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Preliminary Communication

The effective molarity (EM) puzzle in proton transfer reactions

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ABSTRACT

The DFT and HF calculation results for the proton transfer reactions of three different systems reveal that the reaction mechanism (transfer of a proton to a nucleophile) is largely determined by the distance between the two reactive centers (*r*).

Systems with relatively large *r* values tend to abstract a proton from a molecule of water, whereas, these with a relatively small *r* values prefer to be engaged intramolecularly and their interaction with water is only *via* hydrogen bonding. Further, the results indicate that the effective molarity (log EM) for an intramolecular process is strongly correlated with the distance between the two reacting centers (*r*) in accordance with Menger's "spatiotemporal hypothesis".

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1. Introduction

The striking efficiency of enzyme catalysis has inspired many organic chemists to explore enzyme mechanism(s) by studying certain intramolecular processes (enzyme models) which proceed faster than their intermolecular counterparts. Both, enzymes and intramolecular processes are similar in that the reacting centers are held together (covalently with intramolecular systems, and non-covalently with enzymes). Thus, unraveling of an enzyme catalyzed reaction could be achieved by specifying the mechanism of the intramolecular reaction concerned (reaction model for mimicking enzyme catalysis) [1].

Since the early sixties many research groups were engaged in the area of enzyme models. Among these are (a) the group of Bruice who studied the intra-molecular cyclization of di-carboxylic semi-esters and proposed the "near attack proximity orientation" [2]; (b) the Koshland's group who advocated the "orbital steering theory" proposing that the fast intramolecularity arises from a severe angular dependence of organic reactions [3]; (c) the Menger's group who devised the "spatiotemporal hypothesis" by which describes the importance of the distance between the nucleophilic and the electrophilic reactive centers in intramolecular proton transfer processes [4]; and (d) the Cohen's group who studied the acid-catalyzed lactonization of some hydroxy-acids and concluded that freezing a molecule into a productive rotamer could lead to a vast rate accelerations "stereopopulation control" [5].

Recently, we have been extensively investigating the origin of the driving force(s) for the extraordinary accelerations in rate of some intramolecular processes [6]. Using the *ab initio* HF and the DFT molecular orbital at different levels, molecular mechanics and semi-empirical molecular orbital methods, we calculated the kinetic and thermodynamic behavior of the acid-catalyzed lactonization of hydroxy-acids as studied by Milstein and Cohen [5] and Menger et al. [4] the cyclization reactions of di-carboxylic semi-esters as studied by Bruice et al. [2] the intramolecular proton-transfers in rigid systems as studied by Menger et al. [4] and Sn2-based cyclization as studied by Galli and Mandolini [7]. The following salient conclusions that emerged from these studies are: (1) Rate enhancements in intramolecular reactions can stem from proximity orientation of the two reactive centers as a result of strain effects or can due to proximity that is not related to strain imposed on a starting material and/or a corresponding transition state. For example, our study on the cyclization of Bruice's di-carboxylic semi-esters reveals that the reaction's rate in this system is dependent on the strain energy of the transition state and the reactant, and the "reactive rotamer effect" concept is not playing any role in the acceleration. Further it shows that the reactivity extent of the semi-ester is linearly correlated with the strain energy difference between the transition state and the reactant and the rate of the reaction is independent on the distance between the two reactive centers. On the other hand, our results on the acid-catalyzed lactonization of Cohen's and Menger's hydroxy-acids reveal that proximity with un-enforced strain origin is the dominant driving force for accelerations in the lactonization rate, and this rate is solely dependent on the ratio between the attack angle of the nucleophile and the distance between the two reactive centers. This is in accordance with Menger's "spatiotemporal hypothesis" that relates distance between a nucleophile and an electrophile to the rate of a reaction [4]. (2) Both, enthalpy and entropy are important factors for rate enhancements in intramolecular processes. This is contrarily to what was proposed by Bruice that enthalpic effects are the only source for such accelerations. (3) The nature of the reaction (inter- or intra-molecular) is largely

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dependent on the distance between the two reactive centers. For example, our study on Menger's rigid cycloalkanes shows that intramolecular processes are favored over the corresponding intermolecular reactions when the distance between the two reactive centers is $\leqslant$2.4 Å, whereas, when the distance is $\geqslant$3 Å, the reaction prefers to be engaged intermolecularly. Moreover, it reveals that the proximity orientation of the two reacting entities is largely dependent on the strain energy of the reactant.

In general, intramolecularity is quantified by the "effective molarity" (EM) parameter. EM is defined as k_{intra}/k_{inter} for corresponding intramolecular and intermolecular processes driven by identical mechanisms. Kirby's scholarly report of EM values indicates that they can range from less than 0.3 M up to more than 10^{10} M. The factors affecting the value of EM are ring size, solvent and reaction type [8].

In 1985, Menger published an account "on the source of intramolecular and enzymatic reactivity". In this report Menger wrote "Kirby's list of EM values represents one of the largest and most variant bodies of unexplained data in physical organic chemistry" [4].

In this ensuing communication, we disclose the first computational study to explore some of the wild fluctuations in EM values for some proton transfer processes as presented in Kirby's compilation.

We have calculated, using *ab initio* at HF/cc-pVDZ and DFT at B3LYP/cc-pVDZ molecular orbital methods, the kinetic properties of the intramolecular proton transfer processes of **1**–**3** (Chart 1) and the corresponding intermolecular processes $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ (Chart 2).

2. Calculation methods

The HF and DFT calculations were carried out using the quantum chemical package Gaussian-98 [9]. The starting geometries of all the molecules in this study were obtained using the Argus Lab [10] program and were initially optimized by the AM1 method. The calculations were carried out based on the restricted Hartree–Fock (RHF) method with full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles) [11]. To avoid results with local minima optimization, the keyword Freq Opt = (Z-matrix, MaxCycle = 300, CalcAll) GFINPUT IOP (6/7 = 3) was used in the input files of the AM1 optimized starting geometries. An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant [12]. The transition state structures were verified by their only one negative frequency. The verification was accomplished by viewing the frequency results *via* the MOLDEN program [13]. The "reaction coordinate method"

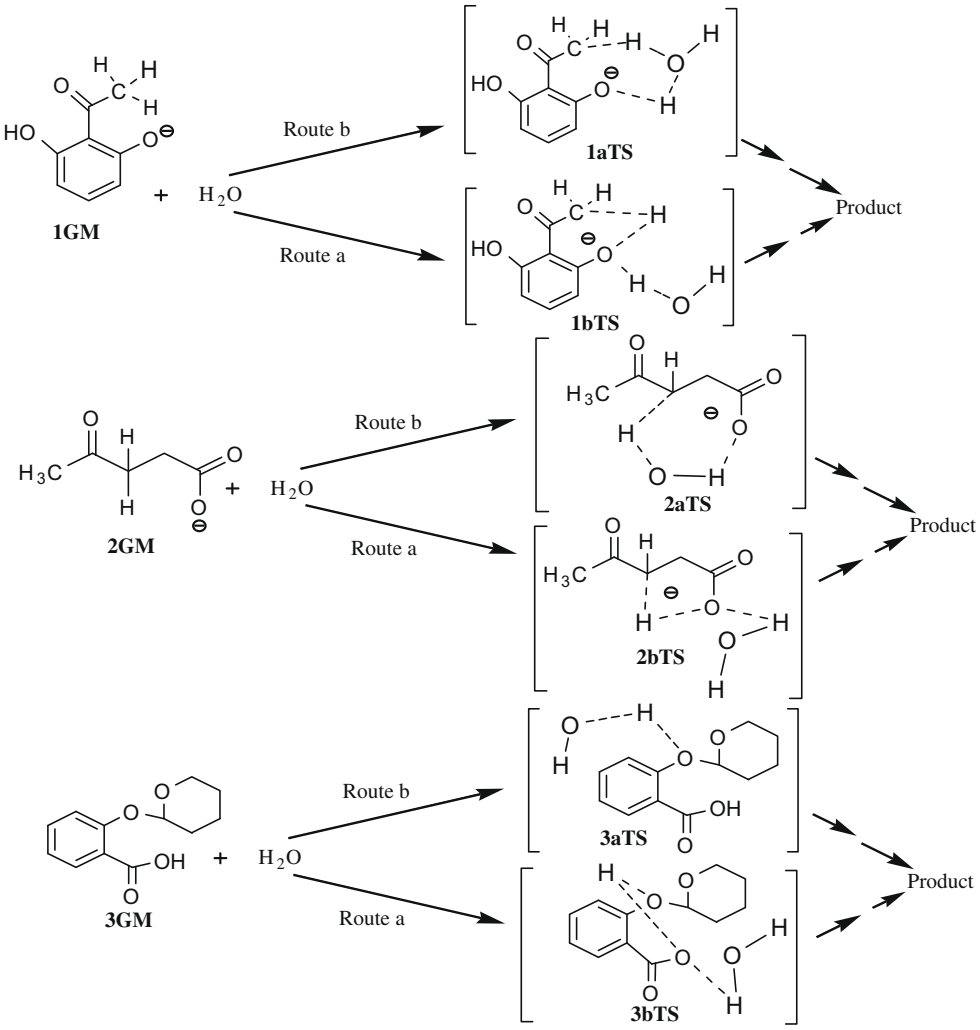


Chart 1. Intramolecular proton transfer of systems **1**–**3**. Route a: A transfer of a proton from water to the reactive nucleophilic center of the system. Route b: An intramolecular proton transfer from the acidic proton to the reactive nucleophilic center within the system (**1**–**3**). **1a**TS, **2a**TS and **3a**TS are the transition state structures formed *via* route a. **1b**TS, **2b**TS and **3b**TS are the transition state structures *via* route b.

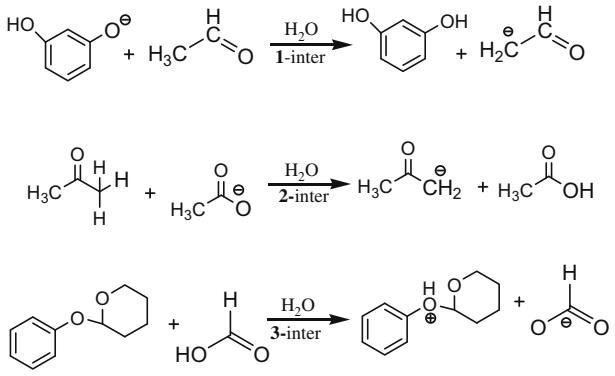


Chart 2. Proton transfer reactions in the corresponding intermolecular systems of **1**–**3** (systems $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$).

[14] was used to calculate the activation energy for the proton processes of **1**–**3** and $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$. In this method, the value of one bond is limited for the appropriate degree of freedom while all other variables are optimized. The activation energy values were calculated from the difference in the energies of the global minimum structures for the reactants and the derived transition states of the proton transfer reactions. The transition state structures for the proton transfer reactions of **1**–**3** and $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ were obtained from the decrease in the distance between the electrophile (H) and the nucleophile (O or C) in increments of 0.1 Å. Full optimization of the transition states was accomplished after removing the constrains imposed while executing the energy profile. The frequency results obtained from the optimization were viewed by MOLDEN program and it was found that all the transition state structures, studied here, have only one negative frequency. The DFT and HF activation energy values for **1**–**3** and $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ were calculated with and without the inclusion of solvent (water). The keywords SCF = Tight SCRF = (iefPCM, Read, Solvent = Water) were used in the input files when calculating energies with the incorporation of a solvent.

In the calculations of the proton transfer processes of **1**–**3** two possible transition state structures could be obtained: aTS and bTS (Chart 1). aTS could be formed when one molecule of water is allowed to interact with the nucleophilic center of the reactant to furnish a partial bond of HOH–X (where X = O or C, see route a in Chart 1), whereas, the formation of bTS could be achieved from the interaction of the acidic proton of the reactant with its reactive nucleophilic center (see route b in Chart 1). In the case of aTS, a water molecule is the source of a proton transfer, whereas in bTS, the source of the proton is the reactant.

3. Results and discussion

Using the HF and DFT calculated enthalpies and entropies for the global minimum structures (GM) of **1**–**3** and $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ and the derived transition states (TS) (Table 1) we have calculated the enthalpic activation energies ($\Delta\Delta H^{\ddagger}$), the entropic activation energies ($T\Delta S^{\ddagger}$), and the free activation energies in the gas phase ($\Delta\Delta G^{\ddagger}$) and in water for the corresponding proton transfer reactions. The calculated results of these kinetic parameters are summarized in Table 2. Fig. 1 illustrates the DFT calculated global minimum (GM) and transition state structures (aTS and bTS) for the proton transfer processes of **1**–**3**.

Inspection of Table 2 reveals that the free activation energy (B3LYP/cc-pVDZ $\Delta\Delta G^{\ddagger}$/water) needed to execute the proton transfer in system **1** *via* route b is much less than *via* route a (29.4 vs. 36.55 kcal/mol), whereas, the picture is the opposite with the processes of **2** and **3** (35.19 vs. 25.19 kcal/mol and 40.72 vs. 19.87 kcal/mol, respectively). The discrepancy between processes **1**, on one hand, and **2** and **3**, on the other hand, is attributed to the fact that the distance between the nucleophile and the electrophile (H–X, where X = C or O) in the reactant of **1** is much larger than for that in **2** and **3** (2.61 Å in **1** vs. 2.49 Å and 1.81 Å in **2** and **3**, respectively). Further, a good correlation was found between the electrophile–nucleophile distance (r) and the activation energy $\Delta\Delta G^{\ddagger}$/water, and the relationship between them is summarized in the following equation:

$$\Delta\Delta G^{\ddagger}/\text{water} = 10.098r + 1.662 \quad R = 0.95 \tag{1}$$

The relatively large r value between the two reactive centers in reactant **1** allows one molecule of water to interact freely and directly with the nucleophilic center in **1** to make a relatively stable transition state **1a**TS, whereas, the shorter distances of r in systems **2** and **3** inhibit any incorporation of a water molecule to be actively engaged in the transfer of a proton.

It should be noted that the time in these three systems is constant hence the driving force for the reaction rate is solely dependent on the distance between the two reactive centers. This is in accordance with our results on other systems [6].

Alternatively, the preference of whether the proton will be transferred *via* route a, or b might be attributed to the stability of the transition state formed. In the cases of systems **2** and **3**, transition states, **2a**TS and **3a**TS are relatively more stable than their corresponding **2b**TS and **3b**TS due to the strong hydrogen bonding net involved. This is in accordance with previous studies by Kirby and Pascal that indicate that the effective molarity of a system is dependent on the strength of the hydrogen bonding net formed

Table 1
HF and DFT calculated properties of the proton transfer reactions of **1**–**3**.

Compound	Enthalpy (Hartree)	HF/cc-pVDZ (Cal/Mol-Kelvin)	Enthalpy (Hartree)	B3LYP/cc-pVDZ Entropy Cal/Mol-Kelvin
1GM	−607.807	109.05	−611.357	108.89
1aTS	–	–	−611.301	–
1bTS	−607.735	97.20	−611.315	98.68
2GM	−494.219	106.44	−497.035	106.97
2aTS	−494.157	104.32	−496.997	105.83
2bTS	–	–	−496.985	–
3GM	−838.144	125.97	−843.098	130.03
3aTS	−838.094	126.14	−843.067	128.63
3bTS	–	–	−843.035	–
1GM-inter	–	–	−536.073	120.17
1TS-inter	–	–	−536.057	99.57
2GM-inter	−419.335		−421.794	103.14
2TS-inter	−419.282		−421.760	100.28
3GM-inter	−763.254		−767.849	129.76
3TS-inter	−763.206		−767.809	121.44

All calculations were performed with the inclusion of water as a solvent.

Table 2
HF and DFT calculated kinetic and thermodynamic properties for the proton transfer reactions of **1–3**.

Process	log EM	HF-aug $\Delta\Delta H^{\ddagger}$ (gas phase)	HF-aug $T\Delta S$ (gas phase)	HF-aug $\Delta\Delta G^{\ddagger}$ (gas phase)	HF-aug $\Delta\Delta H^{\ddagger}$ (water)	HF-aug $T\Delta S$ (water)	HF-aug $\Delta\Delta G^{\ddagger}$ (water)	B3-aug $\Delta\Delta H^{\ddagger}$ (gas phase)	B3-aug $T\Delta S$ (gas phase)	B3-aug $\Delta\Delta G^{\ddagger}$ (gas phase)	B3-aug $\Delta\Delta H^{\ddagger}$ (water)	B3-aug $T\Delta S$ (water)	B3-aug $\Delta\Delta G^{\ddagger}$ (water)
1a	–	–	–	–	–	–	–	–	–	–	35.15	−1.40	36.55
1b	−1.6021	44.55	−3.53	48.08	45.18	−3.53	48.71	26.36	−3.04	29.4	26.36	−3.04	29.40
2a	−1.0000	30.12	−0.63	30.75	39.91	−0.63	40.54	17.57	−0.34	17.91	24.85	−0.34	25.19
2b	–	–	–	–	–	–	–	–	–	–	32.38	−2.81	35.19
3a	3.8129	36.40	0.05	36.35	31.38	0.05	31.43	30.12	−0.42	30.54	19.45	−0.42	19.87
3b	–	–	–	–	–	–	–	–	–	–	39.53	−1.19	40.72
1-inter	–	–	–	–	–	–	–	–	–	–	11.29	−6.13	17.42
2-inter	–	–	–	–	–	–	–	–	–	–	18.83	−0.85	19.68
3-inter	–	–	–	–	–	–	–	–	–	–	25.73	−2.48	28.21

HF-aug and B3-aug refer to calculated by HF/cc-pVDZ and B3LYP/cc-pVDZ methods, respectively. log EM is the logarithm of the effective molarity. $\Delta\Delta H^{\ddagger}$ is the activation enthalpic energy in kcal/mol. $\Delta\Delta G^{\ddagger}$ is the activation free energy in kcal/mol. (Gas phase) is calculated in the gas phase. (Water) is calculated with the inclusion of water as a solvent. $T\Delta S$ is the entropic energy in kcal/mol. –inter refers to intermolecular reaction.

within the transition state of the proton transfer process. Strong hydrogen bonding corresponds to high EM values and *vice versa* [15].

It should be emphasized that for system **3**, activation energy needed for the intramolecular process is 8 kcal/mol less than that for the corresponding intermolecular process. This is equal to EM = 10^5 (the experimental EM = 10^4). This value is comparable to the effective molarities seen in hydride transfer [16].

The HF-aug and DFT-aug calculated free activation energies of **1**–**3** and $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ ($\Delta\Delta G^{\ddagger}$) were examined for linear correlations with the experimental effective molarity (log EM) [8] and the resulting equations along with their correlation coefficients are summarized in Eqs. (2)–(4) and are illustrated graphically in Fig. 2a and b.

$$(\Delta\Delta G^{\ddagger})/\text{water HF-aug} = -1.5089\log \text{EM} + 25.43 \quad R = 0.94 \qquad (2)$$

$$(\Delta\Delta G^{\ddagger})/\text{water B3-aug} = -2.6933\log \text{EM} + 41.31 \quad R = 0.93 \qquad (3)$$

$$\Delta G^{\dagger}_{rel} = 0.1449\log \text{EM} + 0.88 \quad R = 0.99 \qquad (4)$$

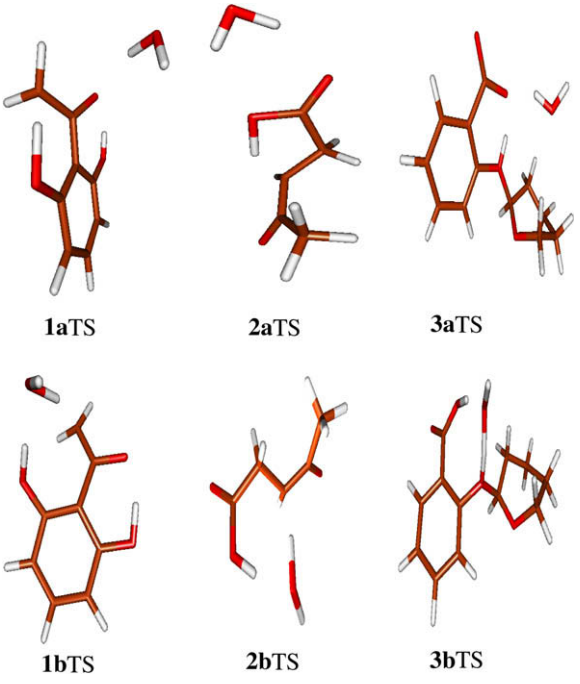
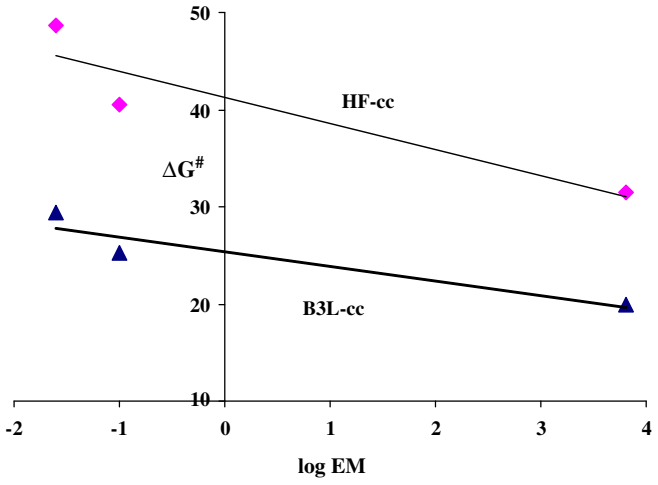


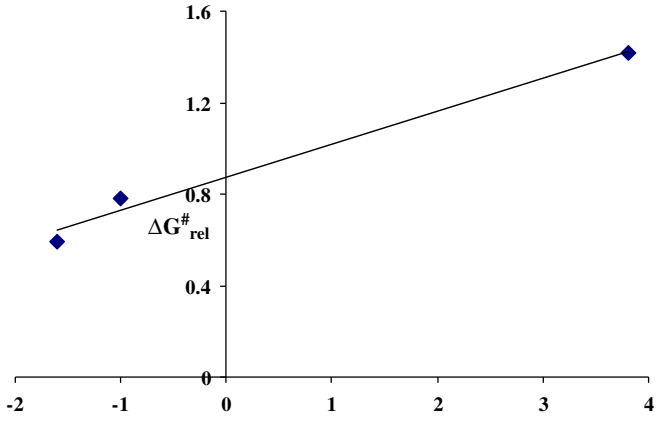
Fig. 1. DFT optimized transition state structures for the intramolecular proton transfer processes of systems **1**–**3** (**1a**TS, **1b**TS, **2a**TS, **2b**TS, **3a**TS and **3b**TS, for details see text).

where $\Delta G^{\ddagger}_{rel}$ is $(\Delta\Delta G^{\ddagger})_{inter}/(\Delta\Delta G^{\ddagger})_{intra}$ as calculated by B3LYP-aug with the inclusion of water as a solvent.

The correlation results show a satisfactory linear correlation of HF and DFT calculated activation energies ($\Delta\Delta G^{\ddagger}$) with the experimental log EM ($R = 0.93 - 0.99$).



(a) $\Delta G^{\#}$ vs. log EM



(b) $\Delta G^{\#}_{rel}$ vs. log EM

Fig. 2. (a) Plot of HF and DFT calculated $\Delta G^{\ddagger}$ vs. log EM. (b) Plot of DFT calculated $\Delta G^{\ddagger}_{rel}$ vs. log EM. EM is the effective molarity and $\Delta G^{\ddagger}_{rel}$ is $(\Delta\Delta G^{\ddagger})_{inter}/(\Delta\Delta G^{\ddagger})_{intra}$.

Careful attention should be drawn to Fig. 2b. When log EM = 0, the $(\Delta\Delta G^{\ddagger})_{inter}/(\Delta\Delta G^{\ddagger})_{intra}$ value is 0.88. Thus, systems having values of $(\Delta\Delta G^{\ddagger})_{inter}/(\Delta\Delta G^{\ddagger})_{intra}$ more than 0.88 will tend to be engaged intramolecularly, whereas, these with less than 0.88 will favor an intermolecular reaction.

Comparisons of the intramolecular to that of the intermolecular process reveal that incorporation of one molecule of water with the intramolecular systems **1**–**3** has a positive effect on the enthalpic and free activation energy ($\Delta\Delta H^{\ddagger}$ values are 2–6 kcal/mol lower with the inclusion of water), whereas, in the intermolecular systems $\mathbf{1}_{inter}$–$\mathbf{3}_{inter}$ it has a negative effect ($\Delta\Delta H^{\ddagger}$ values are 3–7 kcal/mol higher with the inclusion of water).

It should be emphasized that attempts to correlate HF and DFT calculated activation energies ($\Delta\Delta G^{\ddagger}$) in the gas phase or without the inclusion of water with log EM failed to give any satisfactory results.

4. Summary and conclusions

In summary, we introduced the first study on the effective molarity (EM) puzzle from a theoretical approach. The combined results of this study reveal that calculations in the gas phase for processes occur in aqueous solutions are not adequate. Further, they show that calculating ground state and/or transition state geometries using the different methods of solvation alone is not enough to predict real activation energies and it is a must to include at least one molecule of water in the calculations of all the entities involved in the process under investigation in order to achieve more accurate and reliable results.

Additionally, the results confirm again that proton transfer reaction's rate is dependent and linearly correlated with the distance between the two reactive centers. This result is in accordance with Menger's "spatiotemporal hypothesis" [4] and is in perfect agreement with our previous studies on other proton transfer reactions [6].

Further, the study results present the first theoretical approach to prove and to support the conclusions of Kirby drawn on the dependence of the EM value on the strength of hydrogen bonding formed within the transition state of a proton transfer process [15].

I believe that it will be a long way in climbing the high tree of the so called "enzyme catalysis", but slow and confident steps as the one presented herein will prevent tumbling and will contribute to the more competitive" marked science" as Menger wrote in one of his publications [4].

Further work is underway to explore the issue of proton transfer differences (concerted vs. stepwise process) that occur when carbon is the proton donor versus that by which a hetero-atom functions as the proton donor.

Acknowledgments

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