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Theoretical studies on proton transfer reaction of 3(5)-substituted pyrazoles

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Abstract. The inter and intra molecular proton transfer reactions of a series of pyrazole derivatives have been studied by using density functional theory (DFT) and MP2 methods implementing 6-311++G(d,p) atomic basis set. The substituents have been selected to cover a wide range of electronic effects. Proton transfer process was studied for mechanisms including single proton transfer, double proton transfer and proton transfer assisted by a water or ammonia molecule. The results showed single proton transfer reactions for interconversion pyrazole derivatives need highest activation energies in the range of 45.7−51.59 and 49.4−53.96 kcal/mol at B3LYP and MP2 levels, respectively. It was found that for the 3–substituted pyrazoles, electron withdrawing groups form stronger dimers but in the 5-substituted tautomers electron donating groups form stronger hydrogen bond. The double proton transfer reactions between dimers were studied and transition states calculated. The ranges of activation energies were found to be 17.51−19.36 and 17.02−17.80 kcal/mol for the **C→E** and **D→D** reactions respectively. In addition, the activation energies for the proton transfer reaction assisted by water or ammonia molecules were found to be in the range of 26.62−31.78 and 17.25−22.46 kcal/mol, respectively, calculated at MP2/6-311++G(d,p) level of theory.

Keywords. Pyrazoles; substituent effect; solvent assisted proton transfer; double proton transfer.

1. Introduction

Pyrazole is a five-membered heterocyclic compound containing two nitrogen atoms.[1] The growth of pyrazole chemistry over the last 25 years has been significant, mainly as a result of the roles played by its derivatives in coordination chemistry as ligands[2] and in medicinal chemistry. For example, amino-pyrazole derivatives were found to be potentially useful in preventing brain-protein aggregation which is the first phase in the development of Alzheimer's disease.[3] Other examples are Sildenafil,[4] an inhibitor of 5-phosphodiesterase, used for the treatment of erectile dysfunction, Celebrex, an inhibitor of cyclooxygenase-2 (COX-2), used as potent antiinflammatory,[5] and Acomplia, antagonist of the CB-1 cannabinoid receptor, used for the treatment of obesity.[6] In addition, pyrazole derivatives have been used as cardiovascular and oncologytic agents.[7,8] Due to the small size of pyrazole and rigidity of its five-membered ring, it has been used as a model molecule for the evaluation of the accuracy of different computational methods.[9,10] Pyrazole derivatives substituted at 3-position can exist in two tautomeric forms (scheme 1) and its annular tautomerism has been thoroughly studied both experimentally[10] and theoretically.[11]

N-unsubstituted pyrazoles can have N–H···N hydrogen bonds present in their crystals, which can lead to at least six motifs such as monomers, dimers, trimers, tetramers, hexamers, and catemers. Hydrogen-bonding motifs for pyrazoles have been examined in the Cambridge Structural Database (CSD).[12] It was reported that in the gas phase, both pyrazole and 3,5-dimethylpyrazole exist in an equilibrium between monomer, dimer, and trimer. However in solution, the equilibrium between monomer and trimer dominated and no band which could be attributed to dimers were detected.[13,14] Moreover, Castaneda *et al.* studied vibrational spectra and structure of hydrogen bonded complexes formed by pyrazole and 3,5-dimethylpyrazole (DMP) and examined complexation with some proton donating compounds.[15] The double proton transfer reactions between some substituted pyrazoles and guanidine molecule were studied by Schweiger and co-workers.[16] It was shown that in contrast to typical reactions, two of the systems showed broad plateaus of almost constant energy along the minimum energy path (MEP) instead of the well localized transition state. In addition, Limbach and co-workers studied

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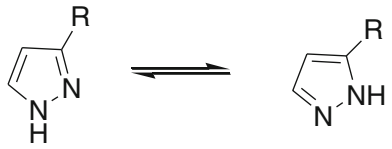

Scheme 1. Tautomeric forms of 3-substituted pyrazoles.

the structure of solid pyrazole-4-carboxylic acid and found that the compound forms quasi-linear ribbons in which the molecules are linked by cyclic hydrogen bonds between pyrazole and carboxylic acid groups with disordered hydrogen-bonded protons.[17] Recently, Ochsenfeld *et al.* have presented an elegant study about the insertion of pyrazole unit in a peptide which associates intermolecularly, giving rise to nanorosette-type structures in water.[18] In another work, Garcia and co-workers studied tautomeric behaviour and aggregation of a series of 3(5)-phenyl pyrazoles in the solid and solution phase.[19] Recently, we have reported the results of our study on the proton transfer reaction in the 4-substituted pyrazoles.[20] In continuation with our program to investigate the effect of substituents on the properties of heterocycles[21–24], here, we report the results of our investigation on the proton transfer reaction of 3(5) pyrazole derivatives.

2. Computational procedures

DFT and MP2 calculations were performed using GAUSSIAN 03 package.[25] The density functional theory was used with the Becke3-Lee-Yang-Parr (B3LYP) exchange-correlation with the conventional 6-311++G(d,p) basis sets.[26,27] According to recent reports, hybrid functionals can provide better description for the systems with hydrogen bonds.[28,29] The nature of all optimized structures was determined using harmonic frequency analysis as true minima with no imaginary frequencies or transition states with only one imaginary frequency. The hydrogen bonding energy of the studied dimer was corrected both with basis set superposition error (BSSE) and zero-point vibrational energies (ZPVE).[30] In our calculation particular emphasizes delivered on the 6-311++G(d,p) basis set because this basis set is of triple-zeta quality[31,32] for valence electrons with diffuse functions, which are useful in calculations for anions and structures with lone-pair electrons.[33,34] Comparisons of results of different basis sets reflect that most crucial achievement of H-bond energy comes with this basis set. This observation reasonably complies with other reports.[35] The geometry of the proton transfer reactions was determined using QST2 method at the MP2/6-311++G(d,p) level of theory. The structure of transition states between each pair of tautomers in the monomers, dimers and proton transfer reactions assisted by solvent molecules, were optimized by applying Schlegel's Synchronous Transit-guided Quasi-Newton (QST2) method started from the fully optimized structure of one tautomer and finished on the fully optimized structure of another tautomer. This route is requested by the keyword Opt = QST2 option. The TSs were verified with frequency calculations to ensure they were first order saddle points with only one imaginary frequency mode.

3. Results and discussion

The structures and arbitrary numbering of monomers and dimers of pyrazole derivatives that considered in the present study has shown in figures 1 and 2. In the **C** and **E**, dimers, the 3-R and 5-R derivatives form the dimer, respectively. In addition, the **D** dimers are formed from a 3-R monomer and a 5-R monomer. For the nitroso and carbaldehyde groups, different conformers may exist, we considered more stable ones.

3.1 *Proton transfer in monomers*

The results of calculated total energies and relative stabilities of tautomers of pyrazole derivatives that considered in the present study are shown in table 1.

The results indicate that for electron donating groups such as $\mathbf{NH_2}$, $\mathbf{CH_3}$, and **F** 3-substituted pyrazoles (**B** forms) are more stable but for electron withdrawing groups 5-substituted ones (**A** forms) are more stable. For example, based on B3LYP/6-311++G(d,p) calculations, 3-fluoro and 3-amino pyrazole are 3.62 and 2.61 kcal/mol more stable than their corresponding 5-flouro and 5-amino pyrazoles, respectively.

The proton transfer reaction of pyrazole derivatives studied and activation energies were calculated and presented in table 1. The obtained results show that activation energies for proton transfer reaction varies in the range of 45.7−51.59 and 49.4−53.96 kcal/mol at MP2 and B3LYP levels, respectively. Analysis of the results indicates proton migration is easier in pyrazoles with electron donating groups. For example, based on MP2 calculations the activation energy of the proton transfer process for the 3-hydroxy and 3-amino pyrazole was found to be 47.52 and 47.34 kcal/mol, respectively. On the other hand, for the 3-nitro and 3-nitroso pyrazole that electron withdrawing groups attached to the ring, the activation energy of proton transfer reaction found 50.69 and 51.59 kcal/mol, respectively. We found a good correlation between substituent constants

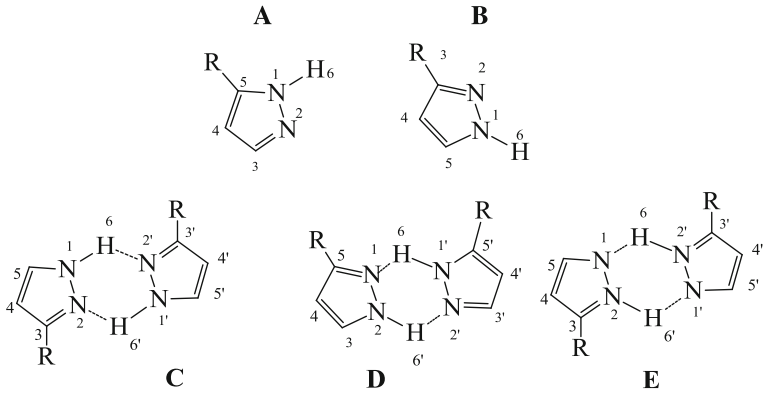

Figure 1. Structures and arbitrary numbering of pyrazole monomers (**A**, **B**) and dimers (**D**, **C**, **E**) which have been considered in this work.

(σ_I) and activation energies with a correlation coefficients 0.947 calculated at MP2/6-311++G(d,p) level of theory.

3.2 *Hydrogen bonding strength in dimmers*

Interaction energies were calculated for the 3- and 5-substituted pyrazole–pyrazole aggregates by taking the energy differences between the fragments and the complexes. The results of calculations are compiled in table 2. Based on our calculations the following results obtained. Complexation of 3-substituted pyrazoles lead to the **C** isomers, the stabilization energies calculated at MP2 and B3LYP methods using 6-311++G(d,p) basis function in the table 2 indicate that the order of stability is **CHO> NO> NO_2> Cl> OH> F> H> CH_3> NH_2** and **CHO> NO> NO_2> Cl> F> CH_3> H> OH> NH_2** at the DFT and MP2 levels, respectively. These data reveals that electron withdrawing groups form stronger hydrogen bonds. The most stable isomer has −15.54 and −21.75 kcal/mol interaction energy calculated at DFT and MP2 levels using 6-311++G(d,p) basis set. For the electron donating groups such as NH_2 and CH_3 the interaction energies were found to be −11.29 and −11.89 kcal/mol at DFT level and −14.68 and −15.56 kcal/mol at MP2 level, respectively. With application of ZPE and BSSE corrections, the stabilization energies of the complexes decrease about 1.62−2.05 and 3.04−3.33 kcal/mol using DFT and MP2 methods, respectively. However, the corrections with ZPE and BSSE have no significant influence on the stability order of dimers. The calculated interaction energies for the 5-substituted pyrazole dimers (**E** dimers) presented in the table 2. Based on DFT results the order of stability was found to be **NH_2> F> CH_3> Cl> NO_2> CHO> NO> OH** and **Cl> CH_3> F> NO_2> NH_2> NO> CHO> OH** calculated using DFT and MP2 methods, respectively. As it can be seen from table 2, the hydrogen bond strengths are significantly lower than homo-dimers between 3- and 5-substituted dimers of pyrazole derivatives. For more evaluation of hydrogen bond formation we studied the dimer formation between 3- and 5-substituted pyrazole derivatives (**D** dimers). Based on DFT results, the order of stability found to be **OH> F> Cl> CH_3> NH_2> NO> NO_2> CHO** indicates that electron donating groups form more effective hydrogen bonds. However, noticeably the order of hydrogen bonding based on MP2 results was found completely different with DFT results and found to be **NO> Cl> CHO> CH_3> OH> F> NO_2> NH_2**. In addition, with application of ZPE and BSSE corrections the order of stability calculated by MP2 method changed to **NO> CHO> Cl> OH> F> CH_3> NO_2> NH_2**. The calculated data for the substituted pyrazoles are comparable with previously reported

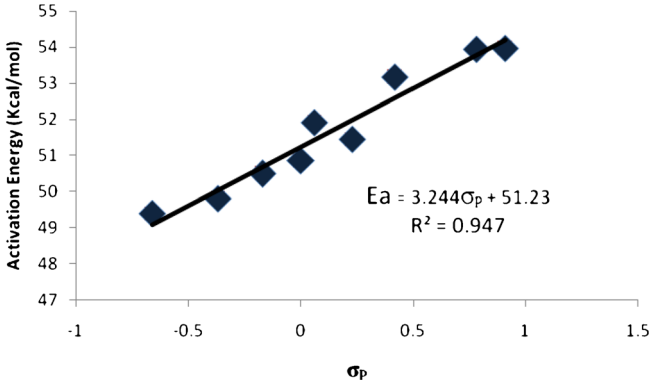

Figure 2. Correlation between substituent constants and activation energies of proton transfer reaction in the pyrazole monomers.

Table 1. Calculated relative stabilities of two tautomers of pyrazole derivatives and activation energies of proton transfer reactions at MP2 and DFT levels.

	MP2/6-311++G(d,p)			B3LYP/6-311++G(d,p)		
	A	**B**	E_a	**A**	**B**	E_a
H	0	–	48.26	0	–	50.87
NH_2	0	−1.56[b]	47.34	0	−2.61	49.40
OH	0	−0.56	47.53	0	−0.37	49.80
Cl	0	−1.36	47.31	0	−1.58	51.46
F	0	−3.62	45.79	0	−3.62	51.91
CH_3	0	−0.25	47.50	0	−0.26	50.49
NO_2	0	1.64	50.62	0	0.23	53.95
CHO	0	4.00	50.84	0	2.16	53.16
NO	0	2.69	51.59	0	0.43	53.96

[a]Relative stabilities in kcal/mol

values for the hydrogen bond strength of heterocyclic compounds. For example, the strength of hydrogen bonds for the various type of tetrazole derivatives found in the range of 8.19 – 13.55 kcal/mol calculated at B3LYP/6-311++G(d,p) level of theory.[28] In addition, for the 4-substituted pyrazoles the range of hydrogen bond strength was found to be 14.9 – 15.4 kcal/mol calculated at MP2/6-311++G(d,p) level of theory.[20]

Table 2. Calculated interaction energies for the 3- and 5-substituted doubly hydrogen bonded pyrazoles using 6-311++G(d,p) basis function at DFT and MP2 level.

	E_{int}	$E_{int(ZPVE)}$	BSSE	$E_{int(Corr)}$	E_{int}	$E_{int(ZPVE)}$	BSSE	$E_{int(Corr)}$
	B3LYP/6-311++G(d,p)				MP2/6-311++G(d,p)			
C dimers								
H	−12.21[a]	−10.98	0.48	−10.50	−15.42	−14.29	2.0	−12.29
NH_2	−11.29	−9.80	0.56	−9.24	−14.68	−13.60	2.25	−11.35
OH	−12.50	−11.03	0.57	−10.46	−15.16	−14.30	2.17	−12.13
Cl	−12.73	−11.67	0.73	−10.94	−16.69	−16.13	2.69	−13.44
F	−12.46	−11.28	0.63	−10.65	−15.67	−14.73	2.22	−12.51
CH_3	−11.89	−10.78	0.55	−10.23	−15.56	−14.86	2.38	−12.48
NO_2	−14.37	−13.41	0.66	−12.75	−18.59	−18.0	2.48	−15.52
CHO	−15.54	−14.38	0.63	−13.75	−21.75	−20.95	2.43	−18.52
NO	−14.90	−13.75	0.68	−13.07	−21.06	−20.13	2.34	−17.79
D dimmers								
NH_2	−12.09	−10.93	0.55	−10.38	−14.48	−13.68	2.21	−11.47
OH	−12.41	−11.26	0.62	−10.64	−15.78	−14.81	2.3	−12.51
Cl	−12.20	−11.16	0.73	−10.43	−16.24	−15.41	2.74	−12.67
F	−12.34	−11.20	0.63	−10.57	−15.60	−14.71	2.27	−12.47
CH_3	−12.10	−11.0	0.54	−10.46	−15.82	−14.74	2.38	−12.36
NO_2	−10.31	−9.49	0.68	−8.81	−14.77	−14.63	2.54	−12.09
CHO	−8.63	−7.80	0.61	−7.19	−16.10	−15.40	2.47	−12.93
NO	−10.83	−9.91	0.63	−9.28	−16.43	−15.69	2.33	−13.36
E dimers								
NH_2	−12.98	−11.88	0.56	−11.32	−13.92	−13.51	2.20	−11.31
OH	−9.13	−8.45	0.61	−6.84	−11.92	−11.86	2.30	−9.56
Cl	−11.97	−10.95	0.72	−10.23	−15.97	−15.31	2.76	−12.50
F	−12.57	−11.43	0.63	−10.80	−15.08	−14.95	2.31	−12.64
CH_3	−12.39	−11.24	0.53	−10.71	−15.69	−14.78	2.26	−12.52
NO_2	−9.8	−9.1	0.68	−8.31	−14.43	−14.06	2.52	−11.54
CHO	−9.35	−8.59	0.58	−8.01	−12.44	−11.88	2.46	−9.42
NO	−9.24	−8.44	0.65	−7.79	−13.18	−12.62	2.42	−10.20

[a]Binding energies in kcal/mol

On the whole, one can conclude that for the 3-substituted pyrazoles, more effective hydrogen bonds formed for the electron withdrawing groups, but for the 5-substituted ones electron donating groups formed stronger hydrogen bonds.

3.3 *Double proton transfer reaction*

The proton transfer reaction is a very important biochemical process, which may occur directly without any assistance of the solvent molecule or assisted by one or more solvent molecule.[29,35–38,40] A vast amount of research has been focusing on various types of proton transfers in ground states as well as in the excited states to explore the associated reaction mechanism.[41–44] The activation energies *Ea* for direct proton transfer reaction of pyrazole derivatives are presented in table 3. Two different double proton transfer reaction was studied: for the **C**→**E** reaction where **C** dimers convert to **E** ones and for the **D**→**D** reactions, the **D** dimers convert to themselves through double proton transfer process. From table 3, it is evident that the proton transfer process is characterized by moderate activation energies. For the **C**→**E** process the activation energies found in the range of 17.51−19.36 kcal/mol, calculates at MP2/6-311++G(d,p) level of theory. For the parent pyrazole molecule, activation energy and zero-point corrected activation energy found to be 17.99 and 13.07 kcal/mol, respectively. Moreover, for the 3-amino pyrazole the activation and corrected activation energies were found to be 17.72 and 12.33 kcal/mol, respectively. However, for the pyrazole substituted by electron withdrawing groups such as nitroso and CHO conversion of **C** isomer to **E** one need 19.36 and 18.92 kcal/mol, respectively.

For the **D**→**D** process the activation energies found in the range of 17.02−17.80 kcal/mol. With inclusion of ZPE values the range of activation energies decreased to 11.56−12.87 kcal/mol. As you can see, the most activation energy obtained for the pyrazole substituted with amino group by 17.80 kcal/mol value. One can compare these values obtained for the double proton, transfer reactions with intramolecular proton transfer the reactions of pyrazole monomers described in previous section. As it has been shown the activation energies observed for the double proton transfer reaction are considerably lower than those found for the intermolecular processes. For example, the intermolecular proton transfer reaction of conversion of 3-nitro pyrazole to 5-nitro pyrazole (**B**→**A**) needs 50.62 kcal/mol, however for this process through double proton transfer route (**C**→**E** reaction) where 5-nitro and 3-nitro pyrazoles form the dimer, the activation energy found to be 18.67 kcal/mol. Similar results for other derivatives was observed (compare tables 1 and 3). The optimized structures of the transition states and some important geometrical parameters of proton transfer reactions of pyrazole dimers have been presented in figure 3.

It is evident that value of the imaginary frequency is a measure of the curvature of the transition state region along the reaction coordinate. The calculated values of imaginary frequencies of double proton transfer reactions of pyrazole derivatives presented in table 3. A close look to results indicates there is good correlation between activation energies and values of imaginary frequencies was observed. The values of imaginary frequencies that correlate with activation energies found in the range of −1231.6 to −1487.7 and −1245.4 to −1489.5 cm^{-1}, for the transition states of **C**→**E** and **D**→**D** reactions, respectively.

3.4 *Solvent assisted proton transfer reaction*

Protic solvents such as water, alcohols or ammonia that can be a strong hydrogen bond donor/acceptor can accept a proton from the donor site of the solute molecule or give another proton to the suitable sites of the solute. Solvent-assisted proton transfer mechanism studies have shown that the assistance of a water molecule significantly lowers the free energy barriers in proton-transfer-related reactions.[20,45–47] In this case, an explicit interaction with a limited number of solvent

Table 3. Calculated activation energies, corrected activation energies and imaginary frequencies of proton transfer reaction in substituted pyrazole dimers at MP2/6-311++G(d,p) level of theory.

Reaction		**H**	**NH_2**	**OH**	**Cl**	**F**	**CH_3**	**NO_2**	**CHO**	**NO**
C→E	Ea	17.99[a]	17.72	17.51	18.86	17.58	17.80	18.62	18.92	19.36
	Ea +ZPE	13.07	12.33	12.31	12.82	15.66	12.77	12.85	13.29	13.37
	υ_1	−1487.7	−1231.6	−1387.3	−1466.5	−1476.1	−1414.8	−1459.5	−1466.4	−1470.3
D→D										
	Ea	–	17.80	17.73	17.02	17.60	17.70	17.20	17.31	17.56
	Ea +ZPE	–	12.87	11.91	11.56	11.97	12.34	11.80	11.88	11.89
	υ_1	–	−1245.4	−1474.2	−1467.9	−1489.5	−1431.3	−1463.6	−1439.7	−1477.3

[a]Activation energies in kcal/mol.

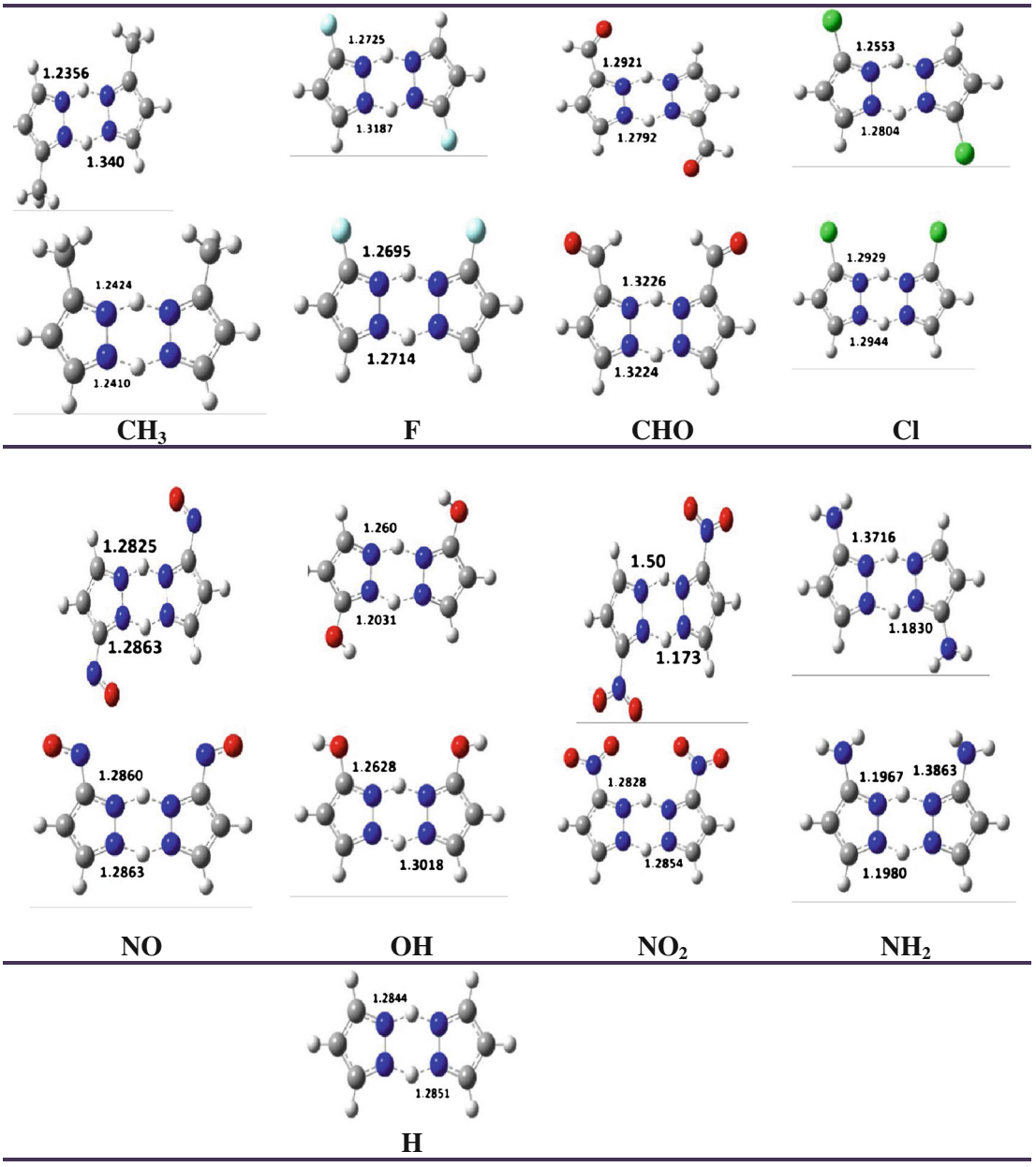

Figure 3. The optimized structures of transition states of hydrogen transfer in the pyrazole dimers calculated at MP2/6-311++G(d,p) level of theory. For each substituent the top structure show the TS of **C**→**D** reaction and bottom show **D**→**D** one.

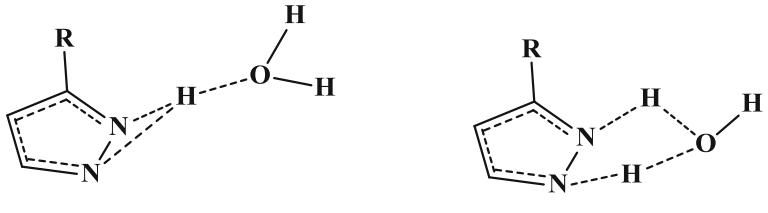

Figure 4. Schematic diagram of two different transition states of proton transfer reaction assisted by one water molecule.

Table 4. The calculated activation energies for proton transfer reaction assisted by water or ammonia molecules at MP2/6-311++G(d,p) level of theory.

	H_2O		NH_3	
	TS1	**TS2**	**TS1**	**TS2**
H	50.77[a]	29.16	33.18	22.46
NH_2	48.20	28.60	32.62	21.82
OH	49.31	28.44	31.37	20.89
Cl	48.97	27.50	28.88	19.21
F	37.38	26.62	28.06	18.24
CH_3	50.54	29.36	33.65	22.79
NO_2	45.37	27.73	29.31	17.25
CHO	51.13	31.78	28.0	18.68
NO	47.27	28.90	25.94	18.73

[a]Activation energies in kcal/mol.

molecules could influence the whole reaction path by lowering the energy barrier due to the direct participation of protic solvent molecules in the proton transfer process. Selecting the hydrophilic centres on the pyrazole derivatives; we searched the most stable monohydrated and monoammoniated forms for all compounds. With consideration of these structures the proton transfer process assisted by solvent molecules was studied. For this purpose, we have investigated two different mechanisms for the proton transfer reaction assisted by one molecule of water or ammonia. In the first mechanism (TS1), the solvent molecule interacts with proton of pyrazole ring in the transition state where a three-member ring is formed. On the other hand, in the second mechanism, solvent molecule simultaneously take the proton of pyrazole ring from position 1 and give the proton to position 2 through a five member ring. A schematic diagram of two different transition states has been presented in figure 4.

The results of calculated activation energies for the proton transfer reaction through two different mechanisms assisted by water or ammonia molecules have been shown in table 4. The results indicate that proton transfer through path 1 needs more energy than path 2. The range of activation energies assisted by water molecule through path 1 was found in the range of 37.38−51.13 kcal/mol calculated at MP2/6-311++G(d,p) level of theory. It is worth to note that one can compare these results with activation energies obtained for the proton transfer process of pyrazole derivatives in the absence of solvent molecules that discussed in previous section. As you can see, the activation energies assisted by water molecule decreased for the pyrazole ring substituted by **F**, **NO_2** and **NO** groups by 8.41, 5.25 and 4.32 kcal/mol, respectively. However, for the parent pyrazole molecule and substituted pyrazole with **NH_2**, **OH**, **Cl**, **CH_3** and **CHO** groups activation energy of proton transfer reaction assisted by water molecule increased by 2.51, 0.86, 1.78, 1.66, 3.04, and 0.29 kcal/mol, respectively. Interestingly, when water simultaneously acts as a proton donor/acceptor the activation energies decreased significantly. As noted in table 4 for the parent pyrazole molecule proton transfer through path 2 needs only 29.16 kcal/mol energy for passing transition state. Similar results were observed for other pyrazole derivatives.

For more precision of effect of explicit solvent molecules, we have investigated the proton transfer reaction assisted by ammonia molecule. As it can be seen, the range of activation energies through path 1 was found to be 25.94−33.65 kcal/mol. The results of activation energies gathered in table 4 reveal ammonia molecule can reduce activation energies more effectively than water. For example, E_a of forward **A→B** reaction of parent pyrazole molecule in the presence of water and ammonia molecules are 50.77 and 33.18 kcal/mol, respectively. In addition, similar results obtained when reaction assisted by ammonia molecule through path 2: the activation energies are lower than those found for mechanism 1. The range of activation energies was found to be 17.25−22.79 kcal/mol.

Water or ammonia molecules through two effects including (a) ring size increasing and (b) increasing the number of hydrogen displacement steps may assist the proton transfer reactions. Through first effect, 4-membered ring of free molecule, in the presence of one solvent molecule expands to a 6-membered ring that results in increasing rate of tautomerism.

4. Conclusions

MP2 and DFT-B3LYP calculations using 6-311++G(d,p) basis set were performed to investigate the proton transfer reaction of a series of substituted pyrazoles at 3 or 5 positions. The main results of the

present study can be summarized in the following manner:

1. The results indicate that for electron donating groups (such as $\mathbf{NH_2}$, $\mathbf{CH_3}$, and **F**) 3-substituted pyrazoles (**B** forms) are more stable but for electron withdrawing groups 5-substituted ones (**A** forms) are more stable.
2. The results show that activation energies for proton transfer reaction varies in the range of 45.7 − 51.59 and 49.4−53.96 kcal/mol at B3LYP and MP2 levels, respectively. Analysis of the results indicates proton migration is easier in pyrazoles with electron donating groups.
3. It was concluded that for 3-substituted pyrazoles, more effective hydrogen bonds are formed for the electron withdrawing groups but for the 5-substituted ones, electron donating groups formed stronger hydrogen bonds.
4. Double proton transfer reaction between pyrazole dimers was investigated and moderate activation energies were observed.
5. Proton transfer reaction, assisted by water or ammonia via two different pathways, was investigated and it was clarified that the reaction proceeding through path 2 is more straightforward.
6. Finally, one can compare the simplicity of proton transfer reaction through various studied mechanisms as follows: double proton transfer reaction > NH_3-assisted via path 2 > water assisted via path 2 > NH3 assisted via path 1 > water assisted via path 1 > single proton transfer reaction.

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