5.71	-884.88489	1.45	2.49
DMSO						
trans-azido	-886.44536	1.52	1.40	-884.88618	1.07	0.95
cis-azido	-886.44800	0	0	-884.88810	0	0
TS	-886.41168	22.28	23.12	-884.84347	27.50	28.33
Tetrazole	-886.44649	2.19	3.00	-884.89181	-1.09	-0.28

The tetrazole isomer is destabilized by an average of 3 kcal/mol on going from the electron-donating NH₂ group (3.72 kcal/mol) to the electron-withdrawing NO₂ group (6.86 kcal/mol) with regard to the cis-azide one.

This means that the electron donating groups (CH₃, OH, OCH₃, and NH₂) enhance the stability of the tetrazole isomer while the electron-withdrawing groups (Cl, CN, and NO₂) favor the azide isomer, which is in agreement with a previously reported finding [30]. It is to be noted here that the resonance effect predominates the inductive effect for these substituents.

Fig. 4 shows an exponential correlation for the CCSD(T)/6-311+G(d,p) relative free energy differences, ΔG_{298} , and the corresponding population percentages of tetrazole isomers of 6-R-2-azidobenzothiazoles (R = H, Cl, NH₂, and NO₂) with regard to the cis-azido form estimated according to equation:

$$\Delta G = -RT \ln K_{eq}$$

where K_{eq} is the equilibrium constant ($K_{eq} = [\text{tetrazole}]/[\text{azide}]$), R is the gas constant ($=1.9872 \text{ cal deg}^{-1} \text{ mol}^{-1}$) and T is the absolute temperature (298.15 K). It is worth noting that the population of tetrazole isomers is drastically low where it varies from 0.004% for NO₂ to 0.51% for NH₂ group, which means that the 2-azidobenzothiazoles favor to exist in the azide forms. However, the population of tetrazole isomers exponentially increases as the electron-donating ability of the substituents at the 6-position increases.

D. Solvent Effect

Careful inspection of the results in Table IV show that the

cis-azide, TS, trans-azide, and tetrazole species are stabilized by 3.1, 3.4, 4.2, and 7.6 kcal/mol upon solvation in water, respectively. These values show that the tetrazole is more stabilized in water than cis-azide isomer by 4.5 kcal/mol, which is consistent with the relatively high dipole moment of tetrazole, where its experimental dipole moment is found to be 5.15 D in dioxane [31], which is in good agreement with the gas-phase value (6.67 D) calculated at MP2/6-311++G(3df,2p) level. Comparing to the gas-phase free energy differences, the tetrazole (trans-azide) is found to be stabilized by 2.0 (0.5), 3.2 (1.0), 4.5 (1.2), and 4.7 (1.1) kcal/mol in CCl₄, CHCl₃, H₂O, and DMSO, respectively at the MP2/6-311++G(3df,2p) level with regard to the corresponding cis-azide isomers.

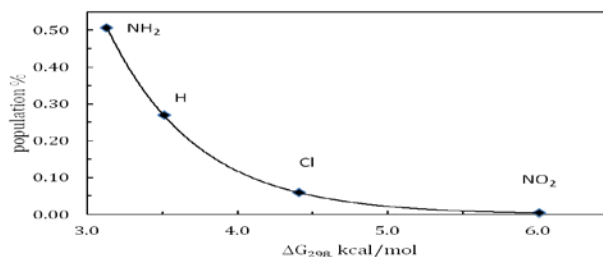


Fig. 4 A plot of the CCSD(T)/6-311+G(d,p) relative free energy differences (ΔG_{298}) of tetrazole isomers of 6-R-ABT (R = H, Cl, NH₂, and NO₂) versus the corresponding population percentage (pop%).

This means that as the polarity of the solvent increases the relative stability of tetrazole increases, and hence its population with regard to the cis-azide increases.

TABLE IV
RELATIVE ENERGIES (ΔE_0) AND FREE ENERGY DIFFERENCES (ΔG_{298}) (KCAL/MOL) OF TRANS-AZIDO, TRANSITION STATE (TS), AND TETRAZOLE SPECIES OF SUBSTITUTED 2-AZIDOBENZOTHAZOLES IN H₂O, DMSO, CCl₄, AND CH₃Cl AND WITH REGARD TO CIS-AZIDO ISOMER CALCULATED AT MP2/6-311++G(3df,2p) LEVEL. ZERO-POINT ENERGIES AND THERMAL CORRECTIONS ARE INCLUDED.

	H ₂ O		DMSO		CH ₃ Cl		CCl ₄	
	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG
6-Cl								
trans-azido	2.17	0.99	1.10	0.99	1.48	1.205	1.79	1.57
TS	28.25	28.81	27.89	28.81	27.94	28.847	28.02	28.92
Tetrazole	4.41	0.92	-0.04	0.99	1.22	2.252	2.45	3.47
6-Br								
trans-azido	2.24	0.95	2.36	2.22	1.51	1.379	1.82	1.70
TS	28.26	28.82	29.18	30.10	27.94	28.837	28.02	28.92
Tetrazole	4.47	1.01	1.32	2.35	1.30	2.331	2.52	3.54
6-CN								
trans-azido	2.32	1.12	0.97	0.89	1.29	1.063	1.91	1.70
TS	28.75	29.27	28.38	29.28	28.46	29.356	28.55	29.45
Tetrazole	5.78	2.10	1.17	2.17	2.52	3.512	3.77	4.76
6-NO ₂								
trans-azido	2.37	1.14	1.22	1.17	1.61	1.526	1.93	1.85
TS	28.91	29.44	28.5	29.45	28.60	29.528	28.66	29.59
Tetrazole	5.92	2.43	1.55	2.51	2.86	3.846	4.07	5.06
6-CH ₃								
trans-azido	2.17	0.92	1.05	0.92	1.42	0.609	1.72	1.11
TS	27.71	28.22	27.39	28.22	27.42	28.270	27.50	28.32
Tetrazole	3.16	-0.68	-1.42	-0.61	-0.19	0.494	1.08	1.65
6-CH ₃ O								
trans-azido	2.15	1.06	1.12	1.08	1.52	1.509	1.81	1.81
TS	27.81	28.37	27.45	28.37	27.48	28.425	27.57	28.57
Tetrazole	3.23	-0.37	-1.36	-0.31	-0.10	0.965	1.14	2.20
6-OH								
trans-azido	2.11	1.11	1.11	1.14	1.64	1.939	1.91	2.06
TS	27.96	28.56	27.57	28.60	27.81	29.098	27.88	29.03
Tetrazole	3.56	-0.07	-1.15	0.03	0.41	1.766	1.61	2.89
6-NH ₂								
trans-azido	2.08	0.89	0.97	0.92	1.39	1.342	1.69	1.64
TS	27.57	28.19	27.27	28.20	27.27	28.195	27.34	28.28
Tetrazole	2.70	-1.04	-2.05	-0.97	-0.80	0.274	0.51	1.56

This finding is also revealed in Fig. 5 where the solvent polarity is represented by the dielectric constant, ϵ , of the solvent.

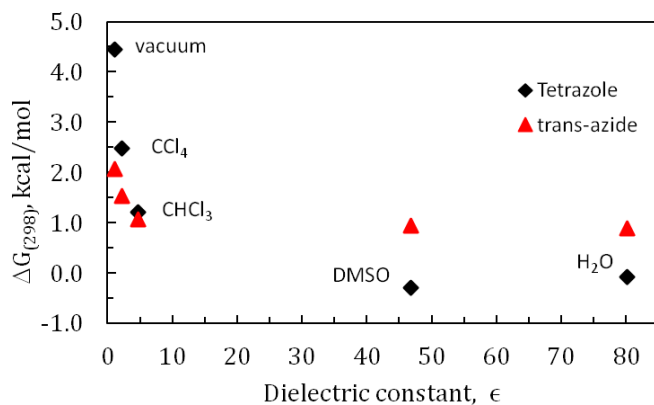


Fig. 5 A plot of the relative free energy differences (ΔG_{298}) of trans-azide and tetrazole isomers of ABT versus the dielectric constant (ϵ) of different solvents calculated at MP2/6-311++G(3df,2p) level.

The results in Table IV reveal the influence exerted by the substituents of various electron-donating and electron-withdrawing strengths on the relative stabilities of trans-azide,

TS, and tetrazole with regard to the cis-azide isomer in solvents of different polarity. The relative stability of the tetrazole species is greatly enhanced as the polarity of the solvent increases. Inspection of Fig. 2 clearly shows the influence of both the solvation and the substituents on the relative stability of tetrazole species. It is obvious that the relative stability of the tetrazole species can be maximized to a great extent by increasing the polarity of the solvent and to a relatively small extent by increasing the electron-donating strength of the substituent, and vice versa for the azide isomer.

IV. CONCLUSION

From the results reported here, one concludes the following: 1) the influence exerted by substituents of different electron donating or withdrawing strength on the geometries of cis-azide and tetrazole species is found to be insignificant. This may be due to the well known fact that the interaction between the azide group and a substituent through an aromatic ring is found to be weak. Moreover, the influence of substitution is expected to be better transmitted from the thiazole to the benzene part than in the opposite direction, 2) the electron donating groups enhance the stability of the tetrazole isomer while the electron-withdrawing groups favor the azide isomer, and 3) the relative stability of the tetrazole species can be maximized to a great extent by increasing the polarity of the solvent, and vice versa for the azide isomer. This may be

explained in terms of the relatively larger dipole moment of the tetrazole.

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