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Analysis of Menger's 'spatiotemporal hypothesis'

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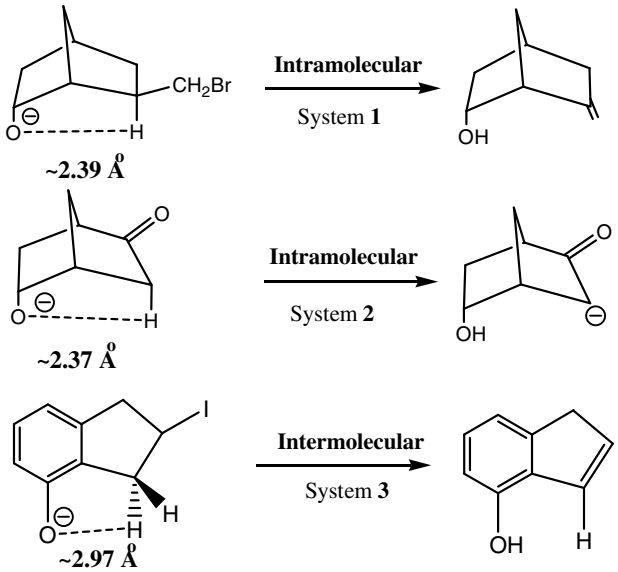
ABSTRACT

Ab initio at HF/6-31G and HF/6-31G(d,p) levels, AM1 and molecular mechanics calculations of thermodynamic and kinetic parameters for Menger's system **1**–**3** (an important enzyme model) indicate that the remarkable enhancement in the proton transfer process is largely the result of a strain effect, and this strain is a function of the bond distance between the two reacting centers and the value of the angle of attack.

Since the historical discovery of enzymes as catalytic proteins for biological systems, a significant number of studies have been carried out to investigate their remarkable power and exquisite specificity. Much of the focus of biochemists, bioorganic and computational chemists through the second half of the 20th century has been on the mechanism or mechanisms by which enzymes achieve their high rate enhancements and specificity. It is estimated that the rate acceleration brought about by enzymes, relative to the uncatalyzed transformations in aqueous solutions, is in the range of 5–17 orders of magnitude.[1] Enzymes accomplish these enormous rate enhancements using amino acid side chains and cofactors that have limited intrinsic reactivity compared to the catalysis in organic synthesis. It is accepted that the rate accelerations manifested by enzymes are brought about via binding of the substrate within the confines of the enzyme active site. Upon binding of a substrate to an enzyme active site, rate acceleration of a biochemical process can be achieved by one of the following: (a) covalently enforced proximity;[2] (b) non-covalently enforced proximity;[3] (c) covalently enforced strain;[4] and (d) non-covalently enforced strain.[5]

Chemical systems have been developed to mimic the rate acceleration achieved by enzymes that catalyze biochemical processes through covalently enforced proximity. Among these models is the one presented by Bruice et al., describing an intramolecular cyclization of dicarboxylic semi esters to give the corresponding cyclic anhydrides.[6] Experimental and computational studies of this model by Bruice led him to conclude that the rate acceleration brought about by enzyme catalysis is primarily due to close proximity of the reactants once the substrate binds to the enzyme active site. Other examples of chemical systems based on rate acceleration as a consequence of proximity effects include: (1) the 'orbital steering' theory proposed by Koshland,[7] (2) the *gem*-tri-methyl lock (stereopopulation control) suggested by Cohen to explain the remarkable rate enhancement seen in the acid catalyzed lactonization of some hydroxyhydrocinnamic acids,[8] and (3) the 'spatiotemporal hypothesis' advocated by Menger which suggests that whether a reaction is intermolecular or intramolecular is determined by the distance between the two reacting centers of the reactant[9] (Scheme 1).

We have been engaged in exploring the real driving forces behind the remarkable acceleration in the rates of some intramolecular reactions. Using molecular mechanics, semi-empirical



Scheme 1.

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molecular orbital, and ab initio calculation methods, we have studied the thermodynamics and transition state behavior of the acid lactonization of hydroxy-acids, the cyclization reactions of ω-bromoalkanecarboxylate anions, and the lactonization of some dicarboxylic semi esters, arriving at the following conclusions: (a) significant rate enhancements in intramolecular reactions are due to both entropic and enthalpic effects (not only to entropic effects) as was suggested by Page[3] and Jencks,[1] not to enthalpic effects alone as was proposed by Bruice et al.,[6] (b) the driving force for rate acceleration in intramolecular processes can be due to proximity or/and steric effects depending on the nature of the system.[10]

Menger's pioneering studies on the acid lactonization of hydroxy-acids, containing a rigid carbon framework at well-defined bond angles and distances, and on intramolecular proton transfer in systems **1**–**3** led him to conclude that (i) the rate of reaction between two reactive centers, A and B, is proportional to the time of A and B being within a critical distance; and (ii) intramolecular reactions can have enzyme-like rates when a critical distance is imposed on A and B (Scheme 1, systems 1 and 2). If the distance between A and B is larger than the critical distance, then an intermolecular reaction prevails (Scheme 1, system 3).[9]

Continuing our study on the origin of the driving force behind the vast acceleration in the rates of intramolecular reactions mimicking enzyme catalysis, using Allinger's molecular mechanics and AM1 semi-empirical molecular orbital methods as well as ab initio HF at levels 6-31G and 6-31G(d,p), we have conducted intensive theoretical work on Menger's proton transfer system (Scheme 1). The purpose of this study was to test if indeed the distance between two reacting moieties is the only crucial factor for determining the nature of the reaction (inter- vs intramolecular) and to explore if other factors, such as the angle of attack, have any important effect on the rate accelerations.

The AM1 semi-empirical calculations and HF ab initio calculations at the 6-31G and 6-31G(d,p) levels were carried out using the quantum chemical package GAUSSIAN-98[11] running on the Al-Quds computer center. The MM2 molecular mechanics strain energy calculations were executed using Allinger's MM2 program installed in Chem 3D Ultra 8.0.[12] The starting geometries of all the compounds in this study were obtained using the ARGUSLAB program.[13] The semi-empirical and the ab initio calculations were carried out based on the restricted Hartree–Fock (RHF) method[14] with full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles). The geometry optimizations included estimations of second derivatives (Hessian matrix) for each of the $3n-6$ parameters in each species ($2n-3$ for planar structures).[15] DEP analytical gradients were used throughout the optimization. Geometries were optimized in internal coordinates and were terminated when Herbert's test was satisfied in the Broyden–Fletcher–Goldfarb–Shanno method (BFGS). All optimizations were terminated when the change in energy on successive iterations was less than 0.00001 kcal/mol, and the change in density matrix elements on two successive iterations was less than 0.001.

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 one and only one negative vibrational force constant.[16] The 'reaction coordinate method'[17] was used to calculate the activation energy for proton transfer in systems **1**–**3**. In this method, a value of one bond is limited for the appropriate degree of freedom while all other variables are optimized. The activation energy values for proton transfer were calculated from the difference in the energies of the global optimum structures for the reactant in **1–3** and the derived transition states of the proton transfer reactions, obtained from the decrease in the distance between the anionic oxygen (O1) and H2 in increments of 0.1 Å. The ab initio at HF/6-31G and HF/6-31G(d,p) levels and the AM1 activation energy values were calculated with and without the inclusion of solvent (water) and the results obtained indicate that the effect of water on the relative rate values was negligible. This is in accordance with the previously reported studies of Houk and coworkers that indicate that the solvation effect is more-or-less cancelled out when comparing the reactivities of species having the same structural features (even though the absolute rate constants cannot be evaluated).[18] This is also supported by Menger's experimental results that indicate the change in rate reactivities to be minor when replacing water with DMSO.[9] It should be emphasized that calculations of activation energy of one process occupy a personal computer for more than one month when using the 'reaction coordinate' at HF (6-31G) and HF/6-31G(d,p) levels. Hence, it is not feasible to use higher levels of ab initio for achieving more accurate results.

In order to determine whether systems **1**–**3** undergo inter- or intramolecular reactions, two AM1 calculation sets were executed: (i) calculating the activation energy values for the approach of H towards O within the molecule, (ii) calculating the activation energies of the approach of H in systems **1**–**3** towards the anionic oxygen of a methoxide anion (intermolecular).The calculations revealed that systems **1** and **2** favor intramolecular over intermolecular reactions (14.05 kcal/mol for **1** and 18.15 kcal/mol for **2** for intramolecular vs 52.32 kcal/mol for intermolecular) while system **3** prefers to engage in intermolecular reaction (57.15 kcal/mol for intramolecular vs 40.27 kcal/mol for intermolecular). This is in exact agreement with Menger's experimental data. In order to give credibility to the AM1 results, calculations of the activation energy values for intramolecular reactions for systems **1**–**3** were performed using ab initio methods at HF/6-31G and HF/6-31G(d,p) levels and the results are listed in Table 1. The activation energy values calculated by the three methods were examined for linear correlations, and it was found that excellent correlations exist between the three different methods (Eqs. 1 and 2).

$$\Delta\Delta\mathbf{H}^{\ddagger}_{\mathrm{HF/6\text{-}31G}} = 1.0912\ \Delta\Delta\mathbf{H}^{\ddagger}_{\mathrm{AM1}} - 6.7349\ (R = 0.999) \quad (1)$$

$$\Delta\Delta\mathbf{H}^{\ddagger}_{\mathrm{6\text{-}31G(d,p)}} = 1.0014\ \Delta\Delta\mathbf{H}^{\ddagger}_{\mathrm{AM1}} - 1.7389\ (R = 0.999) \quad (2)$$

The importance of ground state conformations and the lack of translational entropy in intramolecular and enzymatic reactions have captured the attention of Bruice et al.,[6] and Menger.[9] Both have suggested that the remarkable acceleration in rates found in some systems involving intramolecular cyclization is mainly driven by the proximity of the nucleophile to the electrophile of the ground state molecules. Bruice ascribed enzyme catalysis to be favorable 'near attack conformations'. According to Bruice's idea, systems that have a high percentage of near attack conformers will have a higher intramolecular reaction rate and vice versa. This idea invokes a combination of angle of attack and distance between the two reacting centers. On the other hand, Menger and co-workers developed an equation relating activation energy to distance. Based on this equation, Menger concluded that enzymes achieve their enormous rate accelerations by imposing short distances between the reactive moieties of the enzyme and the substrate.

Table 1
AM1, MM2, and ab initio (at HF/6-31G and 6-31G(d, p) levels) calculated properties of inter- and intramolecular proton transfer in systems **1**–**3**

System	AM1		HF/6-31G		6-31G(d, p)		E_s (MM2)
	S	$\Delta\Delta\mathbf{H}^{\ddagger}$	**S**	$\Delta\Delta\mathbf{H}^{\ddagger}$	**S**	$\Delta\Delta\mathbf{H}^{\ddagger}$	
1	0.3818	14.05	0.2041	6.65	0.2718	11.93	27.48
2	0.4964	25.1	0.2866	15.22	0.3095	16.88	24.55
3	1.7513	57.15	1.6169	55.42	1.423	55.45	5.79

$\Delta\Delta\mathbf{H}^{\ddagger}$ is the enthalpic activation energy, $\mathbf{E_s}$ is the MM2 strain energy, and **S** is the slope of **H** versus $\boldsymbol{\alpha/r}$.

In contrast to Menger's and Bruice's proposals, others believe that a high acceleration of rate in intramolecular reactions is due mainly to steric effects (relief in strain energy of the reactants). The term strain usually describes steric effects that might cause acceleration or an inhibition of a reaction rate. An intramolecular reaction may be faster than the corresponding intermolecular reaction if the intramolecular systems are significantly strained and the strain is relieved when arriving at a transition state. Generally, there are two opposite cases in which a reaction can be driven by strain: (i) when the reaction rate is inhibited and the interaction between the reacting centers is impeded as a result of steric hindrance, as in the case of S_N2 substitution of cyclohexyl halides, and (ii) when the reaction is accelerated due to a relief in strain of the ground state while reaching a transition state, as in the case of S_N2 reactions of epoxides.[19]

To test whether the discrepancy in the reactions of systems **1**–**3** is as a result of a proximity effect (difference in the distances between the two reacting centers) or due to steric effects (strain energy) we calculated, using Allinger's MM2 method, the strain energy values ($\mathbf{E_s}$) for the reactants in systems **1**–**3** and the MM2 calculated values are listed in Table 1. The AM1, HF/6-31G, and HF/6-31G(d,p) calculated activation energy values ($\Delta\Delta\mathbf{H}^{\ddagger}_{AM1}$, $\Delta\Delta\mathbf{H}^{\ddagger}_{HF/6\text{-}31G}$, and $\Delta\Delta\mathbf{H}^{\ddagger}_{6\text{-}31G(d,p)}$, respectively) were examined for correlations with $\mathbf{E_s}$, and the correlation results are summarized in Figure 1a and Eqs. 3–5 in Table 2.

Figure 1a and Eqs. 3–5 reveal that there is an excellent correlation between the calculated enthalpic activation energy values ($\Delta\Delta\mathbf{H}^{\ddagger}$, in all the calculation methods used) and the MM2 strain energy values ($\mathbf{E_s}$). For systems that have high strain energy values (such as system **1**), the corresponding activation energies are low and vice versa. Inspection of the calculated H–O$^-$ distances in systems **1**–**3** reveals that there is no correlation between the calculated activation energy and the distance. For example, the calculated H–O$^-$ distances for systems **1** and **2** are similar (~2.39 Å vs ~2.37 Å), whereas $\Delta\Delta\mathbf{H}^{\ddagger}$ for **2** is much higher than that for **1** (5–9 kcal/mol difference depending on the calculation method used, see Table 1). Further, it was found that the enthalpic energy needed to shorten the H–O$^-$ distance in system **3** from ~2.97 Å (in the calculated global minimum) to the same distance of H–O$^-$ in the global minimum ground state structure of system **1** (~2.39 Å) is about 6 kcal/mol (in all the methods used), whereas the difference in the enthalpic activation energy between the two systems is about 40 kcal/mol. This result, as well as the result from the correlations (Table 2, Eqs. 3–5), excludes the notion that the distance between the nucleophile (O1) and the electrophile (H2) is the only crucial factor for determining the rate of the reaction, and whether it is inter- or intramolecular.

In order to better understand which constituent factors are affected by the strain effect, we calculated the change in the value of the angle of attack α (O1/H2/<α>-C, see Chart 1) and the change

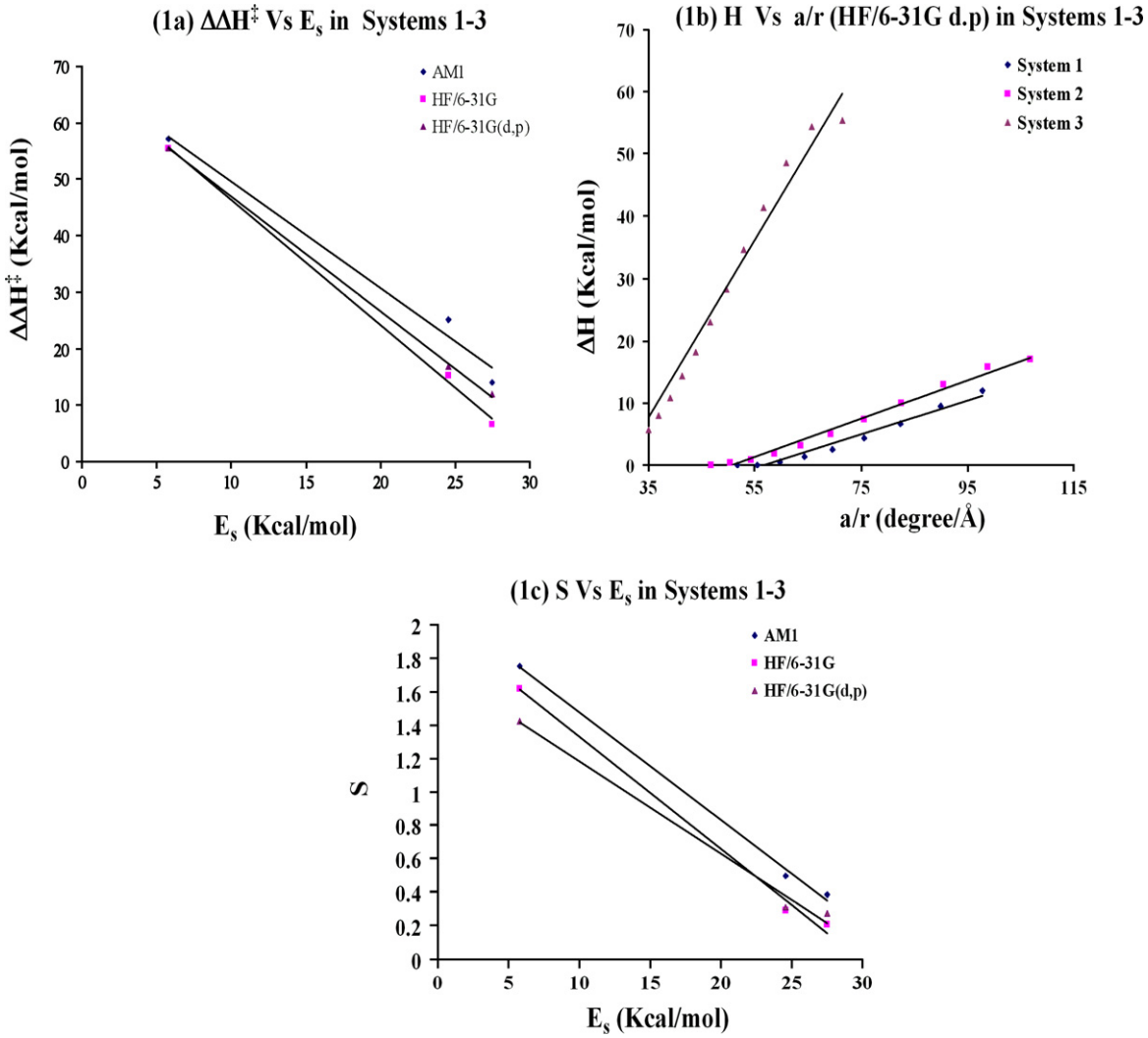

Figure 1.

Table 2
Correlations of the AM1, MM2, and ab initio calculated properties for intramolecular proton transfer in systems **1–3**

	Method			Equation	R^2
$\Delta\Delta H^{\ddagger}$ versus E_s for systems **1–3**	AM1	(3)		$y = -1.8875x + 68.478$	0.9846
	HF/6-31G	(4)		$y = -2.2107x + 68.372$	0.9984
	HF/6-31G(d, p)	(5)		$y = -2.0242x + 67.099$	0.9996
H versus **α/r**	HF/6-31G(d, p)	(6)	**1:**	$y = 0.2718x - 15.445$	0.9655
		(7)	**2:**	$y = 0.3095x - 15.706$	0.9865
		(8)	**3:**	$y = 1.4230x - 42.070$	0.9826
	HF/6-31G	(9)	**1:**	$y = 0.2041x - 12.142$	0.9573
		(10)	**2:**	$y = 0.2866x - 15.008$	0.9790
		(11)	**3:**	$y = 1.6169x - 51.130$	0.9961
	AM1	(12)	**1:**	$y = 0.3818x - 20.354$	0.9961
		(13)	**2:**	$y = 0.4964x - 25.325$	0.9881
		(14)	**3:**	$y = 1.7513x - 59.654$	0.9961
S versus E_s in systems **1–3**	AM1	(15)		$y = -0.0645x + 2.1193$	0.9976
	HF/6-31G	(16)		$y = -0.0672x + 1.9977$	0.9947
	HF/6-31G(d, p)	(17)		$y = -0.0553x + 1.7343$	0.9908

$\Delta\Delta H^{\ddagger}$ is the enthalpic activation energy, E_s is the MM2 strain energy, the **H** is the enthalpic energy during the proton transfer process, **α** is the angle of attack, **r** is O1···H2 distance and **S** is the slope of **H** versus **α/r**.

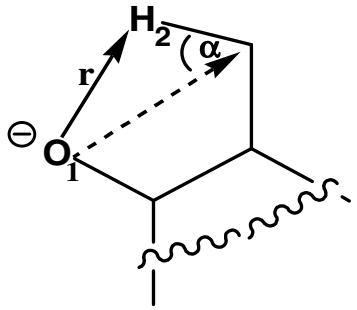

Chart 1. The angle of attack (**α**), and the distance between the two reacting centers (**r**) in Menger's system.

in the distance between the two reacting centers (**r** = H–O$^-$ distance) as a function of the energy **H** (enthalpic energy), since both parameters (**α** and **r**) were reported to play an important role in the reaction rates of intramolecular systems.[6,9] The resulting data were examined for linear correlations, and a strong correlation was observed between the energy **H** (enthalpic energy) and **α/r**, as shown in Eqs. 6–14 in Table 2 and Figure 1b. Careful examination of Eqs. 6–14 indicates that the energy needed to increase the value of angle **α** to reach the optimal value for the formation of a stable transition state is less for **1** than for **3**. This suggests that for O- to approach H in the case of **1** is much easier than in the case of **3**.[20]

Further, it was found that the order of the slope values (**S**) of the curves **H** versus **α/r** in systems **1–3** is **S** (**3**) > **S** (**2**) > **S** (**1**), and when the (**S**) values were plotted against the MM2 calculated E_s values, very strong correlations were obtained (see Fig. 1c and Eqs. 15–17 in Table 2).

The combined results reveal the following: (1) the activation energy in the systems studied herein is dependent on both the angle of attack of nucleophile O- on H and the distance between the nucleophile (O1) and the electrophile (H2), (2) strained reactants such as in system **1** are more reactive than the less strained reactants, and the reactivity extent is linearly correlated with the strain energy (E_s), (3) the energy needed to provide a stable transition state for a strained system is less than that needed for the unstrained systems, since the sensitivity of the angle of attack value to enthalpic energy is higher as is evident from the smaller slope value (**S**), (4) our results do not contraindicate with Menger's postulation on the critical distance of less than 3 Å (diameter of water) to reach rate accelerations as a result of desolvation of water. Further, we believe that the desolvation is a form of strain, and our strain theory in this sense coincides with spatiotemporal effects.

In conclusion, we have expanded on the equation derived by Menger that relates rate and distance to a new equation that relates both angle of attack and distance. This novel equation combines the hypotheses of both Menger[9] and Koshland[7] and shows that neither distance alone nor angle of attack alone is the dominant factor in rates enhancements in intra-molecular reactions. This is in contrast to that suggested by Houk and co-workers that excluded distance and angle of attack in determining the rates of intramolecular lactonization of hydroxy-acids. However, we agree with Houk that the strain energy is a factor in rate accelerations in some intramolecular reactions but this factor (strain) is actually a function of distance and angle of attack.[18]

Further study is underway to explore the nature of the driving force (proximity vs strain effects) behind rate acceleration in Bruice's system, which until now is believed to be as a result of proximity orientation and not due to steric (strain) effects.

Acknowledgments

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