Tetrahedron Letters 50 (2009) 452–456

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reevaluation of Bruice's proximity orientation

Rafik Karaman *

Al-Quds University, PO Box 20002, Jerusalem, Occupied Palestinian Territories

ARTICLE INFO

Article history:
Received 27 August 2008
Revised 5 November 2008
Accepted 11 November 2008
Available online 17 November 2008

ABSTRACT

Ab initio molecular orbital calculations at HF/6-31G, HF/6-31G (d,p) and DFT at B3LYP/6-31G (d,p) levels and molecular mechanics calculations of thermodynamic and kinetic parameters for Bruice's systems **1–6** indicate that the remarkable acceleration in the cyclization of di-carboxylic semi-esters **1–6** is solely the result of a strain effect and not proximity orientation stemming from the 'reactive rotamer effect'.

The mechanism of enzyme catalysis is similar in principle to other types of organic chemical catalysis. Enzymes accomplish enormous rate accelerations using amino acid side chains and cofactors to stabilize intermediates and reduce the energy required to reach the highest energy transition state of the reaction. It is accepted that rate accelerations, manifested by enzymes, are brought about via binding of the substrate within the confines of the enzyme active site. Mechanisms that are thought to contribute to the rate acceleration observed with enzymes are (a) covalently by bond strain which is the principle effect of induced fit binding, where the affinity of the enzyme to the transition state is greater than that to the substrate itself, (b) catalysis involving proton donors or acceptors which activates nucleophilic and electrophilic groups, or stabilizes leaving groups, (c) electrostatic catalysis, (d) covalent catalysis which involves the substrate forming a transient covalent bond with residues in the active site, (e) quantum tunneling which is known as the 'through the barrier' mechanism, and (f) catalysis by proximity and orientation in which the rate of the reaction is increased as enzyme–substrate interactions align reactive chemical moieties and hold them in close proximity.[1] Jencks and Page have offered a possible explanation for such acceleration based on entropic driving forces that are caused from freezing out motions and dampening of vibrational frequencies in the transition state.[2] Bruice[3] and Menger[4] have suggested that the unique acceleration in rates found in such systems is driven mainly by enthalpic effects as a result of the proximity of the nucleophile to the electrophile in the ground state molecules. Examples of chemical systems based on rate acceleration as a consequence of proximity effects include (1) the 'orbital steering' theory proposed by Koshland,[5] (2) the *gem*-tri-methyl lock (stereopopulation control) suggested by Cohen,[6] (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,[4] and (4) the 'reactive rotamer effect hypothesis' proposed by Bruice and Pandit, which explains the discrepancy between cyclization rates of different di-carboxylic semi-esters.[3]

We have been engaged in studying different intramolecular reactions to explore the driving force(s) behind their remarkable acceleration rates.[7a,c] Using ab initio studies at different levels, molecular mechanics and semi-empirical molecular orbital calculation methods, we studied the thermodynamic and kinetic behavior of the tri-methyl lock system, the cyclization reactions of ω-bromoalkanecarboxylate anions, and the proton transfer reaction in Menger's system. The results from these studies revealed the following conclusions: (1) rate acceleration in intramolecular reactions can be driven by proximity orientation that is not related to strain effects of a starting material and/or a corresponding transition state. For example, our study on acid lactonization of hydroxy-acids revealed that the enhancement in rates of the lactonization of Cohen's tri-methyl lock system stems from the close proximity of the electrophile to the nucleophile. Further, it shows that the rate of the lactonization reaction is solely dependent on the ratio between the angle of attack of the nucleophile and the distance between the two reacting centers. This finding is in accordance with Menger's 'spatiotemporal hypothesis' that relates distance between the nucleophile and the electrophile to the rate of the reaction.[7a–d] (2) Significant rate accelerations in intramolecular reactions are due to both entropic and enthalpic effects and not only due to enthalpic effects as was proposed by Bruice. (3) The nature of the reaction (intermolecular or intramolecular) is largely dependent on the distance between the two reacting centers.[7b] For example, our ab initio calculations on Menger's system show that when the distance between the two reacting centers is 2.4 Å, the reaction is intramolecular, whereas when the distance is 3 Å, the reaction prefers the intermolecular process. Further, our study shows that the proximity between the nucleophile and the electrophile is largely dependent on the strain energy of the system. For a strained system, the distance between the two reacting centers is shorter than that in unstrained systems.[7]

* Tel.: +972 2 548132234; fax: +972 2 2790413.
E-mail address: dr_karaman@yahoo.com

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.041

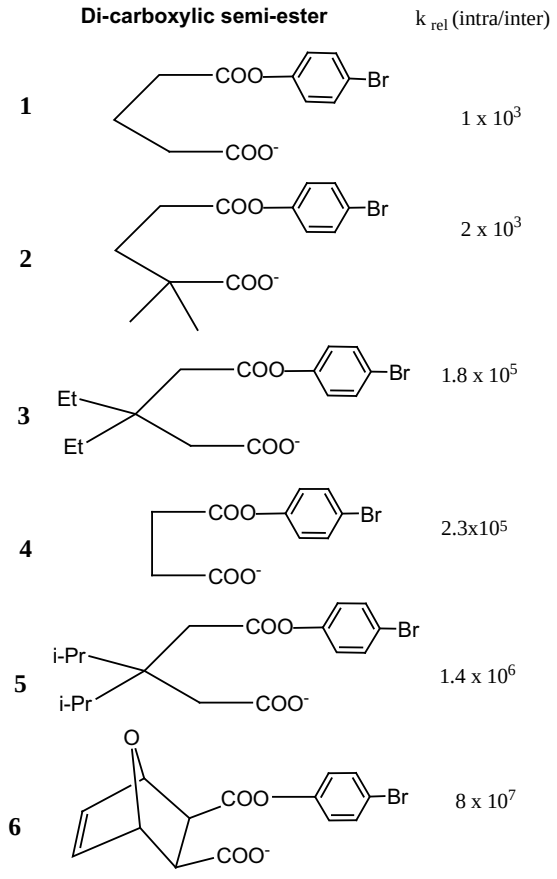
Menger's pioneering studies on the acid lactonization of hydroxy-acids led him to conclude the following rules for proximity orientation: (i) the reactive centers, A and B, must be within a critical distance and (ii) if the distance between A and B is larger than the critical distance, then the proximity effect is not feasible.[4] On the other hand, Bruice and Pandit have provided alternative rules for rate acceleration due to proximity orientation. Using the observation that alkyl substitution on succinic acid influences rotamer distributions (the ratio between the reactive *gauche* and the unreactive *anti*-conformations), they proposed that *gem*-dialkyl substitution increased the probability of the resultant rotamer adopting the more reactive conformation. Thus, for cyclization to occur, the two reacting termini must be in the *gauche* conformation. In the unsubstituted molecule, the reactive termini are almost completely in the *anti*-conformation in order to minimize steric interactions.[3]

Continuing our studies on the origin of the driving force behind the high acceleration in the rates of intramolecular reactions mimicking enzyme catalysis, using Allinger's molecular mechanics and ab initio DFT at the B3LYP/6-31G (d,p) level and HF at 6-31G and 6-31G (d,p) levels, we conducted intensive theoretical work on Bruice's system (Scheme 1). The purpose of this study was to test if the acceleration in the rates of cyclization of di-carboxylic semi-esters is due to unstrained proximity orientation (Bruice's reactive rotamer effect) or to steric effects.

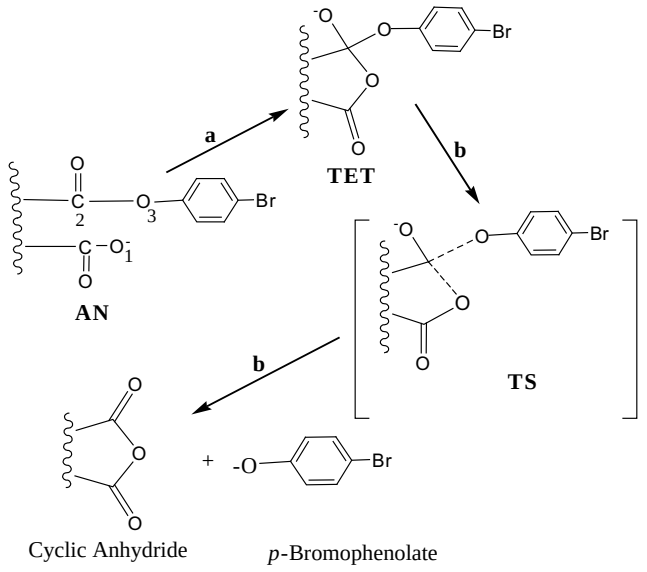
The DFT and HF ab initio calculations were carried out using the quantum chemical package GAUSSIAN-98.[8] The MM2 molecular mechanics strain energy calculations were performed using Allinger's MM2 program installed in Chem 3D Ultra 8.0.[9] The starting geometries of all the molecules in this study were obtained using the ARGUS LAB program.[10] The ab initio 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 starting geometries. 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).[12] 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).

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.[13] The transition state structures were verified using the MOLDEN program.[14] The 'reaction coordinate method'[15] was used to calculate the activation energy for the cyclization processes of di-carboxylic semi-esters **1–6**. 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 for the cyclization reactions were calculated from the difference in the energies of the global optimum structures for the reactants **1–6** and the derived transition states of the cyclization reactions. The transition state structures for the cyclization reactions of **1**–**4** and **6** were obtained from the increase in the distance between the phenolic oxygen (O3) and the carbonyl carbon (C2), in increments of 0.1 Å, whereas the transition state of **5** was achieved from the approach of the anionic oxygen (O1) to the carboxylic carbon (C2). The ab initio DFT at B3LYP/6-31G (d,p) and HF at 6-31G levels of the reactions of **1**–**4** and **6** were calculated with and without the inclusion of solvent (water, dielectric constant = 78.39). The keywords SCF = Tight and SCRF = (Dipole) were used in the input files, when calculating energies with the incorporation of a solvent.

Bruice[3] and Menger[4] ascribed the phenomenon of rate accelerations in some intramolecular reactions to the importance of ground state conformations, namely to the proximity of the nucleophile to the electrophile of the ground state molecules. Menger's group developed an equation relating activation energy to distance. Based on this equation, Menger concluded that enormous rate accelerations in enzymatic reactions are achieved by imposing



Scheme 1. Di-carboxylic semi-esters **1–6** and their k_{rel} values (k (intra/inter)).



Scheme 2. Possible route for the cyclization of di-carboxylic semi-esters. Route a is approach, and route b is collapse.

short distances between the reactive sites of the enzyme and substrate. On the other hand, Bruice attributed enzyme catalysis to favorable 'near attack conformations'. According to Bruice's explanation, systems that have a high quota of near attack conformations 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 moieties.

In contrast to the proximity proposal, others believe that high rate enhancement in intramolecular reactions is a result of steric effects (relief in strain energy of the reactants).[16] The term strain usually describes steric effects that might cause acceleration or 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.[17]

To test whether the discrepancy in the cyclization reaction rates of di-carboxylic semi-esters **1–6** is due to proximity orientation (difference in the distance between the nucleophile and the electrophile) or to strain effects, we calculated, using ab initio molecular orbital methods at B3LYP/6-31G (d,p), HF/6-31G and HF/6-31G (d,p) levels, the transition state structures as well as the activation energy values for the cyclization reactions of **1–6**. Activation energy calculations were performed for the two possible routes (Scheme 2). The first route is the approach of the anionic

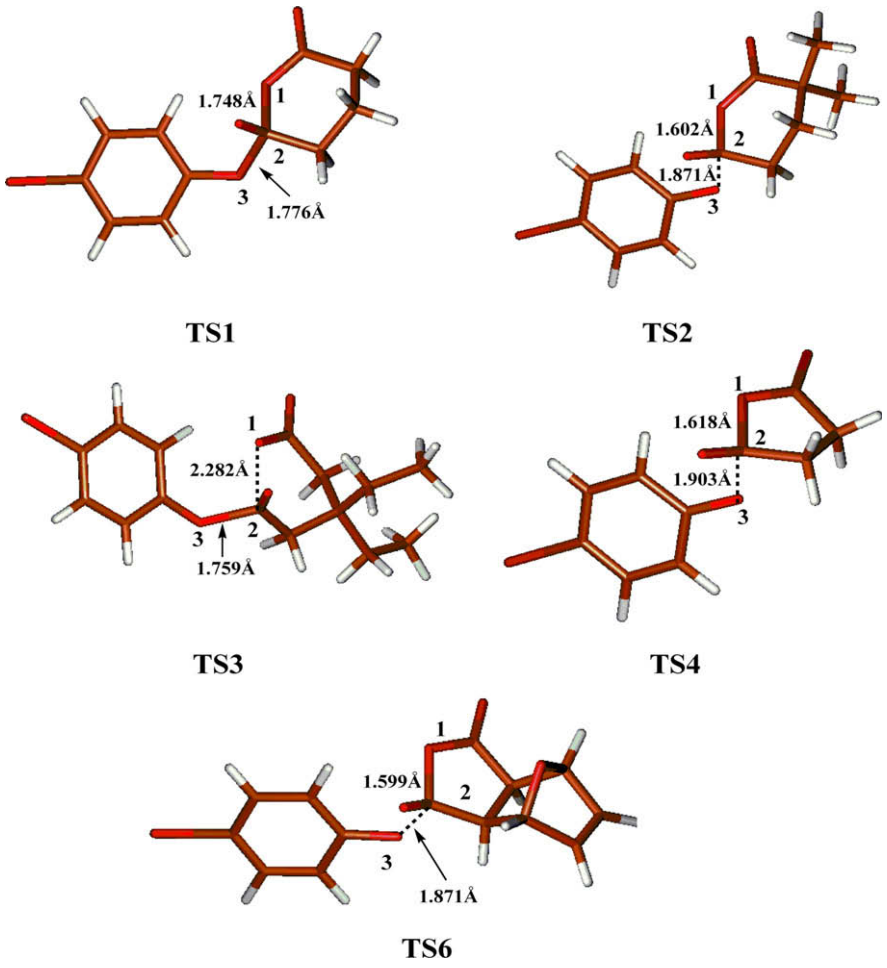


Figure 1. The B3LYP/6-31G (d,p) calculated transition state structures **TS1**–**TS4** and **TS6** for the cyclization reactions of **1**–**4** and **6,** respectively.

Table 1
Experimental, and MM2 and ab initio-calculated thermodynamic and kinetic properties for the cyclization of di-carboxylic semi-esters **1**–**6**

System	$\Delta\Delta Hs^{\ddagger}_{B3LYP}$	$\Delta\Delta H^{\ddagger}_{B3LYP}$	$\Delta\Delta Hs^{\ddagger}_{HF/6\text{-}31G}$	$\Delta\Delta H^{\ddagger}_{HF/6\text{-}31G}$	$\Delta\Delta Hs^{\ddagger}_{HF/6\text{-}31G(d,p)}$	$\Delta\Delta H^{\ddagger}_{HF/6\text{-}31G(d,p)}$	$\Delta\Delta Gs^{\ddagger}_{B3LYP}$	$T\Delta S^{\ddagger}_{B3LYP}$	ΔE_s TS − AN	ΔE_s TET − AN	$\log k_{rel}$
1	11.82	8.88	28.18	23.22	21.52	16.69	12.73	−0.91	12.24	7.08	3.00
2	10.35	9.66	25.89	24.57	20.11	17.54	10.56	−0.21	10.13	4.67	3.56
3	4.56	4.12	14.73	14.60	12.78	11.15	5.13	−0.57	3.12	1.06	5.26
4	6.82	4.13	NC	13.71	13.96	9.85	5.42	1.40	NC	NC	5.36
5	NC	NC	NC	5.16	NC	NC	NC	NC	2.83	0.18	6.11
6	3.51	2.95	4.86	4.30	4.10	2.91	2.63	0.88	−0.76	−1.00	7.90

$\Delta\Delta Gs^{\ddagger}$ is the calculated free activation energy for the cyclization of **1–6** in the presence of solvent. $\Delta\Delta Hs^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ are the calculated enthalpic energies for the cyclization of **1–6** with and without solvent, respectively. k_{rel} is the experimental relative rates of intramolecular cyclization (k_{intra}) and the intermolecular cyclization of the counterparts (k_{inter}). ΔE_s (TS − AN) is the MM2-calculated difference in the strain energies of the transition state (TS) and the di-carboxylic semi-ester (AN) in the cyclization of **1–6**. ΔE_s (TET − AN) is the MM2-calculated difference in the strain energies of the tetrahedral intermediate (TET) and the di-carboxylic semi-ester (AN) in the cyclization of **1–6**. B3LYP refers to DFT at B3LYP/6-31G (d,p), and HF/6-31G and HF/6-31G (d,p) refer to RHF ab initio methods. NC refers to not calculated.

carboxylate oxygen of the reactant (O1) toward the carboxylic carbon (C2) to furnish a tetrahedral intermediate (route a in Scheme 2), and the second route is collapse of the tetrahedral intermediate to yield a cyclic anhydride and *p*-bromophenolate anion (route b, Scheme 2).

The results of the 'reaction coordinate' for both the routes revealed the following: (1) no transition state structures were found for the approach processes (route a) with **1–6** except for **5,** which indicate the presence of a transition state when the distance between O1 and C2 reached 1.7 Å. This transition state structure was verified from its one and only negative frequency and highest enthalpic energy value. (2) The 'reaction coordinate' and the frequency calculations for the collapse route (route b) for each of the intermediates in systems **1–4** and **6** indicate the presence of a transition state. The B3LYP/6-31G (d,p) calculated conformations of the transition state structures are shown in Figure 1. Further, monitoring of the collapse processes indicates that upon increasing the distance between C2 and O3 (departure of the leaving group), opening of the cyclic ring is observed in the collapse processes of **1–4**; however, the energy profile for **6** indicates that the cyclic ring remains intact upon departure of the leaving group.

Table 2
Correlation equations for B3LYP/6-31G (d,p), HF/6-31G (d,p), HF/6-31G, and MM2-calculated properties, for the cyclization of di-carboxylic semi-esters **1–6**, with the experimental $\log k_{rel}$ values

	Equation	*R* value
1	ΔE_s (TS − AN) = −1.9664 $\log k_{rel}$ + 13.949	0.97
2	ΔE_s (TET − AN) = −1.6158 $\log k_{rel}$ + 10.744	0.95
3	$\Delta\Delta Hs^{\ddagger}_{B3LYP(d,p)}$ = −1.7234 $\log k_{rel}$ + 16.054	0.92
4	$\Delta\Delta H^{\ddagger}_{B3LYP(d,p)}$ = −1.4324 $\log k_{rel}$ + 13.131	0.89
5	$\Delta\Delta Hs^{\ddagger}_{HF/6-31G}$ = −4.8541 $\log k_{rel}$ + 42.335	0.99
6	$\Delta\Delta H^{\ddagger}_{HF/6-31G}$ = −4.5831 $\log k_{rel}$ + 38.082	0.95
7	$\Delta\Delta Hs^{\ddagger}_{HF/6-31G(d,p)}$ = −3.8035 $\log k_{rel}$ + 32.565	0.99
8	$\Delta\Delta H^{\ddagger}_{HF/6-31G(d,p)}$ = −3.0435 $\log k_{rel}$ + 26.890	0.99
9	$\Delta\Delta Gs^{\ddagger}_{B3LYP(d,p)}$ = −2.0657 $\log k_{rel}$ + 17.653	0.95
10	$\Delta\Delta G^{\ddagger}_{B3LYP(d,p)}$ = −1.7747 $\log k_{rel}$ + 14.729	0.90
11	$\Delta\Delta Gs^{\ddagger}_{B3LYP(d,p)}$ = −1.0467 ΔE_s (TS − AN) + 3.262	0.99
12	$\Delta\Delta G^{\ddagger}_{B3LYP(d,p)}$ = −0.9101 ΔE_s (TS − AN) + 3.647	0.98

$\Delta\Delta Gs^{\ddagger}$ and $\Delta\Delta G^{\ddagger}$ are the calculated free activation energies for the cyclization processes of **1–6** with and without solvent, respectively. $\Delta\Delta Hs^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ are the calculated enthalpic energies for the cyclization processes of **1–6** with and without solvent, respectively. k_{rel} is the experimental relative rate of the intramolecular cyclization (k_{intra}) and the intermolecular reaction of the counterparts (k_{inter}). ΔE_s (TS − AN) is the MM2-calculated difference in the strain energies of the transition state (TS) and the di-carboxylic semi-ester (AN) in the cyclization of **1–6**. ΔE_s (TET − AN) is the MM2-calculated difference in the strain energies of the tetrahedral intermediate (TET) and the di-carboxylic semi-ester (AN) in the cyclization of **1–6**. B3LYP (d,p), HF/6-31G and HF/6-31G (d,p) refer to DFT and RHF ab initio methods.

Using Allinger's MM2 method,[9] we calculated the strain energy values (E_s) for the transition states (TS), tetrahedral intermediates (TET) and reactants (AN) in the cyclization reactions of **1–6.** The differences in the strain energy values ΔE_s (TS − AN) and ΔE_s (TET − AN) (see Table 1) were examined for correlations with the experimental ratio $\log k$ (intramolecular)/$\log k$ (intermolecular)[3] ($\log k_{rel}$), and the results obtained are summarized in Eqs. 1 and 2 (Table 2) and are illustrated in Figure 2a.

Figure 2a and Eqs. 1 and 2 reveal that there is a good correlation between the calculated MM2 strain energy values (ΔE_s) and the experimentally calculated k_{rel} values. For systems that have small differences in strain energy values between their transition states and intermediates (such as in the case of **6**), the corresponding activation energies are low and vice versa. Moreover, attempts to correlate the distance between O1–C2 with $\log k_{rel}$ failed to give any significant relationship between the two parameters. For example, the calculated O1–C2 distances for the global minimum structures for systems **1–6** are similar (~2.4 Å – ~2.5 Å) depending on the calculation method used, whereas the calculated $\Delta\Delta H^{\ddagger}$ values differ significantly (see Table 1). These results suggest that the

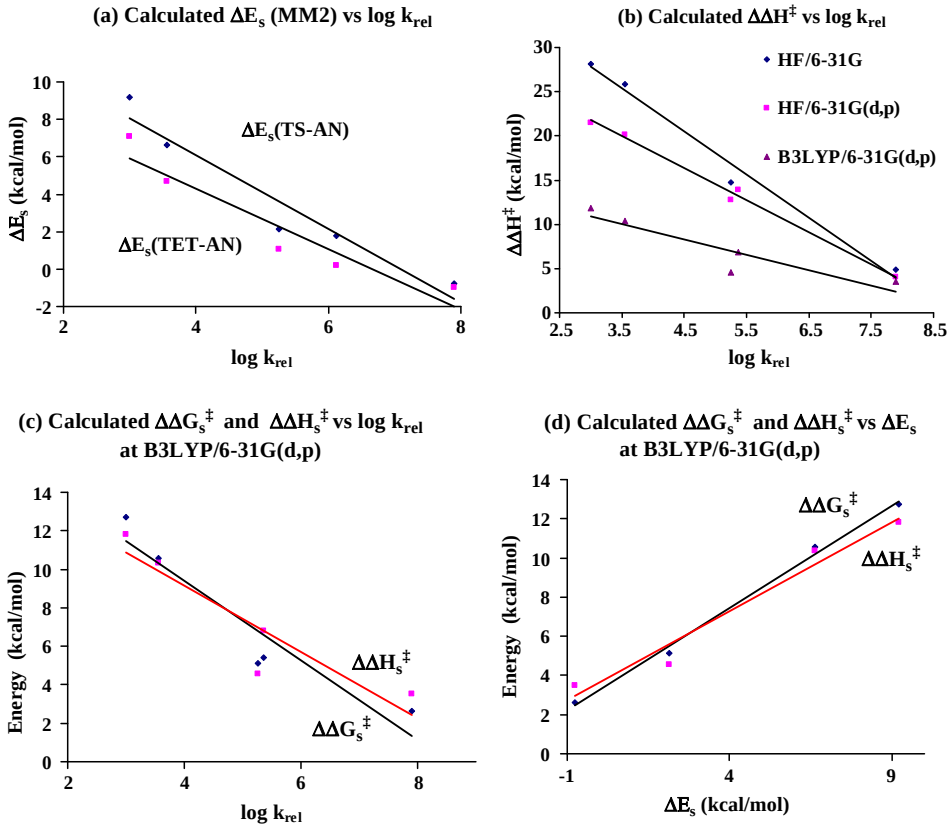


Figure 2. Plots of the ab initio-calculated properties of di-carboxylic semi-esters **1–6** with their experimental data.

driving force for acceleration in the cyclization process is driven by strain effects in contrast to what was the previously suggested near attack proximity orientation.[3]

In order to further support this conclusion, the B3LYP/6-31G (d,p), HF/6-31G and HF/6-31G (d,p) calculated activation energy values with and without the inclusion of water as a solvent $\Delta\Delta Hs^{\ddagger}_{B3LYP(d,p)}$, $\Delta\Delta H^{\ddagger}_{B3LYP(d,p)}$, $\Delta\Delta Hs^{\ddagger}_{HF/6\text{-}31G}$, $\Delta\Delta H^{\ddagger}_{HF/6\text{-}31G}$, $(\Delta\Delta Hs^{\ddagger}_{HF/6\text{-}31G(d,p)}$, $(\Delta\Delta H^{\ddagger}_{6\text{-}31G(d,p)}$ respectively, see Table 1) were examined for correlations with ΔE_s, and the results are summarized in Eqs. 3–8 (Table 2). Eqs. 3, 5, and 7 are represented graphically in Figure 2b. Again the correlation results of the enthalpic activation energy values ($\Delta\Delta H^{\ddagger}$) calculated by the three different methods with the calculated MM2 strain energy difference (ΔE_s) reveal the same conclusions, indicating that the driving force for acceleration is due to strain and not proximity orientation.

In the same manner, the B3LYP/6-31G (d,p) calculated free activation energy values with and without solvent (water) ($\Delta\Delta Gs^{\ddagger}_{B3LYP(d,p)}$ and $\Delta\Delta G^{\ddagger}_{B3LYP(d,p)}$) were examined for correlations with both $\log k_{rel}$ and ΔE_s, and the results indicate excellent correlations between them (Eqs. 9–12 and Figure 2c and d, respectively). Comparisons of the calculated difference in the free activation energy values ($\Delta\Delta Gs^{\ddagger}$) with that from the experimental k_{rel} values indicate that the best among the three calculation methods to predict cyclization rates of di-carboxylic semi-esters is B3LYP/6-31G (d,p). For example, the B3LYP/6-31G (d,p) calculated difference value between the free activation energy in the cyclization of **1** and **6** ($\Delta\Delta Gs^{\ddagger}_{B3LYP(d,p)}$) is 11 kcal/mol, which is in good agreement with the experimentally determined value (10 kcal/mol).

The combined results reveal the following: (1) The activation energy in the studied systems is dependent on the difference in the strain energies of the transition states and the reactants, and there is no relationship between the cyclization rate and the distance between the nucleophile (O1) and the electrophile (C2). (2) The observation of opening of the cyclic ring during the collapse process (the reaction rate limiting step) supports the notion that the difference in the strain energy values of the reactant and the transition states (resembling the tetrahedral intermediates) plays a crucial role in the discrepancy in the rates of cyclization of the di-carboxylic semi-esters studied. (3) Strained reactants such as **6** are more reactive than the less strained reactants, and the reactivity extent is linearly correlated with the strain energy difference between the transition state and the reactant (ΔE_s). (4) The energy needed to provide a stable transition state for a strained system is less than that for the unstrained system, since the conformational change from the reactant to the transition state in the former is smaller.

In conclusion, we have investigated Bruice's theory of proximity orientation, and found that in contrast to that suggested by Bruice and co-workers, the distance between the nucleophile and the electrophile in the systems studied herein is not a factor in determining the rate of intramolecular cyclization. Further study is underway to explore the nature of the driving force (proximity vs strain effects) behind the rate acceleration in other enzyme models.

Acknowledgments

We thank the Karaman Co. and the German–Palestinian–Israeli fund agency for the support of our hardware computational facilities. We would also like to give special thanks to Dr. Omar Deeb and Sherin Alfalah for computational software support and for technical assistance. Special gratitude is given to Nardene Karaman for general help in preparing this Letter.

References and notes

1. (a) Fersht, A. *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding*; W. H. Freeman and Company: New York, 1999; (b) Libman, J. F.; Greenberg, A. *Mechanistic Principles of Enzyme Activity*; VCH: New York, 1988; (c) Warshel, A.; Sharma, P. K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M. H. M. *Chem. Rev.* **2006**, *106*, 3210; (d) Warshel, A.; Levitt, M. *J. Mol. Biol.* **1976**, *103*, 227; (e) Warshel, A.; Naray-Szabo, G.; Sussman, F.; Hwang, J.-K. *Biochemistry* **1989**, *28*, 3629; (f) Marcus, R. A. *J. Chem. Phys.* **1965**, *43*, 679; (g) Warshel, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5250; (h) Ball, P. *Nature* **2004**, *431*, 396; (i) Olsson, M. H. M.; Parson, W. W.; Warshel, A. *Chem. Rev.* **2006**, *105*, 1737.
2. (a) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678; (b) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295; (c) Page, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 449; (d) Page, M. I.; Jencks, W. P. *Gazz. Chim. Ital.* **1987**, *117*, 455.
3. (a) Bruice, T. C.; Lightstone, F. L. *Acc. Chem. Res.* **1999**, *32*, 127; (b) Lightstone, F. L.; Bruice, T. C. *J. Am. Chem. Soc.* **1997**, *119*, 9103; (c) Lightstone, F. L.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595; (d) Lightstone, F. L.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789; (e) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1968**, *90*, 3803; (f) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1965**, *87*, 4846; (g) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858; (h) Bruice, T. C.; Pandit, U. K. *Proc. Natl. Acad. Sci. U.S.A.* **1960**, *46*, 402.
4. (a) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128; (b) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996; (c) Menger, F. M. *Tetrahedron* **1983**, *39*, 1013; (d) Menger, F. M.; Grossman, J.; Liotta, D. C. *J. Org. Chem.* **1983**, *48*, 905; (e) Menger, F. M.; Galloway, A. L.; Musaev, D. G. *Chem. Commun.* **2003**, 2370; (f) Menger, F. M. *Pure Appl. Chem.* **2005**, *77*, 1873 and references cited therein.
5. (a) Dafforn, A.; Koshland, D. E., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 2463; (b) Dafforn, A.; Koshland, D. E., Jr. *Bioorg. Chem.* **1971**, *1*, 129; (c) Dafforn, A.; Koshland, D. E., Jr. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 779; (d) Storm, D. R., ; Koshland, D. E., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *66*, 445; (e) Storm, D. R.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5805; (f) Storm, D. R.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5815.
6. (a) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1970**, *92*, 4377; (b) Milstein, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1143; (c) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158; (d) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166; (e) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9175; (f) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, *95*, 8308; (g) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, *95*, 8313; (h) King, M. M.; Cohen, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 2752; (i) Hillery, P. S.; Cohen, L. A. *J. Org. Chem.* **1983**, *48*, 3465.
7. (a) Karaman, R. In *Presented in Part at the 1st International Conference on Drug Design and Discovery in Dubai*, UAE, February 4–7, 2008; (b) Karaman, R. *Tetrahedron Lett.* **2008**, *49*, 5998; (c) Karaman, R. *Bioorg. Chem.* **2008**. doi 10.1016/j.bioorg.2008.08.006; (d) Karaman, R. *J. Phys. Org. Chem.*, submitted for publication.
8. http://www.gaussian.com.
9. Burker, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.
10. (a) Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024; (b) Casewit, C. J.; Colwell, K. S.; Rappé, A. K. *J. Am. Chem. Soc.* **1992**, *114*, 10035; (c) Casewit, C. J.; Colwell, K. S.; Rappé, A. K. *J. Am. Chem. Soc.* **1992**, *114*, 10046; (d) Rappé, A. K.; Goddard, W. A. *J. Phys. Chem.* **1991**, *95*, 3358; (e) Rappé, A. K.; Colwell, K. S.; Casewit, C. J. *Inorg. Chem.* **1993**, *32*, 3438.
11. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
12. Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Thoel, W.; Yamaguchi, Y. *J. Mol. Struct.* **1978**, *43*, 135.
13. Murrell, J. N.; Laidler, K. J. *Trans. Faraday Soc.* **1968**, *64*, 371.
14. http://www.cmbi.kun.nl/~schaft/molden/molden.html.
15. (a) Goldblum, A.; Loew, G. H. *J. Am. Chem. Soc* **1985**, *107*, 4265; (b) Muller, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1; (c) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4290.
16. (a) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698; (b) Houk, K. N.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107.
17. (a) Newman, M. S. *Steric Effects in Organic Chemistry*; Wiley: New York, 1956; (b) Streitweiser, A., Jr.; Heathcock, C. H. *Introduction to Organic Chemistry*, 3rd ed.; MacMillan: New York, 1985.