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Ground State Conformations and Entropic and Enthalpic Factors in the Efficiency of Intramolecular and Enzymatic Reactions. 1. Cyclic Anhydride Formation by Substituted Glutarates, Succinate, and 3,6-Endoxo-Δ^4-tetrahydrophthalate Monophenyl Esters

Felice C. Lightstone[1] and Thomas C. Bruice*

Contribution from the Department of Chemistry, University of California,
Santa Barbara, California 93106

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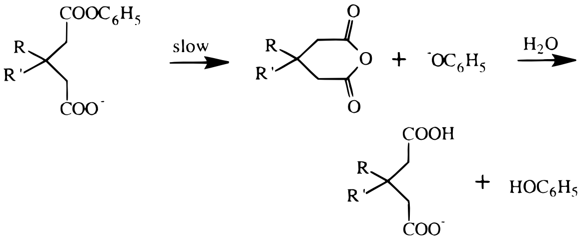
Abstract: Intramolecular and enzymatic reactions require conformations in which the orbitals of reactants are properly aligned and van der Waals surfaces are in a near-attack conformation (NAC). Much of the changes in steric and electrostatic energies that take place in moving from the favored ground state conformation (FGSC) to the transition state are accounted for when the NAC has been assumed. Upon assessing the steric, electrostatic, and zero point energies, one is in position to calculate the probability of NAC formation. Using a series of monoesters of dicarboxylic acids, we have (i) created, via stochastic search, 10 000−40 000 minimized conformations per ester; (ii) chosen only the unique local minima conformations for each ester; (iii) determined the energies of each minimum conformation using MM3(92); (iv) identified the geometry of the NACs where the van der Waals overlap has not begun for the approach of carboxyl anion and ester carbonyl; and (v) calculated the mole fraction (probability, P) of each ester present as NACs. The values of log $k_{\rm rel}$ for the intramolecular reactions of each ester are a linear function of log P with slope = 1. Using the most energetically stable ground state conformation and the lowest energy NAC for each ester, values of ΔH° directly correlate to $\Delta G^\ddagger$, while ΔS° has no correlation with $\Delta G^\ddagger$. Like results were obtained when the phase space of the system was taken into account. Thus, the rate constants of these intramolecular reactions find quantitative explanations in the distribution of ground state conformations, such that the free energy of activation is determined by ΔH°. In a trajectory from most stable ground state to the transition state, these features will become evident in the lowering of the transition state energy. The conformations of the monoesters of the dicarboxylic acids are considered in detail.

Introduction

Organic chemists have been familiar with the concept of neighboring group participation for over 50 years.[2] As might have been anticipated, the discovery in 1956 of nucleophilic catalysis of ester hydrolysis[3,4] quickly led to investigations of systems involving "intramolecular catalysis".[5−7] It was argued that, just as the proximity of electrophile and nucleophile in an intramolecular reaction increases the rate of reaction, the juxtaposing of reactants in a productive enzyme substrate complex is responsible for a sizable portion of the rate enhancements characteristic of enzyme catalysis. Bruice referred to this as the *proximity* or *propinquity* effect. (Proximity, propinquity, adjacency, and vicinity are synonyms describing the *observed* structural requisite for rapid intramolecular reactions.) Pandit and Bruice[8] determined the efficiencies of intramolecular carboxyl group nucleophilic catalysis of the hydrolysis of the esters in Table 1 (eq 1). These structures



(1)

where chosen on the basis of differences in chain length and the presence of *gem* substituents. The experimental results of Table 1 are commonly employed in textbook discussions of proximity and entropy effects in intramolecular and enzymatic reactions.[8−16] A new method for examining these accelerated rates is the subject of this report.

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[1] Contribution in partial satisfaction of the Ph.D. degree in chemistry.

[2] Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc*. **1942**, *64*, 2780.

[3] (a) Bruice, T. C.; Schmir, G. L. *Arch. Biochem. Biophys*. **1956**, *63*, 484. (b) Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc*. **1957**, *79*, 1663.

[4] Bender, M. L.; Turnquest, B. W. *J. Am. Chem. Soc*. **1957**, *79*, 1656.

[5] (a) Schmir, G. L.; Bruice, T. C. *J. Am. Chem. Soc*. **1958**, *80*, 1173. (b) Bruice, T. C.; Sturtevant, J. M. *J. Am. Chem. Soc*. **1959**, *81*, 2860.

[6] Bender, M. L.; Chow, Y. L.; Choulpek, F. *J. Am. Chem. Soc*. **1958**, *80*, 5380.

[7] Zimmering, P. E.; Westhead, E. W.; and Morawetz, H. *Biochim. Biophys Acta* **1957**, *25*, 376.

[8] (a) Bruice, T. C.; Pandit, U. K. *Proc. Natl. Acad. Sci. U.S.A.* **1960**, *46*, 402. (b) Bruice, T. C. *Ann. Rev. Biochem*. **1976**, *45*, 331.

[9] Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; Benjamin: New York, 1966; Chapter I.

[10] Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Chapter I.

[11] Lehninger, A. L. *Biochemistry*; Worth: New York, 1970; Chapter 9.

[12] Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman and Co.: San Francisco, CA, 1979; Chapter 2.

[13] Rawin, J. D. *Biochemistry*; Harper and Row: Philadelphia, PA, 1984; Chapter 6.

[14] Czarnik, A. W. Intramolecularity: Proximity and Strain. In *Mechanistic Principles of Enzyme Activity*; Lieberman, J. F., Greenberg, A., Eds.; VCH Publishers, Inc.: New York, 1988; p 80.

[15] Voet, D.; Voet, J. G. *Biochemistry*; John Wiley: New York, 1990; Chapter 14.

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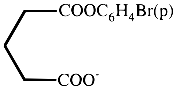
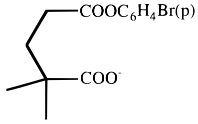
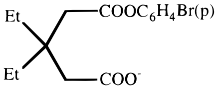
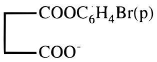
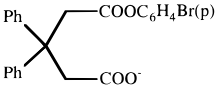
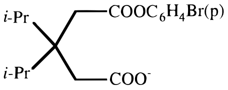
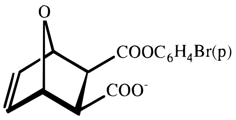
Table 1. List of the Monophenyl Esters Used and Their Relative Rate Constants

		k_{rel}
	$CH_3COO^- + CH_3COOC_6H_5Br(p)$	1.0
I		1 x10^3M
II		~3.6 x 10^3M
III		1.8 x 10^5M
IV		2.3 x 10^5M
V		2.7 x 10^5M
VI		1.3 x 10^6M
VII		~8 x 10^7 M

From investigations between 1956 and 1960 (Table 1), Bruice and Pandit[8,17−19] concluded that (i) "The results point to the tremendous enhancement of rate that an enzyme could achieve (10^8) by fixing the reacting species in a steric conformation closely resembling that of the transition state for the reaction"; (ii) "—in the enzymatic and intramolecular reactions considerable loss of translational entropy must accompany the bringing together of reactants—if the bond undergoing scission is held in the proper orientation to the catalytic group(s), then an additional advantage is gained over the bimolecular reaction"; and (iii) the increase of the rate constant by ∼230-fold on removing a freely rotating single bond in each step, going from glutarate to succinate to 3,6-endoxo-Δ^4-tetrahydrophalate, must be due to the ground state of each ester existing as a collection of rotamers with the most stable rotamer(s) possessing an extended conformation (eq 4).[20] At this early date, the proximity effect was shown to enhance the effective molarities, resulting in rate enhancements of 10^8 M. It also showed that the relative rates of intramolecular reactions (as in Table 1) were dependent upon the distribution of rotamers in the ground states. At that time, these conclusions were not embraced by all; though recently, investigations support the "reactive rotamer effect".[23]

In the following 10-year period, Koshland[24] and Jencks[25] asserted that the maximum rate enhancement that could be achieved by approximation of reactants was ∼55 M. Their arguments, in essence, were based on the assumption that, if reactants A and B are the size of water molecules, and substrate A is dissolved in neat B, then the observed pseudo-first-order rate constant (k_{obsd}) could only be 55.5 times greater than k_{obsd} when B is at 1.0 M. Yet, the intramolecular reactions shown in Table 1 are characterized by effective molarities (EM) of 10^3-10^8 M. Still maintaining the view that proximity *per se* can only be maximally responsible for an EM of ∼55 M, Koshland and Jencks introduced divergent concepts to rationalize these large EM values.

Koshland[26] sought an explanation for rate enhancements exceeding 55 M in the angular dependence for nucleophilic attack (the theory of "orbital steering"). It was proposed that changes in angular approach of less than a few degrees for a nucleophilic displacement have a kinetic significance "far greater than previously estimated." This severe dependence of rate constants on the angle of approach has no basis according to known force constants.[27]

Jencks proposed[10] that the close proximity of reactants results in the squeezing out of solvent from in-between reacting atoms. Thus, the EM of ∼10^8 M for the 3,6-endoxo-Δ^4-tetrahydrophthalate monoester in Table 1 was attributed to steric desolvation of carboxylate and ester groups. However, we established (1970) that the relative rate constants of Table 1 are not appreciably altered when the reactions are transferred from solvent H_2O to DMSO.[28]

In 1971, Jencks reversed his position and was "forced to the conclusion that entropic contributions to rate accelerations in intramolecular reactions must be larger than generally believed."[29] Using the "standard formulas for the partition function and using estimated moments of inertia",[29] Page and Jencks approximated gas phase entropy values for two nonpolar molecules undergoing pericyclic condensations and corrected for the transfer to water.[30] They concluded that the entropy lost by bringing together A and B, and for dampening low-frequency motions in the transition state, ignoring any change in ΔH, would be sufficient to provide an increase in rate of 10^8 M. It was their opinion that the distribution of ground state conformations is of little importance in the determination of the rate constants for intramolecular reactions. Page and Jencks concluded that, in discussions of the rate constants of intramolecular reactions, such terms as neighboring group participation, rotamer or conformer distribution, anchimeric assistance, proximity (or its synonym propinquity), and other terms descriptive of ground state conformations should no longer be used.[32]

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(16) Abeles, R. H.; Frey, P. A.; Jencks, W. P. *Biochemistry*; Jones and Bartlett: Boston, MA, 1992; Chapter 5.

(17) Pandit, U. K.; Bruice, T. C. *J. Am. Chem. Soc.* **1960**, *82*, 3386.

(18) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.

(19) Bruice, T. C. *Brookhaven Symp. Biol.* **1992**, No. 15, 52.

(20) For reactions whose rate constants were much less effected by the number of single bonds between the electrophile and nucleophile, we proposed (refs 21 and 22) that there was a smaller free energy difference between unproductive extended conformations and conformations where electrophile and nucleophile were juxtaposed for reaction.

(21) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1.

(22) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 418.

(23) Jung. M. E.; Gervay, J. *J. Am Chem. Soc.* **1991**, *113*, 224 and references therein.

(24) Koshland, D. E. *J. Theor. Biol.* **1962**, *2*, 75.

(25) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGaw-Hill: New York, 1969; pp 16−20.

(26) Storm, D. R.; Koshland, D. E. *Proc. Natl. Acad Sci. U.S.A.* **1970**, *65*, 445.

(27) Bruice, T. C.; Brown, A.; Harris, D. O. *Proc. Natl. Acad. Sci U.S.A.* **1971**, *68*, 658.

(28) Bruice, T. C.; Turner, A. *J. Am. Chem. Soc.* **1970**, *92*, 3422.

(29) (a) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678. (b) Page, M. I.; Jencks, W. P. *Gazz. Chim. Ital.* **1987**, *117*, 455.

(30) Such pericyclic reactions were chosen because of the belief that their rate constants are insensitive to the nature of the solvent. Breslow (ref 31) has shown, however, that solvent water catalyzes the pericyclic condensations through hydrophobic squeezing together of reactants.

(31) (a) Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

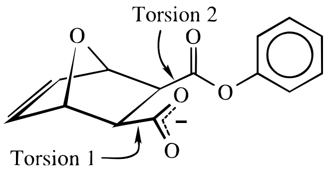
(32) Subsequently, Jencks proposed that the process of luring the substrate to surrender with rotational and translational entropy in an enzymatic embrace to provide a product of altered form be known as the Circe effect (see ref 33).

We report here the MM3(92) free energies of the conformers of the dicarboxylic acid monoesters in Table 1. The distribution of energies of ground state conformations determines the probabilities (*P*) of the formation of pretransition state conformers (near-attack conformations, NACs). This probability is equivalent to the mole fraction of conformations present as NACs. There exists a linear free energy relationship between log k_{rel} and log ***P*.** Further, we show that the internal enthalpy rather than entropy controls the formation of the productive conformer (NAC). Our results and conclusions are discussed in terms of the findings and proposals of Schowen,[34] Houk,[35] and Menger.[36]

Materials and Methods

All the calculations in this study were performed on Silicon Graphics Indigo^2, Indigo, or 4D/340GTX computers. To simplify the stochastic search and minimizations, monophenyl esters that correspond to the *p*-bromophenyl ester of Table 1 were used in all the calculations. The structures of the monophenyl esters (**I**−**VI**) were composed in Sybyl (v. 6.0.3),[37] and a stochastic search[38] through MM3(92)[39] was performed on all the structures except for the ester of 3,6-endoxo-Δ^4-tetrahydrophthalate (**VII**). Following the creation of ≥10 000 conformers and the removal of duplicate structures and structures containing imaginary frequencies, all conformations with unique local minima generated by a single stochastic search were collected in a database in Sybyl. All local minima structures were subsequently individually minimized through full-matrix minimization in MM3 where the statistical thermodynamical values ($G°$, $H°$, and $S°$) of each conformation were provided. Because of the difficulty in controlling the chiral centers in the 3,6-endoxo-Δ^4-tetrahydrophthalate compound (**VII**), a dihedral driver was used to search the potential energy surface. The dihedral angles around two bonds were incremented every 20° (Chart 1). A total of 361 structures were generated and then individually minimized in MM3, as was done with the other compounds. These conformations were then compared, and duplicate conformations (with matching rms deviations of <0.001) were deleted.

Chart 1



Once the local minima conformations were found for each compound, a program was written to calculate the probabilities of each conformer existing. The probability of formation of each local minimum conformer was calculated using a Boltzmann distribution (eq 2), where P_i is the probability of a given conformation *i*, E_i is the MM3

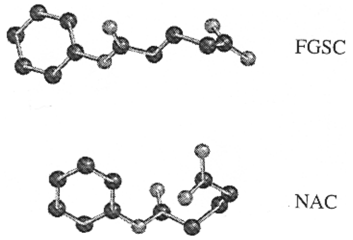
$$P_i = \frac{e^{-\beta E_i}}{\sum_j^N e^{-\beta E_j}} \tag{2}$$

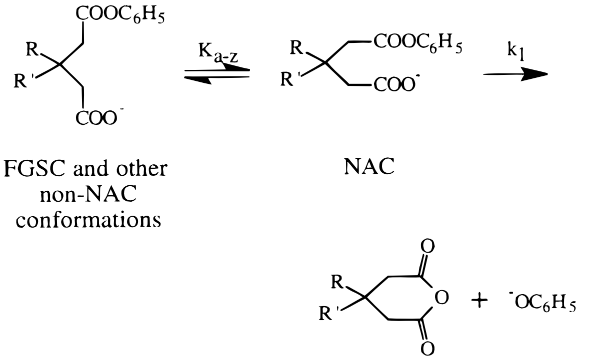
final energy of conformation *i*, *N* is the total number of conformations found, and β is $1/(kT)$, given that *k* is the Boltzmann constant and *T* is the temperature. The MM3 final energy of conformation *i* is the sum of the steric energy, electrostatic energy, and the zero point energy. Examination of eq 2 shows that the higher energy conformations will have the lowest probabilities. All minimizations and probabilities were calculated at T = 298.16 K and with a dielectric of 1.5. The conformational probabilities of selected compounds (**I**, **IV**, and **VII**) were also calculated with a continuum dielectric medium of the water dielectric constant ($\epsilon = 80$). The overall probability of occurrence of nearest attack conformations (*P*) was taken as the sum of the probabilities of all individual attacking conformations.

Results

By searching conformational space, we have created the various rotational isomers that the esters in Table 1 may assume (loc. cit.). The energies associated with each conformer have been computed using Allinger's molecular mechanics program [MM3(92)]. The rotamer of lowest MM3 final energy, for each ester, will be referred to as the favored ground state conformation (Chart 2, FGSC). In order that the carboxylate anion may attack the ester carbonyl, a preequilibrium conformation must exist in which a carboxylate oxygen is in position to enter the transition state. Rotamers which meet this set criteria for preattack are called near-attack conformations (Chart 2, NAC)—eq 3. The criteria for choice of NAC conformations was reached in the following manner. In a separate experiment, AM1 calculations were employed to determine the distance at which van der Waals interactions begin. The transition of making and breaking bonds begins upon entering van der Waals interaction, so the NAC should be a ground state conformation where the van der Waals overlap has yet to begin. The approach of the nucleophile also has an angle dependence. Thus, the structure of the NAC has to meet two criteria: (i) the distance of approach of the nucleophilic oxygen to the carbonyl carbon is between 3.2 and 2.8 Å, and (ii) the approach of the nucleophile is within a cone of 30° with the axis being 15° off of the normal to the carbonyl plane (Chart 3). This set of criteria are within proposed

Chart 2





(3)

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[33] Jencks, W. P. Binding Energy, Specificity, and Enzyme Catalysis: The Circe Effect. *Adv. Enzymol.* **1975**, *43*, 223.

[34] Schowen, R. L. In *Transition States of Biochemical Processes*; Schowen, R. L., Gandour, R. D., Eds.; Plenum Press: New York, 1978; Chapter 2.

[35] (a) Houk, N. H.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107. (b) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.

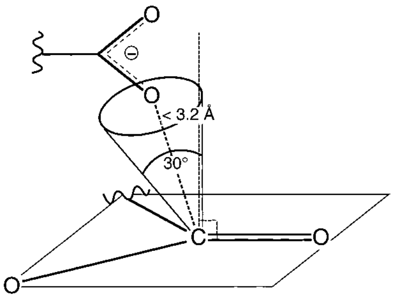
[36] Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

[37] A software product of Tripos Associates, Inc., of St. Louis, MO.

[38] (a) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150. (b) Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203.

[39] Allinger, N. L.; Zhu, Z-Q. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, *114*, 6120 and references therein. Dr. Peter Fox kindly provided additional parameters assembled by N. L. Allinger, J. P. Bowen, and P. Fox.

Chart 3



attack formations by Scheiner, Lipscomb, and Kleier.[40a] Their *ab initio* calculations, using PRDDO,[40b] for the nucleophilic attack of methanol on formic acid show that no stringent angular requirements are necessary. A deviation of the methanol molecule away from its preferred direction of approach by 20° changes the calculated energy by less than 1 kcal/mol. We have written a program which sorts through all conformations and tabulates the conformations that meet the NAC criteria. A numeric tabulation of the conformations generated and those that qualify as NAC is provided in Table 2.[41] An example of the different conformations for glutarate ester is shown in Figure 1 with their respective MM3 final energies.

Table 2. Number of NACs Found, Total Number of Local Minima, Total Number of Structures Generated by Stochastic Search, and the Probability of NAC Existence

ester	no. of NACs	no. of local minima	no. of structures	probability
I	1	112	≥20 000	5.06×10^{-5}
II	2	90	≥40 000	1.47×10^{-5}
III	6	104	≥20 000	7.87×10^{-3}
IV	6	108	≥10 000	8.00×10^{-3}
V	58	553	≥20 000	2.46×10^{-2}
VI	56	453	≥20 000	1.93×10^{-2}
VII[a]	5	8	361	5.41×10^{-1}

[a] Dihedral driver used to generate structures.

Looking at the different "local minima conformations" generated by the stochastic search, the favored ground state conformation of the glutarate ester (Chart 2, FGSC) was found to be extended, while the FGSCs found for the geminally substituted glutarate esters were not as extended. The FGSC of the succinate ester (**IV**) was also found to be fully extended, but the number of NACs was 6 times more than for glutarate (Table 2, **I**). The *β-gem*-diphenylglutarate (**V**) and *gem*-diisopropylglutarate (**VI**) esters have the largest number of local minima conformations as well as NACs. With these *β-gem*-substituted glutarate esters, any given conformation of the glutarate backbone can have many different rotational conformations of the two *gem* substituents.[43] This explains the large number of NACs and other local minima conformations. This feature is shown in the finger print energy plots of Figure 2. In Figure 2, all local minima MM3 conformational final energies for each ester, relative to the FGSC,[44] are presented in one column followed by an adjacent column for the relative MM3 final energies of the NACs.

Knowing the energies of all local minimum conformations, we are in a position to calculate the probability of the formation of any given conformation. Our interest is in the probability of NACs (eq 2, Materials and Methods). In Figure 3, the log of the relative rate constants for intramolecular displacement at the ester carbonyl to provide anhydride (eq 3) are plotted against the log of the probability (P) of formation of the sum of near-attack conformations ($\epsilon = 1.5$). Inspection of Figure 3 shows there is a direct linear relationship between $\log k_{\mathrm{rel}}$ and $\log P$ (eq 4) with slope ≅ 1 ($R^2 = 0.92$). Because there is a

$$\log k_{\mathrm{rel}} = 0.94 \log P + 7.48 \tag{4}$$

direct linear relationship between $\log k_{\mathrm{rel}}$ and $\Delta G^{\ddagger}$, then there is also a direct linear free energy relationship between $\Delta G^{\ddagger}$ and $\log P$.

The thermodynamic values ($G°$, $H°$, and $S°$) for each conformation are provided by the MM3 output. A simple calculation of the thermodynamic energy difference between the FGSC and the lowest energy NAC supplies the values for the changes in free energy ($\Delta G°$), enthalpy ($\Delta H°$), and entropy ($\Delta S°$) for an equilibrium between two of the many ground states (FGSC and NAC for each ester). These values are reported in Table 3. For a given ester, many conformations may meet the NAC criteria. The actual probability of achieving NAC formation is the sum of the individual probabilities of each NAC. From Table 3, there is a direct linear correlation between $\Delta H°$ and $\log P$ with a $R^2 = 0.98$ (Figure 4a) and a direct linear correlation between $\Delta H°$ and $\log k_{\mathrm{rel}}$ with a $R^2 = 0.85$. It is important to note (Figure 5a) that there is no correlation between $\Delta S°$ and $\log P$ ($R^2 = 0.22$) or between $\Delta S°$ and $\log k_{\mathrm{rel}}$ ($R^2 = 0.098$).

Table 3. Thermodynamic Parameters [MM3(92)] for NAC Formation with Monophenyl Esters ($T = 298.16$ K)

	$\epsilon = 1.5$			$\epsilon = 80$[a]		
	$\Delta G°$ (kcal/mol)	$\Delta H°$ (kcal/mol)	$T\Delta S°$ (kcal/mol)	$\Delta G°$ (kcal/mol)	$\Delta H°$ (kcal/mol)	$T\Delta S°$ (kcal/mol)
I	4.92	4.66	−0.26	4.92	4.66	−0.26
II	5.85	5.37	−0.48	NA	NA	NA
III	2.11	2.20	0.09	NA	NA	NA
IV	0.75	2.33	1.58	0.76	2.34	1.58
V	(−1.10)[b]	1.23	2.33	NA	NA	NA
VI	1.17	2.32	1.16	NA	NA	NA
VII	0.11	0.09	−0.02	0.12	0.09	−0.02

[a] The calculations using a water dielectric ($\epsilon = 80$) were only performed on glutarate (**I**), succinate (**IV**), and 3,6-endoxo-Δ^4-tetrahydrophthalate (**VII**). NA means not available. [b] See ref 49.

Up to this point, we have dealt with the correlation of rate constants determined in solution and energies calculated in the gas phase. Figure 6 shows the log of the relative rate constants for glutarate, succinate, and 3,6-endoxo-Δ^4-tetrahydrophthalate esters plotted against the log of the probability of formation of

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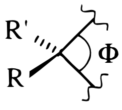
(40) (a) Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770. (b) Halgren, T. A.; Lipscomb, W. N. *J. Chem. Phys.* **1973** *58*, 1569.

(41) The geminal effect should slightly stretch the C−C bond between the backbone and the phenyl groups. However, this effect is not accounted for in MM3(92) force field, such that these C-C bonds may be slightly shorter than in reality (ref 42). Thus, this would result in the over calculation of the number of NACs for the *β-gem*-diphenylglutarate.

(42) Personal communication with Dr. Norman Allinger, 1994.

(43) The calculations show the methylene—*β-gem*-carbon—methylene angle, Φ, in the *β-gem*-substituted glutarates to be slightly smaller than Φ is in the glutarate ester. The Φ angle for glutarate is 114.4°, while Φ for the *β-gem*-dialkyl glutarates ranges from 112° to 113° for *β-gem*-diethyl, from 107° to 112° for *β-gem*-diphenyl, and from 107° to 114° for *β-gem*-diisopropyl.



(44) The MM3 final energies (kcal/mol) for the FGSC are as follows: 221 system, −640.75; succinate, −678.46; glutarate, −677.01; α-*gem*-dimethylglutarate, −671.54; *β-gem*-diethylglutarate, −663.59; *β-gem*-diphenylglutarate, −2048.23; *β-gem*-diisopropylgluarate, −649.90.

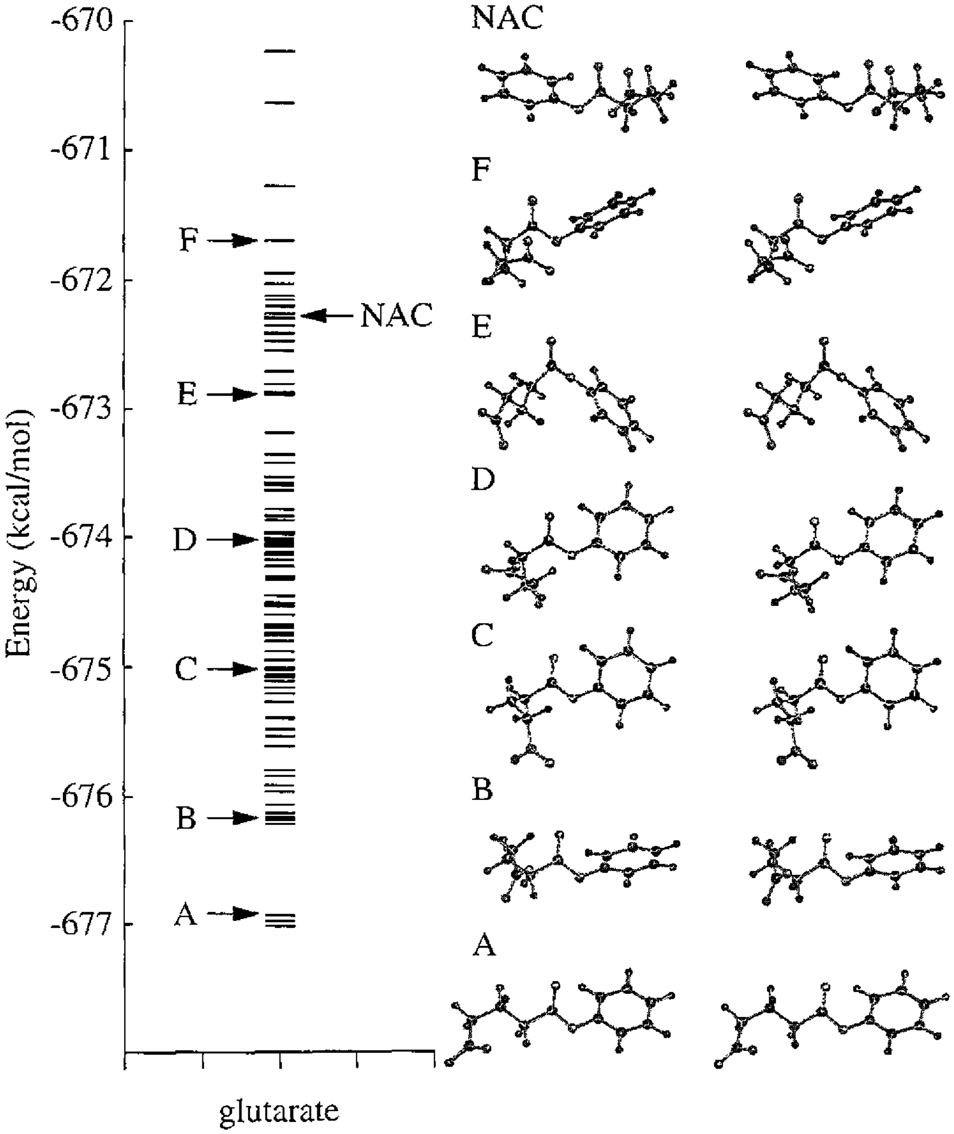


Figure 1. Plot of MM3(92) calculated final energies of all local minimum conformation for monophenyl ester of glutaric acid anion. Stereoviews are of selected conformations (A to F) and the near-attack conformation (NAC). Notice that A, a representative member of the three most stable conformations, is extended.

near-attack conformations calculated with a water dielectric of $\epsilon = 80$. Inspection of Figure 6 shows log P having a direct linear correlation to log k_{rel} (eq 5) with slope $\cong 1$ ($R^2 = 1.00$),

$$\log k_{\mathrm{rel}} = 1.23 \log P + 8.21 \qquad (5)$$

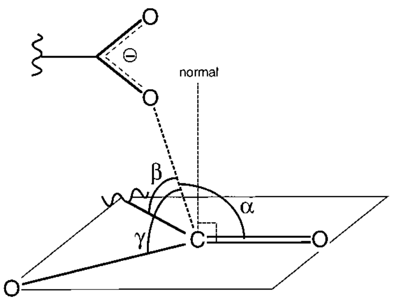
as in Figure 3. Thus, a direct linear relationship of $\Delta G^{\ddagger}$ and log P is computed to exist in water. Similar to the gas phase calculations, the slope is close to 1 with a maximum relative rate of 10^8 M. Also, as shown in Figures 4 and 5, ΔH° ($\epsilon = 80$) is linearly correlated with log P ($R^2 = 1.00$) and log k_{rel} ($R^2 = 1.00$), while there is no correlation between ΔS° and log P ($R^2 = 0.030$) or between ΔS° and log k_{rel} ($R^2 = 0.015$).

We have taken advantage of our molecular mechanics calculations to better define the geometrical requirements for nucleophile approach to an ester carbonyl function. There are three angles that describe the attack of the oxygen of the carboxylate to the carbon of the ester moiety (Chart 4). The apparent angle defined by carboxylate oxygen, ester carbon, and carbonyl oxygen is α. The NACs for all esters possess an average α of 108° ($\sigma = 7.45°$), where 0° is the position of the carbonyl oxygen. The apparent angle from the carboxylate oxygen to the ester carbon to the α-carbon to the ester is termed β (mean = 80.3°, $\sigma = 15.1°$), and angle γ is the angle from the carboxylate oxygen to the ester carbon to the leaving oxygen (mean = 85.1°, $\sigma = 11.2°$). Figure 7 shows that these angles for the NACs of all compounds fit a plane defined by eq 6,

$$0.00530(\alpha) + 0.00180(\beta) + 0.00332(\gamma) = 1.00 \qquad (6)$$

which shows the interdependency of these three angles, defining the approach. As one of the three angles deviates from the normal to the plane, the other two angles proportionally change toward the normal.

Chart 4



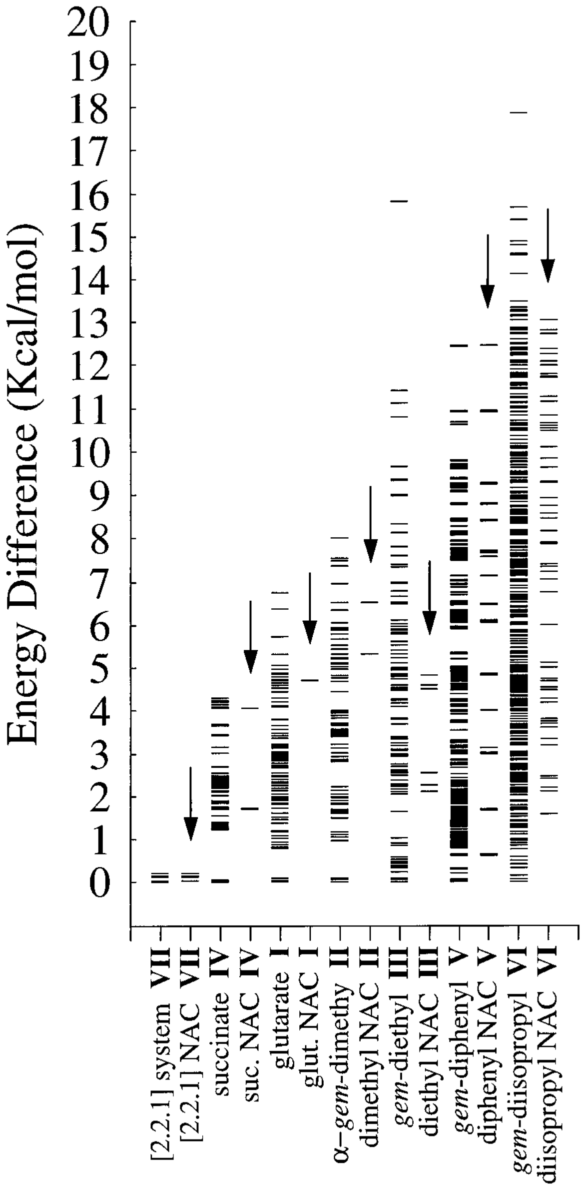


Figure 2. Plot of differences in MM3 final energies of all local minimum conformations relative to the favored ground state conformation (FGSC) energy for each ester as listed in Table 1. The arrows point to the columns of MM3 final energy differences of those conformers that meet the near-attack conformation criteria (labeled NAC). Those conformations to the right of glutarate are *β*-geminally substituted glutarate esters, unless marked. Those conformations to the left of glutarate are the rotationally more constrained esters.

Discussion

Considerable effort has been expended to explain the efficiency of intramolecular reactions. The conclusions from these studies have led to presently accepted concepts concerning enzymatic reactions. The large rate constants for intramolecular reactions have been suggested to arise from (i) the removal of translational and rotational degrees of freedom, (ii) the probability of formation of a reactive conformer, and (iii) transition state stabilization. Changes in translational and rotational energies (primarily entropy) on juxtaposing the nucleophile and electrophile are not sufficient to explain the large rate enhancements which may be seen in intramolecular reactions (see Table 1). These rate enhancements must then be explained by the probability of formation of ground state conformers where the reacting groups are held in conformations to enter the transition state (NACs) and/or transition state stabilization.

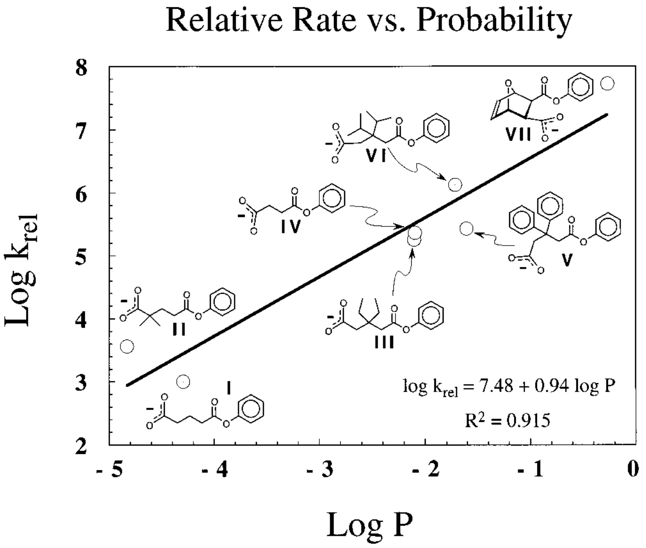


Figure 3. Plot of the log of the relative rate constants (k_{rel}) for anhydride formations from the mono-*p*-bromophenyl esters vs the log of the probability (*P*) for NAC formation of each monophenyl ester in Table 1. (For simplicity in determining *P*, computations of the distribution and stabilities of conformers were carried out with monophenyl esters, corresponding to the mono-*p*-bromophenyl esters used in the kinetic studies.)

Bruice and Pandit[17,18] proposed an explanation for the rate constants in Table 1 based on three assumptions: (i) the favored ground state conformation (the FGSC of this study) is extended, (ii) geminal substitution decreases the population of kinetically unprofitable extended conformers and increases the population of conformers which can undergo ring closure, and (iii) removal of carbon−carbon bonds allowing free rotation decreases the number of extended conformations. This study confirms that the ground states of glutarate and succinate monoesters do exist in extended conformations, that *gem* substitution does decrease the population of extended conformations and that the removal of a freely rotating single bond significantly decreases the number of extended conformations.

The General Problem. The NACs are local minimum conformations that exist just prior to entering the transition state for nucleophilic attack and have been defined as having the following characteristics: (i) the carboxylate $-O^-$ is at a distance of 3.2−2.8 Å to the carbonyl carbon, and (ii) the angle of approach of the carboxylate $-O^-$ to the carbonyl carbon is 105° ± 15° (Chart 3). Using the MM3 final energies of all conformers (Figure 1) we have calculated the probability (*P*) of formation of NACs. It should be made clear that *P is not an equilibrium constant but rather it is equal to the mole fraction of conformations that are NACs.* A plot of the log of the rate constant for carboxylate nucleophilic displacement on the ester bond vs the log *P* is linear with a slope of approximate unity (Figure 3). If those factors determining the rate of the intramolecular reactions are completely encompassed in the distribution of ground state conformations, then the slope of a plot of log k_{rel} vs log *P* would be unity. This we observed. At this juncture, it is important to understand that the calculated probability of each NAC formation with a given ester is based solely upon the stabilization energy of each conformation. *P* is not dependent on the probability of finding a certain conformation within the stochastic search.

Conformation Energy Distribution. Compared to the other monoesters studied, the glutarate monoester (**I**) has a very small relative rate constant for intramolecular ring closure such that the probability of forming a NAC conformation is small. Only

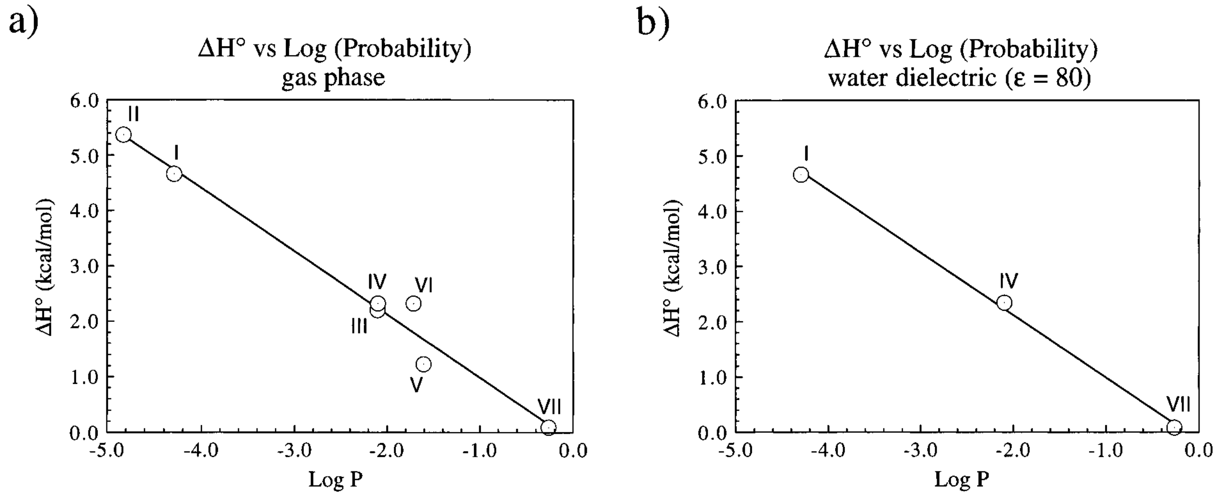


Figure 4. Plot of the enthalpy difference ($\Delta H°$) between the favored ground state conformation (FGSC) and the lowest energy near-attack conformation (NAC) of the monophenyl esters listed in Table 1 vs the log of the probability of each ester being in a near-attack conformation: (a) gas phase calculation with a fit of $R^2 = 0.851$; (b) simulated water dielectric ($\epsilon = 80$) calculation with a fit of $R^2 = 1.00$.

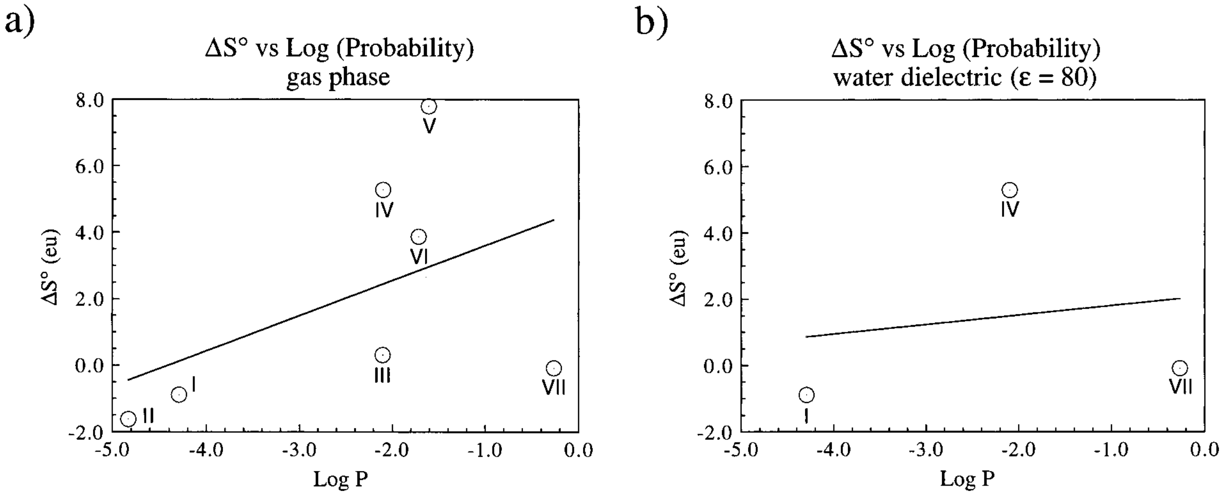


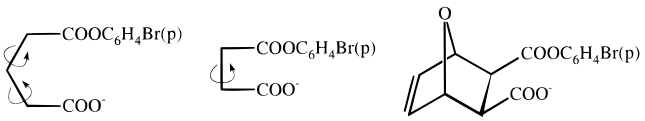
Figure 5. Plot of the difference between the favored ground state conformation entropy and the entropy of the lowest energy near-attack conformation ($\Delta S°$) of the monophenyl esters listed in Table 1 vs the log of the probability of being in a near-attack conformation: (a) gas phase calculation with a fit of $R^2 = 0.098$; (b) simulated water dielectric ($\epsilon = 80$) calculation with a fit of $R^2 = 0.015$.

one structure out of the 112 conformations of the glutarate ester (**I**) and two out of the 90 conformations for the α-*gem*-dimethylglutarate ester (**II**) meet the NAC criteria. Any error in these MM3 conformational final energies contributes to an error in the calculation of *P*. While for the other compounds, the error associated with this calculation is distributed over the sum of NACs. With those esters where the probability of forming NAC structures is less favored, a very large number of stochastic search structures were required to be generated in order to obtain a representative sample of all conformations, *e.g.*, 20 000 structures were required for the glutarate ester (**I**) and ≅40 000 structures were required for the α-*gem*-dimethylglutarate ester (**II**).

Those esters with increased rate enhancements due to geminal substitution (Figure 2, right of glutarate, **II**, **III**, **V**, **VI**) have an increased range of MM3 conformational final energies as well as an increased total number of conformations. The larger the *gem* substituent the more space it occupies; therefore, the carboxyl and ester must spend more time near each other, increasing the probability of NACs. As the *gem* substituent increases in size above methyl, it exists in various conformations, and this, in turn, leads to an increase in the number of ester conformations observed. These features are readily apparent in Figure 2.

Comparing the rate constants for the monoesters of glutaric acid (**I**), succinic acid (**IV**), and 3,6-endoxo-Δ^4-tetrahydrophthalic acid (**VII**) (see Table 1), there is an increase in rate constant by about 230-fold upon removal of each single rotatable bond (Chart 5). *Computationally*, in going from glutarate to succinate to 3,6-endoxo-Δ^4-tetrahydrophthalate monoester, there is (i) a decrease in both the number of conformations and in the energy range for the conformations, (ii) an increase in the number of NACs, and (iii) a calculated rate enhancement of ~200-fold upon removal of each rotatable single bond. This clearly supports the Bruice and Pandit theory[8,17,18] of 1960.

Chart 5



The MM3 final energy difference between the FGSC and the NAC is decreased as the rate constants increase. In comparing between succinate and 3,6-endoxo-Δ^4-tetrahydrophthalate, the number of possible conformers greatly decreases from 108 to 8 while the number of NACs remains constant at 5. Of the five NACs for the 3,6-endoxo-Δ^4-tetrahydrophthalate

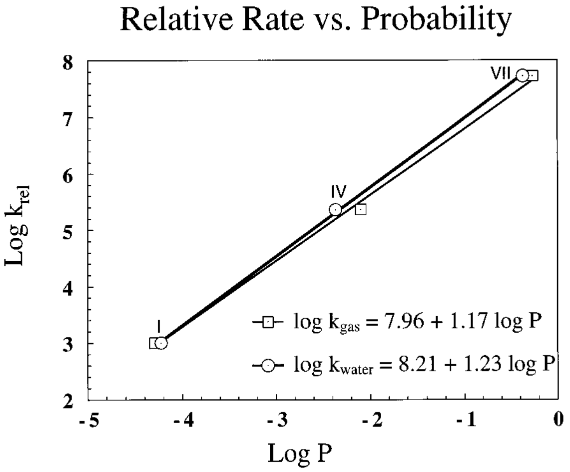


Figure 6. Plot of the log of the relative rate constants (k_{rel}) for anhydride formation from the mono-*p*-bromophenyl esters vs the log of the probability of glutarate, succinate, and 3,6-endoxo-Δ^4-tetrahydrophthalate esters being in a near-attack conformation, as calculated in the gas phase and in a simulated water dielectric of 80.

ester, all are within 1 kcal/mol of the FGSC. This verifies that fixing the reacting species in a steric conformation closely resembling that of the transition state for the reaction (thus decreasing the activation energy) can increase the mole fraction of reacting conformations and, thus, increase the rate of reaction. When *P* approaches unity, as in the case of the 3,6-endoxo-Δ^4-tetrahydrophthalate ester ($P = 0.5$), an ester effectively exists exclusively in the NAC. In the present system, when $P = 1$, the relative rate constant (or EM value) equals $\sim 10^8$ M.

Examination of the distribution of conformations for succinate (**IV**), glutarate (**I**), and α-*gem*-dimethylglutarate (**II**) esters (Figures 1 and 2) shows a number of conformations very close to the FGSC in energy, and just above these is a gap in the MM3 final energies where no conformations are found. Those conformations lowest in energy appear to have limited conformational changes and might be considered the fluctuations in the conformations of the extended absolute ground state. For glutarate monoester, the lowest energy conformations arise from rotations around bonds 1, 5, and 6 (Chart 6) in the backbone of the FGSC. A similar energy gap exists for the α-*gem*-dimethylglutarate ester. As we look at the distribution of conformations for *β*-*gem*-dialkyl-substituted esters (**III**, **V**, and **VI**), the MM3 final energy gap becomes noticeably absent. Contrasting the extended FGSCs of the glutarate and α-*gem*-dimethylglutarate esters, all the FGSCs of the *β*-*gem*-dialkyl-substituted esters are not as extended; they all show a marked curvature brought about by the *gem* substituents which favor rotations about bonds 3 and 4 (Chart 6). Thus, lower MM3 final energy conformations, which are limited to rotations around bonds 1, 5, and 6, do not exist for the *β*-*gem*-dialkyl-substituted esters. More conformations exist where the ester and carboxylate groups are in closer proximity. Looking at the succinate monoester (**IV**), the energy gap between the lower energy conformations and other conformations is larger than the energy gap for glutarate. Again, succinate has an extended ground state with the conformations of lowest energy being formed by rotations around bonds 1 and 5 (Chart 7) of the FGSC backbone. Similar to the glutarate monoester, bonds 3 and 4 prefer to remain in the least sterically hindered conformation. For the glutarate monoester, bonds 5 and 6 (Chart 6) rotate freely, while for the succinate monoester, free rotation is around bond 5 (Chart 7). For both the glutarate and succinate esters the MM3 final energy gap reflects a jump in energy related to rotation around bond 4.

Chart 6

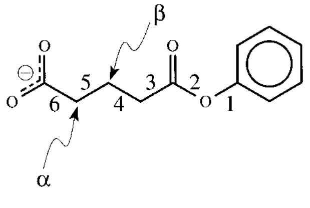
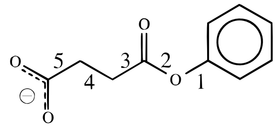


Chart 7



In the considerations of Page and Jencks,[29] they assume that the freezing of an internal rotation to create a NAC can only correspond to an increase in rate constant by 5-fold, based on the fact that the rotation about a methylene bond, HCH_2-CH_2H, is associated with 4.5 eu. On this basis, they stated that the difference of 230-fold in the rate constants, going from glutarate to succinate to the 3,6-endoxo-Δ^4-tetrahydrophalate, cannot be due to the removal of rotation about a single bond. From the discussion involving Charts 6 and 7, we see that this is not true. Page and Jencks neglected to consider the influence of stereoelectronic preferences in determining the energy differences between conformations which are associated with internal rotations. When the favored ground state conformation (FGSC) is extended, as for glutarate, α-*gem*-dimethylglutarate, and succinate esters, there exists a gap in the distribution of MM3 conformational final energies, as shown in Figure 2. Close examination of the conformations above and below the energy gap shows that the jump in energy is a result of an internal rotation around bond 4 (Charts 6 and 7). For the *β*-*gem*-substituted glutarate esters, the FGSC is "curved" and there is already rotation around bond 4; thus, the energy gap does not exist. Clearly, internal rotations around bond 5 (and bond 6) cost less in energy than internal rotations around bonds 4 and 3. In a review of rate constants for intramolecular reactions, Kirby comments[45] that, upon the basis of the Page–Jencks model, the rate enhancements observed in some series of intramolecular reactions are much smaller than expected. Kirby's observations can be explained as follows. Only in those systems where the FGSC is extended will one observe a large rate enhancement upon the removal of a single bond or upon having *gem* substituents. If the FGSC is not extended and, therefore, the ground state approaches a NAC, then there will be little measurable rate enhancement.

Geometry of Nucleophilic Attack. The approach of the carboxylate oxygen of all the NACs to the *re* or *si* face of the ester carbonyl is expressed by three related angles (α, *β*, and *γ*) as represented in Chart 4 and eq 6. The average *β*, the angle from carboxylate oxygen to the carbonyl carbon to the α-carbon to the ester, being 80.3° is only slightly smaller than *γ*, the angle from carboxylate oxygen to the carbonyl carbon to the leaving oxygen ($\gamma = 85.1°$). This difference can be explained by the greater repulsion felt by the incoming oxygen due to the negatively charged ester oxygen as compared to the α-carbon of the ester. Also, α (108°), the angle from carboxylate oxygen to the carbonyl carbon to the carbonyl oxygen, appears to play a more critical role in determining the nucleophilic approach

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(45) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 1983.

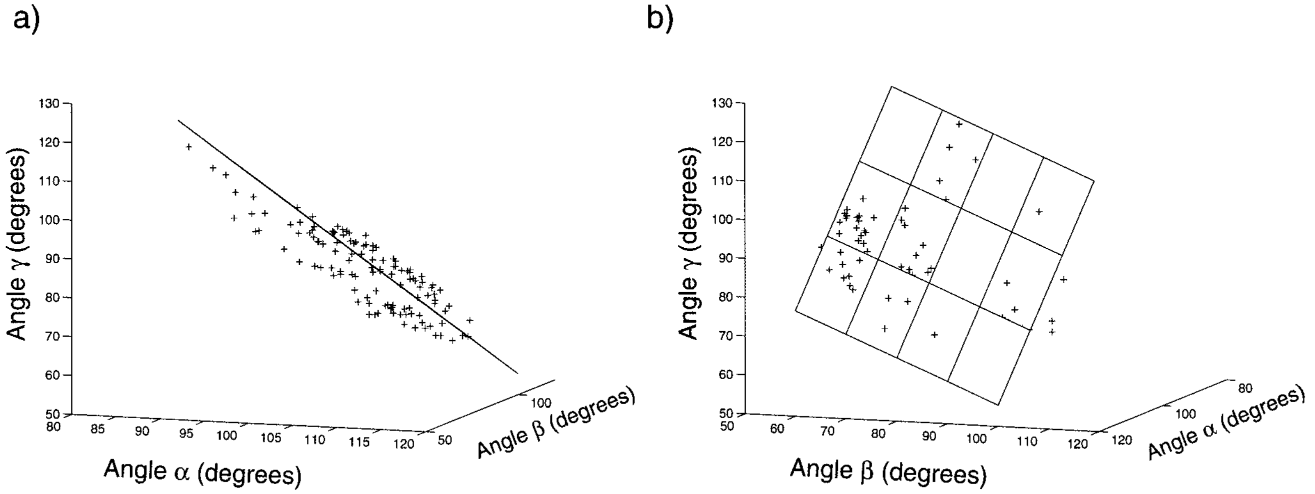

Figure 7. Plot of the relationship between angles α, *β*, and *γ* for the carboxylate oxygen approach to the carbonyl carbon in the ester moiety of all near-attack conformations for the monophenyl esters listed in Table 1, as shown in Chart 4: (a) side view of the fitted plane (eq 6) for all near-attack conformations; (b) 90° rotation around the angle *γ* axis of the same fitted plane as in a).

because its standard deviation is 7.45°, the lowest standard deviation of the three angles ($\sigma_\beta = 15.1°$, $\sigma_\gamma = 11.2°$).

From a survey of available crystal structures showing carboxylate attack of ester carbonyls, Burgi[46] observed that nucleophiles when <3 Å from the ester carbonyl displaced the carbonyl carbon from the sp^2 plane. In our calculations of NACs, the nucleophile is at an average distance from the carbonyl carbon of 2.96 Å ($\sigma = 0.11$ Å), where the ester carbonyl carbon has yet to be displaced from the carbonyl plane. Thus, the NACs represent ground state conformations. In this article, we are not concerned with the higher energy states that would be created if the carbonyl carbon became displaced from the carbonyl plane, but solely in the local ground state conformations just prior to entering the uphill trajectory of the reaction coordinate to provide the transition state (steric compression in intramolecular reactions, *i.e.*, forced overlap of van der Waals surfaces, in the ground state can bring about remarkably large rate constants).[47] The general trend from our calculations is that the greater the distance of the carboxylate oxygen from the carbonyl carbon, the lower the energy for the conformer. Because the conformer has a lower energy, the probability of that conformer existing is greater.

Our calculations agree with the basic premise of Menger's "spatiotemporal" hypothesis that "the rate of reaction between functionalities A and B is proportional to the time that A and B reside at a critical distance."[36] Better stated, the rate of reaction between functionalities A and B is directly proportional to the mole fractions of A and B that reside at a critical distance. Thus, when $P = 1$, the ester is permanently fixed in the NAC. Menger's "spatiotemporal" hypothesis is, however, incomplete in that it ignores the role of orientation and strain in the explanation of experimental results. This study has shown that orientation of the nucleophilic approach is necessary but not stringent. Also, strain (or enthalpy) will be shown to be essential to the explanation of the rate enhancements in Table 1 (see Probability vs Thermodynamics).

Solvent Effects. Bruice and Turner[28] showed that there is a rate enhancement when the reactions in Table 1 are transferred from water to 1.0 M H_2O in DMSO. However, when $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ in water and 1.0 M H_2O in DMSO were compared, they were essentially identical. Our calculations confirm that conformation distributions are not sensitive to the solvent dielectric. In Figure 6, there is plotted the log of the probability for NAC formation, determined using both gas phase and water dielectric, vs the log of the relative rates of anhydride formation from the monoesters of glutarate, succinate, and 3,6-endoxo-Δ^4-tetrahydrophthalate determined in water. The slopes of the two plots are comparable. This shows that the probability for NAC formation has little dependence upon the dielectric of the medium. Because the simulated water data are very similar to the gas phase results, the gas phase data seem to be sufficient to compare with the experimental relative rates.

Probability vs Thermodynamics. The probability of formation of near-attack conformations (P) is not an equilibrium constant but the sum of the probabilities of formation of each NAC. Thus, P is equal to the mole fraction of all conformations present that are NACs. There is a natural tendency among chemists to seek comparisons using the ΔG, ΔH, and ΔS thermodynamic parameters. Our correlation is of $\Delta G^{\ddagger}$ to log P. The free energy, enthalpy, and entropy ($G°$, $H°$, and $S°$) for all conformations are calculated by MM3(92). The changes in free energy, enthalpy, and entropy ($\Delta G°$, $\Delta H°$, and $\Delta S°$) are easily calculated in an equilibrium between one conformation and another. However, there are, in most cases, numerous NACs that are in equilibrium with more numerous nonproductive conformations. Most simplistically, we can calculate the energy differences between the favored ground state conformation (FGSC) and the NAC of lowest energy. The results are shown in Table 3.[49] Plots of $\Delta H°$ vs log P (Figure 4) are linear in both gas and simulated water phases ($R^2 = 0.851$ and $R^2 = 1.00$, respectively). It is most important to note that there is no correlation between $\Delta S°$ and log P [Figure 5, $R^2 = 0.098$ (gas phase) and $R^2 = 0.015$ (water dielectric)]. It is correct that the entropy difference between two conformations is simply determined as $\Delta S° = S_2° - S_1°$. However, the thermodynamic entropy necessary to attain a NAC from the ensemble of NACs should also include the entropic contribution of having multiple

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[46] (a) Burgi, H. B.; Dunitz, J. D.; Shefter, E. *Acta Crystallogr.* **1974**, *B30*, 1517. (b) Burgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

[47] Buttressing of a *gem*-dialkyl substituent can, in extreme cases, bring about conformations where there is overlap of van der Waals surfaces of reacting atoms. This can bring about increases in rate constants for ring closure of $>10^{11}$ (see ref 48).

[48] (a) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. (b) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166, 9175. (c) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, *95*, 8308, 8313, 8319. (d) Hillery, P. S.; Cohen, L. A. *J. Org. Chem.* **1983**, *48*, 3465. (e) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275. (f) Winans, R. E.; Wilcox, C. F., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 4281.

NACs. This entropy difference between the NACs and all conformations is determined by the following:

$$\text{knowing,}\quad \Delta A_{\text{NAC}} = -RT\ln\frac{Q_{\text{NAC}}}{Q} \quad\text{and}\quad Q = \sum_i e^{-\beta E_i} \qquad (7)$$

$$\text{multiplying by}\quad 1 = \frac{e^{-\beta\langle E_{\text{NAC}}\rangle+\beta\langle E_{\text{NAC}}\rangle}}{e^{-\beta\langle E\rangle+\beta\langle E\rangle}},$$

$$\Delta A_{\text{NAC}} = -RT\ln\left[\frac{e^{-\beta\langle E_{\text{NAC}}\rangle}}{e^{-\beta\langle E\rangle}}\,\frac{\sum_i e^{-\beta\Delta E_i^{\text{NAC}}}}{\sum_j e^{-\beta\Delta E_j}}\right] \qquad (8)$$

rearranging,

$$\Delta A_{\text{NAC}} = \langle E_{\text{NAC}}\rangle - \langle E\rangle - RT\ln\left[\frac{\sum_i e^{-\beta\Delta E_i^{\text{NAC}}}}{\sum_j e^{-\beta\Delta E_j}}\right] \qquad (9)$$

$$\text{knowing,}\quad \Delta A = \Delta E - T\Delta S \qquad (10)$$

$$\therefore \Delta S = R\ln\left[\frac{\sum_i e^{-\beta\Delta E_{i\text{NAC}}}}{\sum_j e^{-\beta\Delta E_j}}\right] \qquad (11)$$

rearranging,

$$\Delta S = R\ln[e^{\beta\langle E_{\text{NAC}}\rangle-\langle E\rangle}P_{\text{NACS}}] \qquad (12)$$

where ΔA is the change in Helmholtz free energy, ΔE is the change in the internal energy (given no changes in pressure and volume, ΔE is related to ΔH by RT), ΔS is the change in entropy, Q is a macroscopic state, R is the gas constant, T is temperature, $\beta = 1/RT$, $\Delta E_i^{\text{NAC}} = E_i^{\text{NAC}} - \langle E^{\text{NAC}}\rangle$, $\Delta E_i = E_i - \langle E\rangle$, $\langle E_{\text{NAC}}\rangle$ is the Boltzmann average of all the NACs, and $\langle E\rangle$ is the Boltzmann average of all conformations. After taking into account the phase space of the system (as shown in eqs 7−12), Figure 8 is a plot of the phase space entropy and the internal energy vs ln P. The calculated $T\Delta S$ was found to have no correlation to ln P, but the change in internal energy (in our case, ΔE can be assumed to be ΔH) is well correlated to ln P. The lack of correlation of phase space entropy with ln P is in agreement with our simple calculation from the difference in MM3 entropies, $\Delta S° = S_2° - S_1°$, and is expected because restrictions in conformation usually result in enthalpic changes.[35] Also, from Figure 8, the total energy range for the internal energy is ~5 kcal/mol while the total energy range for $T\Delta S$ is 1.7 kcal/mol. This entropy change could not create a rate enhancement of 10^4, even if the change in entropy had a better correlation to ln P. The inevitable conclusion is that the increase in rate constants is enthalpy driven.

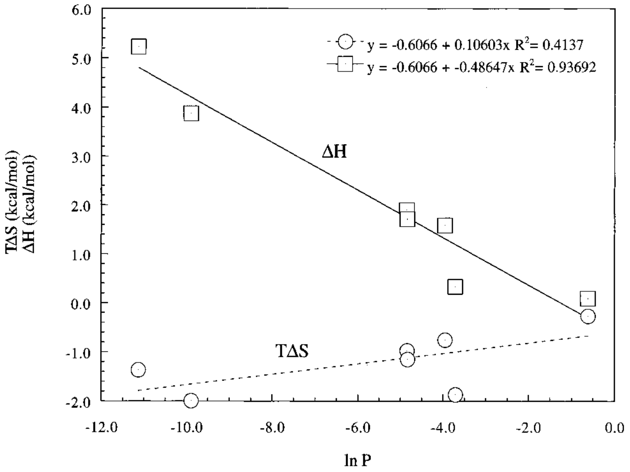

Figure 8. Plot of the phase space calculated (eqs 7−12) thermodynamic entropy change ($T\Delta S$) and internal energy change (in this case, ΔE can be assumed to be ΔH) to attain a near-attack conformation vs the natural log of the probability of being in a near-attack conformation. The correlation between $T\Delta S$ and ln P is $R^2 = 0.414$ with an energy range of 1.7 kcal/mol. The correlation between ΔH and ln P is $R^2 = 0.937$ with an energy range of 5 kcal/mol. The intercepts of both fit lines correspond to when the probability is 1 and all conformations are NACs with a $\Delta G = 0$.

Page and Jencks proposed that entropy changes account for all known examples of chelate effects and rate accelerations in intramolecular reactions that do not involve strain.[29] However, changes in strain control intramolecular rates! In this study, we show that the log of relative rate constants (k_{rel}) are best correlated to the change in enthalpy ($\Delta H°$) and not entropy ($\Delta S°$). Concerning the chelate effect, in a series, the most effective chelating agent for a particular metal provides a match in size between the metal ion and the cavity in the ligand. This was originally spoken of in terms of entropy effects and differences in motions of ligands.[50] However, thermodynamically, changes in binding constants appear in the enthalpy term and are now usually associated with difficulties in bringing together dipoles and charges and with the steric strain due to size mismatch.[51] The chelate effect associated with the binding of ditopic substrates into dimerized cyclodextrins has been reported to be due entirely to an improved enthalpy of binding which overcomes an unfavorable entropy change.[52]

According to Dorigo and Houk, "the real determinant of reactivity is the energy required to distort the reacting functional groups into the geometry of the rate determining transition state."[35b] Their calculations for acid-catalyzed lactonizations from the ground state to the rate-determining transition state show that the reactivities are due to changes in strain, "which occur upon deforming reactants to highest transition-state geometries."[35b] Similarly, our calculations show that changes in strain determine the rate of reaction. However, because Dorigo and Houk calculated only the starting ground state and the transition states, it is difficult to determine where within this reaction coordinate most of the change in enthalpy is occurring (starting ground state (FGSC) to NAC *or* NAC to transition state). Instead of concerning ourselves with the calculation of the transition state geometries, we have better defined a nucleophilic attack geometry such that there exists a conformation (NAC) that must be assumed for the reaction to occur. The strain involved in creating this ground state

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(49) The negative $\Delta G°$ value (−1.1 kcal/mol) for the β-*gem*-diphenylglutarate ester is simply due to the accuracy of the computation[41] and the fact that FGSC and NAC are seperated by but <0.5 kcal/mol. We compare the lowest energy FGSC and NAC in order to have two conformations between which one could consider an equillibrium. Actually, there are a total of 553 FGSCs and 58 NACs for the β-*gem*-diphenylglutarate ester. If we take those conformations which are +2 kcal/mol above the lowest MM3 final energy conformation (FGSC) and within a 2 kcal/mole from the lowest energy NAC, there are then 179 FGSCs and 6 NACs. Now, if we take the lowest energy FGSC and the average thermodynamic values for the six NACs we obtain $\Delta G° = 0.0$.

(50) Orgel, L. E. *An Introduction to Transition-Metal Chemistry: Ligand-Field Theory*; John Wiley & Sons: New York, 1960; p 15.

(51) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.

(52) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353.

conformation controls the reactivity. This change in $\Delta H°$ would have been included in a calculation going from the starting ground state to the transition state such that our concept may have few differences from the concepts of Dorigo and Houk.

Schowen[34] suggests that the origins of catalytic power can be broken down into three parts: "1) the determination of standard-reaction and enzymic transition state structures; 2) the determination of the energy requirements for distortion to the 'poised structures;' 3) the determination of the free energy changes associated with combination of the poised structures."[34] In his concept of stabilization of the transition state, he included the necessity to have poised structures. Schowen's "poised structures" would be our determined near-attack conformations (NACs). In fact, limitations on the distribution of conformers in the ground state, such as the use of *gem* substituents or the removal of the number of rotatable bonds, are similar to restricting the energy requirements for distortion to the poised structures. These ground state effects would effectively result in lowering the transition state.

Entropy and Probability. The MM3(92) final energies can be partitioned in three different ways. The following information can be obtained directly from the MM3(92) program: (i) force field energies: steric, electrostatic, and zero point energies, (ii) mechanical energies: translational, rotational, vibrational, potential, and mixing energies, or (iii) thermodynamic energies: free energy ($G°$), enthalpy ($H°$), entropy ($S°$), and heat capacity (c). The probabilities (P) that we calculate are not equivalent to entropies. In the present context, the probability is calculated using the force field energy values because they are the most reliable. However, because the MM3 energy can be partitioned into thermodynamic values, both enthalpy and entropy are part of the calculated probabilities. Therefore, probability and entropy are not the same in our discussion of conformational energy.

When is entropy the dominant energy? Page and Jencks[29] proposed that entropic contributions provide the proper explanations for rate accelerations in enzymatic and intramolecular reactions and for the chelate effect. Of course, there is no doubt concerning the entropy change in activation upon bringing together the reactants of the corresponding bimolecular reactions.[8,9] However, from Table 3 (an equilibrium between two conformations) and after considering the entropic contribution of having multiple NACs (eq 12), entropy of the conformation appears to play a minimal role in determining the relative rate enhancements in these intramolecular reactions. We have shown that $\Delta G^{\ddagger}$ values for a series of intramolecular reactions are directly dependent upon the mole fraction (P) of conformers that exist in near-attack conformations. $\Delta G^{\ddagger}$ and P, though showing no relationship to $T\Delta S°$, are linearly related to $\Delta H°$. Thus, $\Delta G^{\ddagger}$ is under ground state *enthalpic control*. For the reactions of this study, experimental values of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ were not made available due to the range of rate constants involved. It is conceivable that $\Delta G^{\ddagger}$ values could be related to the overall Arrhenius $T\Delta S^{\ddagger}$ rather than $\Delta H^{\ddagger}$. If this plausibility were true, it would amount to a compensation between $\Delta H°$ and $T\Delta S^{\ddagger}$; therefore, the reactions would not be considered as entropically driven. A simple interpretation of our calculations is that decreasing the energy between the absolute ground state and the near-attack conformation is associated with a decrease of $\Delta H°$, such that the value of $\Delta G^{\ddagger}$ for conversion of the absolute ground state to product is decreased.

Summary and Conclusion

In the process of an intramolecular reaction there occurs the (i) formation of ground state conformations in which the nucleophile and electrophile are closely arranged (near-attack conformation, NAC) such that van der Waals surfaces are properly *juxtaposed* and (ii) overlap of van der Waals surfaces and creation of the transition state. The purpose of this study has been to determine the extent to which the rate of reaction is determined by the probability of forming a NAC. To do so, one must identify ground state conformations (accomplished by use of Saunder's stochastic search program) and determine the energies of each conformation [MM3(92) final energies]. With this information, the calculation of the probability (P) of formation of NACs is simple. This procedure has been employed in the study of the intramolecular reactions of the dicarboxylate monoesters of Table 1. Geometry of the carboxylate attack on the ester carbonyl was determined. The effects of the geminal substitutions are shown to increase the conformer distribution and to increase the energy range of possible conformers (Figure 2). The effects of the loss of one rotatable bond (Chart 5) are shown to decrease the conformer distribution but increase the number of NACs (Figure 2). The probabilities (P) are equivalent to the mole fraction of all conformations present as NACs. Plots of the log of relative rate constants vs log P (calculated for both gas phase and water dielectrics) are linear with slope of $\sim$1.0. Thus, $\Delta G^{\ddagger}$ values of these intramolecular reactions are directly correlated to the mole fraction of conformations present as NACs. In turn, this means that the $\Delta G^{\ddagger}$ is also dependent upon the $\Delta G°$ for formation of NACs. Further, the log of the relative rate constants (log k_{rel}) is linearly correlated to the $\Delta H°$ and not to the $\Delta S°$.

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