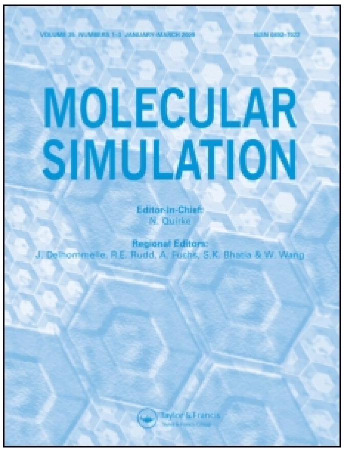

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Solvent and substituent effects on the electronic structures of triazoles: computational study

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Solvent and substituent effects on the electronic structures of triazoles: computational study

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The tautomerisation reaction of 1,2,3-triazole and some of its derivatives has been studied and the transition states were located. The analysis of results indicates that 2H-triazole is more stable than the 1H-tautomer in all studied compounds in gas phase and in solution. The proton detachment energies and the geometries of the compounds studied were analysed using density functional theory (DFT) and Hartree–Fock (HF) methods in gas phase and solution. Deprotonation takes place in all cases studied by the detachment of N–H proton. The solvent effect on the stability the tautomeric and anion forms of studied compounds has been examined using B3LYP/6-31G* level of theory by applying the polarisable continuum model.

Keywords: triazole; PCM; detachment energies (PDE); tautomerism; activation energy

1. Introduction

Triazoles and benzotriazoles were the subject of numerous investigations over the last four decades. The interest in this class of compounds continues not only because of their basic chemistry, but also in view of their industrial applications. The 1,2,4-triazole is used much more frequently as a drug component (e.g. anastrozole, estazolam, ribavirin, triazolam, etc.). Moreover, its 1,2,3-isomer ring is a moiety present in antiallergic [1], antibacterial [2], antifungal [3], antiviral [4] and analgesic [5] drugs.

Triazoles and benzotriazoles were established as a restrainer in photographic emulsions and as a reagent for analytical determination of silver [6]. However, their corrosion inhibitor capacity, especially for copper and copper alloys, has brought these classes of compounds to the attention of researchers concerned with the conservation of antiquities [7].

Two constitutional triazole isomers, which occur in nature, 1,2,3-triazole and 1,2,4-triazole, may exhibit tautomerism: the *N*-hydrogen atom can be attached to the first, second, third or fourth nitrogen atom. Some theoretical and experimental studies addressed this problem [8–18]. Begtrup et al. [11] studied 1,2,3-triazole using microwave spectroscopy, gas phase electron diffraction and theoretical *ab initio* methods. Based on the experimental data, they estimated 1H:2H tautomer ratio in the gas phase as 1:1000 and calculated the self-consistent field method (SCF) energy difference between the 1H and 2H forms to be ca. 215 kJ/mol, which roughly corresponds to ratio 1:200 at room temperature. Tornkvist et al. [10] calculated the equilibrium geometry, the harmonic force field and the vibrational frequencies for the 1H-1,2,3-triazole and 2H-1,2,3-triazole molecules at the B3LYP/6-31G* level. They found that the N_2 tautomer is ca. 21 kJ/mol more stable than the N_1 form. Recently, Billes et al. [17] have studied the vibrational spectroscopy of selected triazoles and tetrazoles. They calculated the vibrational frequencies using the B3LYP/6-31G* level of theory.

Tautomerism of five-membered heterocycles is of importance for pharmacy, as substituted diazoles and tetrazoles were the subject of several theoretical and experimental studies [17–31].

These compounds act as weak organic acids in neutral and slightly alkaline media. Acknowledgement of the acidity constants of weakly acidic substrates is of central importance to the study of reaction mechanisms taking place in alkaline media. One of the most important chemical processes is the protonation–deprotonation reaction. It does not only play an important role in general chemistry but is also of highest physiological importance. The basicity of various heterocycles has been the subject of numerous investigations, both experimentally and theoretically [32–40].

The aim of this work is to investigate the 1,2-proton transfer reaction of triazoles, then locate and characterise its corresponding transition states. The effect of substituents of different electron donating/accepting strength are examined. Solvent effects on 1,2-proton transfer reactions are explored. Moreover, the ground state geometries of the studied series of triazoles and benzotriazoles have been computed at the B3LYP/6-31G* level of theory. Charge density distribution, substituent and solvent effects are examined. In addition, the electronic structure features of proton detachment processes in triazoles and benzotriazoles are closely

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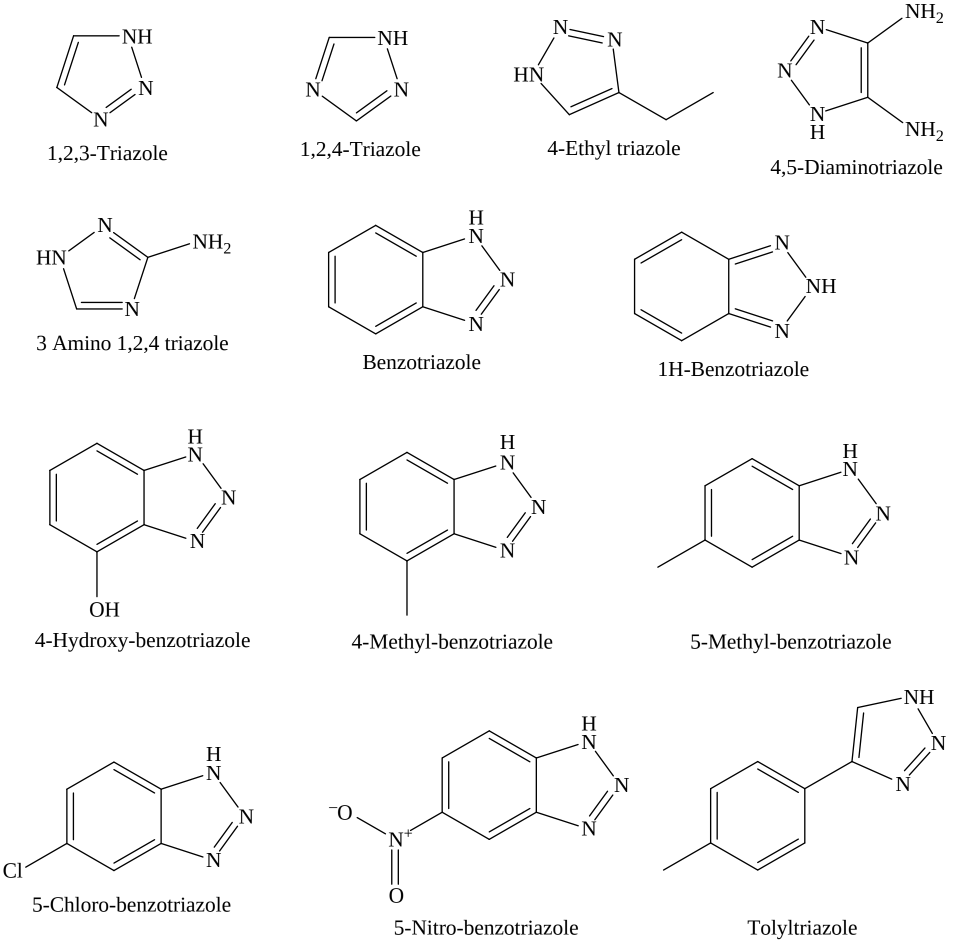
1,2,3-Triazole
1,2,4-Triazole
4-Ethyl triazole
4,5-Diaminotriazole
3 Amino 1,2,4 triazole
Benzotriazole
1H-Benzotriazole
4-Hydroxy-benzotriazole
4-Methyl-benzotriazole
5-Methyl-benzotriazole
5-Chloro-benzotriazole
5-Nitro-benzotriazole
Tolyltriazole

Figure 1. The structural formulas of the studied compounds.

examined. The electronic structure parameters and the proton detachment energies (PDEs) of the corresponding anions are reported in the gas phase and in solution, which are computed at the B3LYP/6-31G* level.

2. Method of calculations

The quantum chemical calculations were carried out with suite of GAUSSIAN 03W programs [40,41]. DFT calculations were performed by using a combination of Becke's three parameter hybrid [42] exchange potential with the correlation functional of Lee et al. (B3LYP) [43,44]. The basis set used was 6-31G*.

The vibrational frequencies have also been calculated at the same level for all minima and transition states. The calculated transition states were confirmed to have one imaginary frequency. Solvent effects on the stability of tautomeric forms were examined by applying the polarisable continuum model (PCM) [45] at the B3LYP/6-31G* level of theory. The PCM method defines the cavity from a set of overlapping spherical atoms having the appropriate van der Waals radii.

3. Results and discussion

The studied compounds of triazole derivatives are shown in Figure 1. The triazole ring with 1,2,3 form seems more stable than 1,2,4 form. The relative energy between the

Table 1. Energies and dipole moment of the studied compounds calculated at the B3LYP/6-311G* level of the theory.

	E_{total} (a.u.)		
Compounds	DFT	HF	Dipole (D)
1,2,3-Triazole	−242.22562	−240.83685	0.014
Ethyl triazole	−320.85957	−318.92622	0.475
Diaminotriazole	−352.93063	−350.92807	1.245
1,2,4-Triazole	−242.20568	−240.85777	2.871
3-Amino-1,2,4-triazole	−297.80432	−295.91773	1.944
Benzotriazole	−359.86413	−393.50917	0.110
1H-Benzotriazole	−359.86264	−393.51339	3.964
4-Hydroxy-benzotriazole	−471.08098	−468.39752	2.932
4-Methyl-benzotriazole	−435.18233	−432.56002	3.526
5-Chloro-benzotriazole	−855.45635	−852.44145	4.206
5-Methyl-benzotriazole	−435.17893	−432.55621	4.035
5-Nitro-benzotriazole	−471.08092	−597.04726	2.9323
Tolyltriazole	−512.60335	−509.48282	0.716

Table 2. Geometric parameters of some studied compounds as computed at the B3LYP/6-31G* level in the gas phase.

	Bond length (Å)			Bond angle (degr)	Charge (*e*)		
Compound	N_1-N_2	N_1-C_5	C_4-C_5	$N_1-N_2-N_3$	N_1	N_2	N_3
1H-1,2,3-Triazole	1.290	1.410	1.406	109.8	−0.287	−0.011	−0.518
TS of 1,2,3-triazole	1.295	1.390	1.378	109.8	−0.267	−0.197	−0.59
2H-1,2,3-Triazole	1.299	1.308	1.402	104.1	−0.250	−0.117	−0.035
1,2,4-Triazole	1.398	1.326	–	–	−0.420	−0.390	−0.254
1H-Benzotriazole	1.254	1.374	1.386	109.7	−0.362	−0.023	−0.550
TS of benzotriazole	1.293	1.331	1.397	107.9	−0.352	−0.185	−0.555
2H-Benzotriazole	1.301	1.334	1.414	118.2	−0.362	−0.157	−0.362
4-Hydroxy-1H-1,2,3-triazole	1.227	1.331	1.302	107.9	−0.389	−0.019	−0.479
TS of 4-hydroxy-1,2,3-triazole	1.299	1.329	1.337	109.7	−0.369	−0.178	−0.394
4-Hydroxy-2H-1,2,3-triazole	1.320	1.307	1.406	122.0	−0.377	−0.256	−0.239
4-Chloro-1H1,2,3-triazole	1.268	1.342	1.391	108.6	−0.283	−0.170	−0.488
TS of 4-chloro-1,2,3-triazole	1.392	1.245	1.378	109.9	−0.412	−0.019	−0.253
4-Chloro-2H-1,2,3-triazole	1.305	1.308	1.351	116.0	−0.259	−0.242	−0.250
Ethyl triazole	1.301	1.306	1.405	118.0	−0.250	−0.179	−0.335
Diaminotriazole	1.322	1.295	1.417	117.1	−0.350	−0.208	−0.352

two structures is 12.49 kcal/mol as shown in Table 1. 1,2,3-Triazole possesses a very low dipole moment (0.015 D) as computed by the DFT/6-31G* level, which does not reflect the considerable separation of charge in that molecule, thus although the central nitrogen (N_1) atom carries −0.287*e* and the two other nitrogen atoms carry −0.42*e* each. Table 2 presents the fully optimised geometric parameters computed for 1,2,3-triazoles and 1,2,4-triazoles and their derivatives using the B3LYP/6-31G* level of theory.

Alkyl substitution (ethyl group) in the C_4 position interacts via the inductive effect with the triazole ring. Thus, while the C_4—C_5 bond lengths are almost unaffected by the ethyl group substitution, the N_1—N_2 bond length shows slight elongation (Table 2). The net charges on the N_3 atom, however, are markedly affected and show migration of charge away from N_3 causing a slight increase in the dipole moment. The electron donating substituents are expected to have considerable effect on the geometric features and charge density distribution of triazoles. Diaminotriazole shows the longation of N_1—N_2 and N_4—N_5 bonds in the triazole rings and slight deformation as reflected by bond angles. The net charges on N_1 and N_2 increase, so also the dipole moment. Substituent effects on triazoles are pronounced and some trends can be pinpointed. These may be summarised as follows:

1. In case of all compounds studied, substituents of different electron donating–accepting strengths seem to have but slight effect on bond lengths.
2. Effect of substituents is marked on the charge density distribution. Substitution on the triazole carbon atom C_4 causes the accumulation of the negative charge density on the active nitrogen atoms.

3.1 Tautomerism

A very important tautomeric feature of 1,2,3-triazole is the 1,2-proton shift (Figure 2).

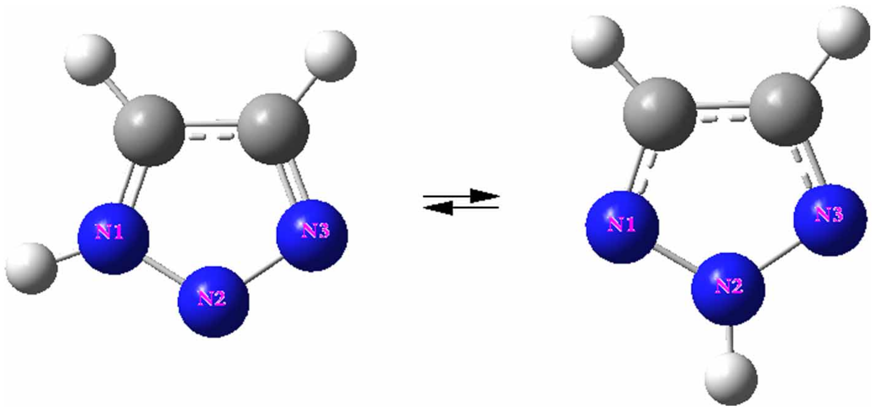

Figure 2. 1,2-proton shift in 1,2,3-triazole.

Table 2 depicts the electronic energies of the 1,2-proton shift for 1,2,3-triazoles in the gas phase and in solution. The results are in a relatively good agreement with the previous results [7–17]. In the gas phase, the 2H-tautomer is more stable (by some 11 kcal/mol) with a transition state of $\Delta E^* \sim 68$ kcal/mol. ΔE^* does not include the thermal corrections energy. The transition structure does not show major geometric deformations; however, the migration of charge into the N–N–N region can be clearly observed with N_2 accumulation of the negative charge (~20 times as much as dipole moment direction) and a decrease in its magnitude. This would suggest that, in polar media, the 1H-form will be stabilised and consequently the solvation energy will be small and the barrier will not be reduced considerably. Indeed, this is the case in water as a solvent, where the net solvent effect amounts to −4 kcal/mol only where the PCM model, on the one hand, seems to pick up most of the solvation stabilisation. In case of the transition, the solvent stabilisation energy amounts to only 6% of the total activation energy, whereas 2H-triazole shows much more solvent stabilisation which amounts to ~40% of the enthalpy change.

Now, let us investigate the substituents effects on the tautomerism of 1,2,3-triazole. Substitution by the electron withdrawing chlorine atom at the C_4-position alters the general feature of the tautomeric equilibrium. Thus, while the 2H-triazole is more stable than the 1H-tautomer, the chloro derivative shows the opposite trend where the 2H-chlorotriazole is less stable as shown by positive ΔH^0 of the reaction. In the chloro substitution case, the activation energy is elevated by 5 kcal/mol in the gas phase. PCM model follows the same trend discussed in case of the unsubstituted triazole. The PCM model seems to be suitable for modelling the solvation stabilisation where it picked up about 13.5 kcal/mol (Table 3).

On the other hand, substitution with the electron-donating hydroxyl group reduces the activation barrier by about 4 kcal/mol. The transition state of the 3-hydroxy-triazole derivative is less polar than 1H-triazole. Before leaving this point, the tautomeric reaction of 1H-benzotriazole is also investigated. The fused benzene ring causes a considerable reduction of the activation energy in the gas phase. This transition state is highly destabilised with the PCM model showing the highest destabilisation.

Table 3. Energies of the 1,2-proton transfer reaction (kcal/mol) calculated at B3LYP/6-31G* level of theory in the gas phase and in water as a solvent.

Compound	ΔE^*	ΔH
1,2,3-Triazole		
Gas phase	67.931	−11.271
PCM	62.7956	−5.962
Benzotriazole		
Gas phase	59.553	2.608
PCM	65.838	0.658
Chlorotriazole		
Gas phase	73.085	5.123
PCM	60.591	2.189
Hydroxyl triazole		
Gas phase	63.677	5.893
PCM	61.181	12.028

3.2 *Geometric features of anions*

Table 4 presents the geometries (bond lengths, bond angles and charge densities) of the studied anions computed at the B3LYP/6-31G* level of theory. It seems worthwhile to consider in detail the important changes in geometrical parameters in going from the neutral structure to the corresponding anion. It is evident from the data given in Table 4 that the deprotonation introduces a marked variation in the bond length not only in the vicinity of the deprotonation site but it is also transmitted to the other parts of the heterocyclic ring. In all cases, the average net charge densities seem to be affected by the deprotonation process. Deprotonation takes place in all cases studied by the detachment of the N–H proton. This bond is by far of more ionic character (at least three times more ionic) than the other C—H bonds. Deformation of triazole ring is associated with slight shrinking of the N_1—N_2 and N_2—N_3 bond lengths and more marked shrinking of the N_1—C_3 and N_3—C_5 bond lengths. The C_1—C_2 bond length is elongated. The charge density redistribution upon deprotonation is associated with increase in the negative charge density on almost all centres. This delocalisation of the charge would explain the relative stability of the anions. 3-Amino-1,2,4-triazole shows a considerable transmission of the deprotonation electronic effects to the side chain. Therefore, the amino group accumulates ~20% of the delocalised negative charge. This is more or less concentrated on the amino nitrogen atom. Furthermore, the C_4—N_3 bond length represents a considerable elongation from a value of 1.336 Å in the neutral molecule to a value of 1.416 Å in the corresponding anion. Ring bond angles increase slightly in case of the anion, yet a marked increase in the NH_2-bond angles can be noted. The case of *p*-tolyl-triazole is very interesting since the electronic effect of the deprotonation is not only marked in the vicinity of the protonation site but also transmitted to the *p*-methyl substituent where the bond length elongates slightly and net charges are also affected.

3.3 *Proton detachment energies*

PDE of a bond BH is defined as the standard enthalpy change for the gas phase reaction:

$$BH = B^- + H^+.$$

Table 4. Geometric parameters of some studied anions as computed at the B3LYP/6-31G* level of theory.

	Bond length (Å)			Bond angle (degr)	Charge (*e*)		
Anions	N_1–N_2	N_1–C_5	C_4–C_5	N_1–N_2–N_3	N_1	N_2	N_3
1H-1,2,3-Triazole	1.308	1.339	1.374	111.6	−0.408	−0.192	−0.408
Ethyl triazole	1.308	1.341	1.374	106.6	−0.403	−0.188	−0.466
Diaminotriazole	1.316	1.327	1.370	110.9	−0.470	−0.203	−0.466
1,2,4-Triazole	1.354	1.337	–	–	−0.511	−0.381	−0.381
1H-Benzotriazole	1.303	1.359	1.405	114.3	−0.493	−0.107	−0.493
4-Hydroxy-benzotriazole	1.308	1.362	1.403	114.2	−0.497	−0.108	−0.471
4-Methyl-benzotriazole	1.305	1.349	1.397	113.6	−0.498	−0.115	−0.490
5-Chloro-benzotriazole	1.303	1.356	1.408	114.4	−0.485	−0.098	−0.485s
5-Methyl-benzotriazole	1.302	1.355	1.405	114.2	−0.490	−0.110	−0.496
5-Nitro-benzotriazole	1.319	1.335	1.404	114.3	−0.495	−0.087	−0.455
Tolyltriazole	1.319	1.329	1.381	111.7	−0.410	−0.161	−0.455

Thus, PDE may be written as

$$\mathrm{PDE} = -\Delta E^0 - \Delta \mathrm{ZPE} - \int_0^{298} C_\mathrm{p}\, \mathrm{d}T,$$

where PDE is the electronic energy difference $E(\mathrm{BH}) - E(\mathrm{B})$, ΔZPE is the zero point energy difference and $-\Delta C_\mathrm{p}\mathrm{d}T$ is the molar heat capacity difference at constant pressure.

In the present work, PDE is used to indicate the PDE calculated as $\Delta E_\mathrm{el} - \Delta\mathrm{ZPE}$, whereas PDE_el refers to ΔE_el alone.

Table 5 represents the PDE computed using both DFT/B3LYP and HF methods combined with 6-31G* basis set. Zero point energies are also presented for the studied molecules. The value of ZPE is proportional to the sum of the vibrational frequencies, and therefore, it is primarily affected by larger frequencies (e.g. bond stretching and bending vibrations).

Deprotonation means the disruption of a covalent X—H bond and also marked deformation of the geometry and strength of vicinal bonds. Therefore, the differences in the ZPE for the parent molecule and its anion are not small and in our case amount to 10 kcal/mol. For this reason, ΔZPE must be accounted for in PDE calculations.

Furthermore, systematic over-and underestimation of frequencies will be as much as the ZPE and in the same direction. Moreover, it should be noted that ZPE in our case is calculated within the harmonic approximation. There is a general tendency of the HF-method to overestimate vibrational frequencies and hence the HF-computed ZPE are systematically greater than that computed by the DFT method. Overestimation of PDEs at the RHF level has been well illustrated by the work on similar molecules [46–50]. This trend in the RHF calculations is mainly due to the overestimated ΔE_el; however, ΔZPE is usually exaggerated. DFT-computed PDEs are usually of much better agreement with the experimental values and this is probably due to the

Table 5. PDEs and ZPEs calculated at the HF and B3LYP combined with 6-31G* in the gas phase and in water as a solvent in kcal/mol.

	PDE (kcal/mol)			ZPE (kcal/mol)			
	Gas phase		Solvent	Neutral		Anions	
Compounds	DFT	RHF	DFT	DFT	RHF	DFT	RHF
1,2,3-Triazole	353.105	403.5766	349.323	38.444	40.911	29.33	31.20
Ethyl triazole	354.422	413.535	345.969	73.698	78.580	64.63	68.88
Diaminotriazole	357.207	427.9362	353.670	58.500	63.145	50.40	54.21
1,2,4-Triazole	330.879	397.2514	296.150	37.633	37.005	29.88	31.74
3-Amino-1,2,4-triazole	354.105	414.1688	352.764	48.396	52.261	40.36	43.07
Benzotriazole	339.250	410.3034	334.966	68.029	72.378	58.88	62.62
1H-Benzotriazole	349.006	419.1637	337.214	67.556	72.050	58.87	62.61
4-Hydroxy-benzotriazole	347.553	432.9248	337.214	69.931	75.119	61.07	65.59
4-Methyl-benzotriazole	343.231	417.7393	338.512	85.007	90.483	76.52	81.28
5-Chloro-benzotriazole	335.03	424.0331	327.712	61.298	65.667	52.81	56.34
5-Methyl-benzotriazole	346.156	417.2938	333.947	84.796	90.403	76.21	61.95
5-Nitro-benzotriazole	326.719	435.7737	326.893	69.309	74.283	61.13	65.26
Tolyltriazole	355.895	431.5443	340.892	106.846	113.638	106.84	104.07

Table 6. Energies of solvation (kcal/mol) of triazole and benzotriazole anion derivatives calculated using PCM model of solvation at the B3LYP/6-31G* level of theory.

Compounds	ΔE
1,2,3-Triazole	68.675
Ethyl triazole	66.716
Diaminotriazole	73.552
1,2,4-Triazole	65.736
3-Amino-1,2,4-triazole	69.779
Benzotriazole	61.245
1H-Benzotriazole	61.245
4-Hydroxy-benzotriazole	67.362
4-Methyl-benzotriazole	60.440
5-Chloro-benzotriazole	55.620
5-Methyl-benzotriazole	61.179
5-Nitro-benzotriazole	51.226
Tolyltriazole	60.479

effective inclusion of the correlation effects in these methods. Results in Table 5 clearly indicate the sensitivity of the PDE to substitution.

Thus, the fused benzene ring in benzotriazole reduces PDE by 14 kcal/mol. This value is also reduced by the substitution in the benzene ring, for instance, 5-nitrobenzotriazole and 5-chloro-benzotriazole show 27 and 18 kcal/mol reduction in their PDEs as compared to that of triazole itself.

3.4 *Solvent effect*

PCM model has been used in the present section to study the effect of the solvent on the deprotonation process. The solvent stabilisation energies of PCM model used were computed at the B3LYP/6-31G* level of theory. Table 6 presents the relative energies (calculated with respect to the gas phase energies), computed using the PCM model. As it can be easily noted from the data collected in this table that the solvation energy computed with PCM model spans a wide range of values. The PCM model predicts much larger changes in solvation energies. The degree of stabilisation as computed for the neutral and the corresponding anions varies significantly with the substituents.

4. Conclusions

(1) In the gas phase, the 2H-tautomer is more stable than the 1H-tautomer. This is less than the thermal energy at room temperature. However, 1H-tautomer will be stabilised in the polar media, because the dipole moment value of 1H-tautomer is 4.39 D and that of the 2H-tautomer is 0.06 D only.

(2) The redistribution of the charge density in the transition state seems to be responsible for the destabilised solvent–solute interaction.

(3) DFT–PDEs results are in a relatively good agreement with the available experimental data.

(4) Fused benzene and substituted benzene to the triazole ring reduce the values of PDE.

(5) Stabilisation of the different compounds in solution is very sensitive to the substituent.

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