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Origin of High Predictive Capabilities in Transition-State Modeling

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Abstract: Rates of 15 acid-catalyzed lactonizations, calculated by transition-state modeling, have been reported to correlate well with experimental rates ($r = 0.95$). It is now found that the ability of transition-state modeling to predict rates depends less on the accurate portrayal of a transition state than on how closely the associated parameters coincide with a family of parameter sets that happens to give a good correlation. Success of transition-state modeling relies on unrealistic force constants (e.g., stretching parameters for partial bonds at 50% of ground-state equivalents) arbitrarily and fortuitously assigned to the transition structures. When these force constants are replaced by ab initio derived parameters, the correlation degenerates into scatter. Rate correlations near unity are achievable with "nonsense" force fields created by our FUDGIT software. Caution is advised in deducing from transition-state modeling any notions about chemical reactivity including transition-state structure and the relationship between rate and distance.

Introduction

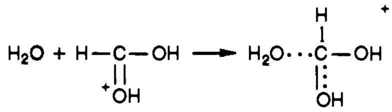
Transition-state modeling, pioneered by K. N. Houk,[1] has become one of the more widely published computational methods for correlating organic reactivity with structure. A molecular mechanics parameter set for a transition state is first derived by applying ab initio calculations (usually at the 3–21 G level) to a simple model reaction. Transition-state energies of related but more complicated reactions, obtained with the aid of the parameter set, are then compared with ground-state energies to give "calculated activation energies". Success in the venture has been generally excellent, judging from the remarkably high correlations between the calculated data and experimental rates or product ratios.

Our interest in transition-state modeling evolved indirectly. We had been determining experimentally the relationship between lactonization rates and attack angle in compounds such as **1** and **2**.[2] It was found that, contrary to published predictions, the rates varied little with the angular disposition between functional groups. Distance, on the other hand, was considered to be a crucial factor in organic reactivity, an idea embodied in our "spatiotemporal hypothesis".[2] The role of distance was recently affirmed by Paquette et. al.[3] who wrote, "Consequently, distance is critically important to reactivity. Modulation on the order of 0.1 Å in the size of the intracavity gap is reflected in a rate spread of greater than 10^4." Yet, the distance concept is not universally accepted. In particular, Dorigo and Houk[4] concluded from transition-state modeling that rate and distance are unrelated. We felt pressed, therefore, to enter the theoretical arena and examine the basis of transition-state modeling from which the disagreement emerged. In dissecting the method, we uncovered uncertainties and pitfalls, described in the following text, inherent to transition-state modeling and relevant to theoretical organic chemistry in general.

Poincaré once wrote, "To doubt everything or to believe everything are two equally convenient solutions; both dispense with the necessity of reflection." When the present work began, we were in a position neither to believe nor to disbelieve transition-state modeling. Our goal was simply to probe the intricacies of the method and to address questions such as the following: What is the mechanistic significance of a high correlation between the calculated and experimental rates from which Dorigo and Houk drew their conclusions? Which components of their force fields are important and which are trivial with regard to achieving high correlations? Is a transition state realistically represented by the force field? This last question took on added meaning with the discovery, already published,[11] that replacing transition states with ground-state structures actually improves rate correlations. Several other troublesome points will be discussed, including the ability of "nonsense" force fields, derived by our FUDGIT software, to predict rate constants with greater success than can transition-state modeling.

Methodology Section

Our calculations focused on one particular reaction: the acid-catalyzed lactonization. Dorigo and Houk had applied their transition-state modeling to this same reaction in a key paper that, as mentioned, repudiated a connection between rate and distance.[4] The procedure was to define first a transition state for attack of water on protonated formic acid (eq 1) by use of the 3–21 G basis set. The resulting geometry was



$$\mathrm{H_2O + H{-}\underset{{}^{+}OH}{\underset{\|}{C}}{-}OH \longrightarrow H_2O\cdots\underset{\underset{OH}{\vdots}}{\overset{\overset{H}{|}}{C}}{-}OH^{+}} \qquad (1)$$

then translated into molecular mechanics parameters. When the transition-state model was coupled to the acid-catalyzed lactonization of the 15 hydroxy acids in Figure 1, the calculated activation energies correlated well ($r = 0.95$) with the ln k_{obs} values.

All our calculations were performed on the Emory University VAX 8550. RHF ab initio computations were carried out with the GAUSSIAN82 series of programs by Pople et al.[5] Semiempirical molecular orbital calculations were accomplished with the aid of AMPAC.[6] For molecular mechanics analyses, we selected the MODEL program of Still and Steliou,[7] a widely distributed software package that allowed easy access to the force field via external data files. Adopting a molecular mechanics program identical with that of Dorigo and Houk was not an option since several minor parameters were not specified in their article.

Upon transferring the Dorigo–Houk parameter set into MODEL, we were initially unable to duplicate the reported activation energies. This problem was ultimately traced to their having inadvertantly reversed all carbon–oxygen dipoles at the reactive center.[8] Correcting this error[9] improved the correlation between calculated and observed rates from 0.95 to 0.98. It is instructive to note that a respectable correlation (0.95) is achievable in transition-state modeling even when carbon is rendered more electronegative than oxygen!

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[1] Houk, K. N.; Duh, H.; Wu, Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2195. Wu, Y.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. Mukherjee, D.; Wu, Y.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328.

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

[3] Paquette, L. A.; Kesselmayer, M. A.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 284.

[4] Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.

[5] Binkley, J. S.; Frisch, M.; Krishnan, R.; DeFrees, D.; Schlegel, H. B.; Whiteside, R.; Fluder, E.; Seeger, R.; Pople, J. A. *GAUSSIAN82*; Department of Chemistry, Carnegie-Mellon University: Pittsburgh, PA, 1982.

[6] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

[7] *MODEL*; W. Clark Still, Columbia University, Version KS 2.94, May 1989, K. Steliou, University of Montreal.

[8] Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 4874.

[9] Dorigo, A. E.; Houk, K. N. *Adv. Mol. Modeling* **1988**, *1*, 135. Menger, F. M. *Adv. Mol. Modeling* **1988**, *1*, 189.

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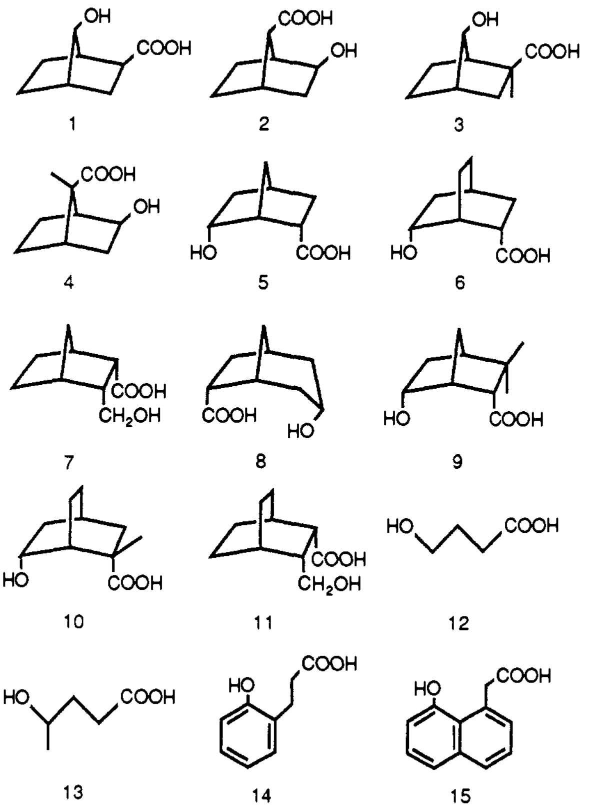

Figure 1.

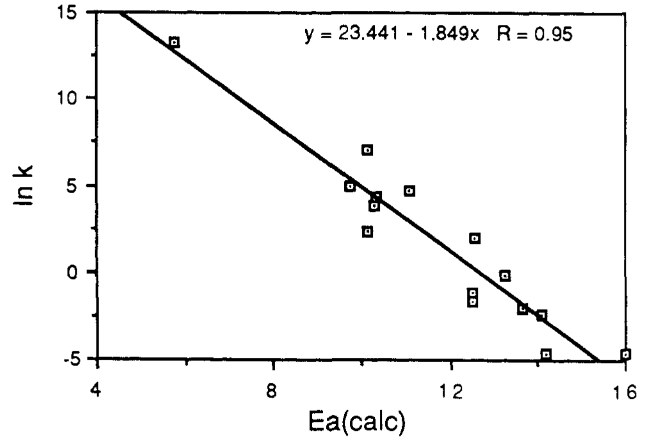

Figure 2. Plot of ln k_{obs} vs activation energies for lactonization of the hydroxy acids in Figure 1. Activation energies were calculated by MODEL-based transition-state modeling. The correlation coefficient is 0.95.

Beckhaus parameters[10] for aromatic rings had been previously employed for compounds **14** and **15** in Figure 1. Since full incorporation of these parameters into MODEL would have required modifying the source code, we relied on the MODEL default values for aromatic rings.

Figure 2 shows the MODEL-derived plot of ln k_{obs} vs E_a(calc) for the hydroxy acids in Figure 1. The corresponding correlation coefficient (0.95) is only 0.03 less than the (corrected) published number, a satisfactory agreement indicating that the two molecular mechanics approaches are essentially equivalent. Having now demonstrated our ability to repeat the lactonization calculations with the cited parameter set, we were ready to examine the parameters themselves.

Transition-State Parameters. A wide variety of assumptions were, of course, invoked both by Dorigo and Houk and by ourselves during the studies of the lactonizations. Although the assumptions do not necessarily negate the predictive utility of transition-state modeling, the more important uncertainties must be specified forthwith to ensure that the foundations of the construct are fully appreciated: (a) The transition geometry for lactonizations in water (an energy *maximum*) was equated with the transition geometry for eq 1 (an energy *minimum* according to gas-phase 3-21G calculations with a $H_2O\cdots C{=}O$ distance of 2.05 Å). (b) A 2.05-Å $HO\cdots C{=}O$ distance was imposed identically on the transition states of all 15 lactonizations, a clear violation of the Hammond principle. (c) Stretching and bending constants of partial bonds in the transition states were, arbitrarily, set at half their ground-state equivalents. (d) Torsional barriers around the $H_2O\cdots C{=}O$ partial bonds were removed. (e) All atoms in the transition state were assigned sp^3-like parameters even though a nearly planar 3-21G structure, evident in Figure 3, suggests a great deal of sp^2 character at the central carbon. (f) Dipoles were set to normal hydroxyl values (molecular charge 0) even though the model 3-21 G structure bears a full positive charge. This approximation seriously distorts the contribution of powerful electrostatic forces to the overall energy of the molecule.

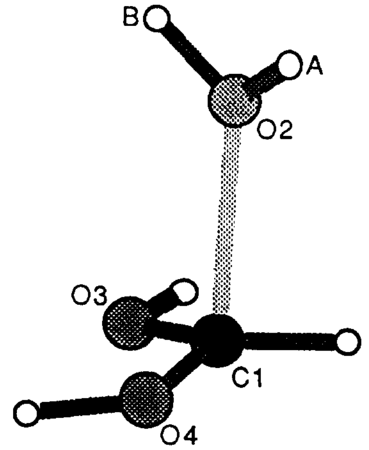

Figure 3. Transition state, derived by 3-21G calculations, for addition of water to protonated formic acid. Bond distances and angles are given in Table I. The O2–C1 bond length is also referred to in the text as the $H_2O\cdots C{=}O$ distance.

Table I. Geometries of the Transition State for Attack of Water on Protonated Formic Acid (Eq 1)[a]

	Dorigo–Houk[b]	this work
	Bonds, Å	
H–C1		1.063
C1–O2	2.05	2.023
C1–O3	1.280	1.294
C1–O4	1.292	1.282
O2–HA		0.969
O2–HB		0.969
O3–H		0.972
O4–H		0.976
	Angles, Deg	
H–C1–O2	85.8	86.5
H–C1–O3	123.2	123.1
H–C1–O4	116.3	116.2
O2–C1–O3	97.4	97.8
O2–C1–O4	102.2	102.2
O3–C1–O4	118.1	118.0
C1–O2–HA	123.1	122.0
C1–O2–HB	123.1	123.8
HA–O2–HB	110.2	110.5
C1–O3–H	119.8	119.7
C1–O4–H	118.4	118.2
	Torsional Angles, Deg	
H–C1–O2–HA		-59.2
H–C1–O2–HB		144.7
H–C1–O3–H		-12.5
H–C1–O4–H		-173.6

[a] See Figure 3 for a picture of the transition state and definition of the bonds. [b] Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.

Assumptions were not the only source of uncertainty. While the transition structure for water addition to protonated formic acid (eq 1) was being generated, it became apparent that Dorigo and Houk had inadvertently exchanged the C1–O3 and C1–O4 bond lengths when transcribing the 3-21G-based geometries to the molecular mechanics parameter set. Thus, the C1–O3 and C1–O4 bond lengths should have been 1.292 and 1.280 Å, respectively, rather than the reverse (Table I).

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[10] Beckhaus, H. D. *Chem. Ber.* **1983**, *116*, 86.

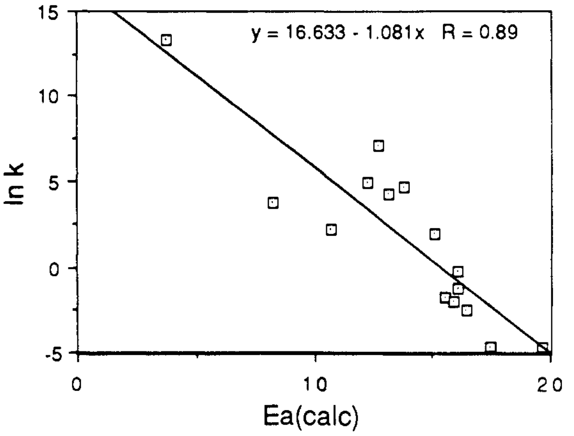
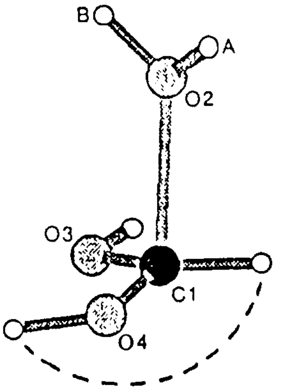


Figure 4. Plot of ln k_{obs} vs activation energies for lactonization of the hydroxy acids in Figure 1 calculated by transition-state modeling. Figure 4 differs from Figure 2 owing to a reassignment of two bonds (see text). The correlation coefficient drops to 0.89.

We naturally wanted to correct this error not only for the sake of accuracy but, more interestingly, to learn how transition-state modeling responds to a seemingly minor alteration. In actual fact, the bond transposition was serious in that it meant that the nucleophilic oxygen in the developing lactone ring had to be reassigned from O4 to O3 relative to the transition-state model in Figure 3. The following transition structure helps clarify the point: forming a lactone ring with O4 (as in the original assignment) in essence "switches" the geometric parameters of the protonated carbonyl with those of the ester oxygen. When the correct oxygen, O3, was utilized in the calculation of the 15 lactonization rates, the correlation coefficient decreased from 0.95 to 0.89. The resulting increase in scatter can be seen by comparing Figures 2 and 4.



Reversing the two bonds had a larger impact on the quality of the calculations than reversing all carbon–oxygen dipole moments (see the Methodology Section). It is extremely difficult to predict exactly what aspects of transition-state modeling are important to the rate correlations because certain perturbations, although large, could conceivably affect the 15 lactonizations to an equal extent. Transition-state modeling, and all multiparametered constructs, should be tested for their sensitivity to the "computational environment" if the methodology is to be fully understood and sensibly employed. Indeed, this was a prime motivation for our calculations.

In all fairness, it must be mentioned that Dorigo and Houk did indeed test the effects of parameterization on predictive ability by altering *all* force constants by a factor of 2.0. However, this can by no means be considered a rigorous examination of computative response as a function of complex interactions among the relevant parameters.

Our next objective was to investigate the dependence of transition-state modeling upon the particular molecular orbital regimen applied to eq 1. Two semiempirical methods (MNDO and AM1) and two ab initio basis sets (3-21G and 6-31G) served the purpose. Both semiempirical methods gave reaction coordinates (for the attack of water on protonated formic acid) possessing energy maxima. The ion–dipole complex located by the 6-31G basis set was (as with the previously discussed 3-21G structure) an energy minimum. Activation energies for the 15 lactonizations were computed by use of the transition geometries from the four MO methods while a constant set of force constants was retained (i.e., the original Dorigo–Houk values). Table II lists the resulting correlation coefficients from the four methodologies. It is seen that the "sophistication" of the MO procedure has little bearing on our success in correlating calculated and experimental data. All correlation coefficients are similar despite widely divergent computational approaches and corresponding $H_2O\cdots C{=}O$ distances. One begins to suspect (a suspicion buttressed by additional data presented momentarily) that the ability of transition-state modeling to predict depends less on the accurate portrayal of a transition state than on how closely the associated parameters coincide with a family of parameter sets that happens to give a good correlation.[11]

Table II. Partial Bond Distances[a] in the Transition State and Correlation Coefficients between ln k_{obs} and E_a(calc) as a Function of Computational Method

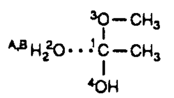
MO method	$H_2O\cdots C{=}O$, Å	r
MNDO	1.847	0.87
AM1	2.140	0.91
3-21G	2.023	0.89
6-31G	2.308	0.89

[a] Distances correspond to C1–O2 in Figure 3.

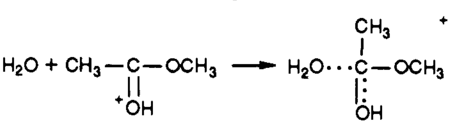
Table III. 3-21G Geometries for Transition State of Water Attack of Protonated Methyl Acetate

Bonds,[a] Å			
H(C)–C1	1.481	O2–HA	0.967
C1–O2	2.367	O2–HB	0.967
C1–O3	1.275	O3–H(C)	1.488
C1–O4	1.288	O4–H	0.974
Angles, Deg			
H(C)–C1–O2	90.2	C1–O2–HA	123.7
H(C)–C1–O3	125.5	C1–O2–HB	122.5
H(C)–C1–O4	117.2	HA–O2–HB	108.5
O2–C1–O3	90.1	C1–O3–H(C)	124.9
O2–C1–O4	99.1	C1–O4–H	116.9
O3–C1–O4	116.5		
Torsional Angles, Deg			
H(C)–C1–O2–HA	−43.7	H(C)–C1–O3–HB	−15.9
H(C)–C1–O2–HB	165.3	H(C)–C1–O4–H	−176.5

[a] Numbering is given according to the following scheme:


$$\left[{}^{A,B}H_2{}^2O\cdots{}^1C({}^3O{-}CH_3)(CH_3)({}^4OH)\right]^+$$

A More Realistic Model. A possibility existed that attack of water on protonated formic acid (eq 1) was not an ideal model for the lactonizations except, perhaps, from the point of view of simplicity. This prompted us to calculate at the 3-21G level the transition structure for a more realistic system: reaction of water with protonated methyl acetate in the lactone-like conformation (eq 2). Table III lists the resulting structural parameters. Comparison of Table III with the formic acid data in Table I shows widespread differences between the two models, particularly in the $H_2O\cdots C{=}O$ distance. Despite these differences, and despite the greater authenticity of the ester model, the rate correlation was little affected. If anything, the correlation was harmed slightly (decreasing from 0.89 to 0.87). Once again, our calculations show that predictive ability and transition-state geometry are only casually related. By default, it would appear that the second category of input data, the force constants, likely play the key role in dictating the success of the correlations—an unpleasant conclusion considering that several force constants for the transition state were assigned arbitrarily.


$$H_2O + CH_3{-}C({=}\overset{+}{O}H){-}OCH_3 \longrightarrow \left[H_2O\cdots C(CH_3)(\text{---}OH){-}OCH_3\right]^+ \qquad (2)$$

Realistic Force Constants. In the absence of hard data, Dorigo and Houk assumed that bond stretching and bending constants for partial bonds at the reactive center were 50% of their normal sp^3 values. Torsional interactions were either given normal sp^3-like values (even though the central carbon retained much of its original sp^2 character in the transition state) or, in the case of the $H_2O\cdots C{=}O$ bond, neglected altogether. How accurate are these parameters? How will our applying more reliable values affect the ability of the model to predict reactivity? In answering these questions, we had first to establish a scheme for transferring 3-21G force constants, obtained by vibrational analysis

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(11) For an example of this statement in hydride transfers, see: Sherrod, M. J.; Menger, F. M. *J. Am. Chem. Soc.* **1989**, *111*, 2611.

Table IV. Force Constants (mdyn/Å or mdyn Å/rad^2) Assumed by Dorigo and Houk Compared with Values Calculated by 3-21G

interaction	assumed	3-21G
C1-O2	2.68	0.58
C1-O3	5.36	9.45
C1-O4	5.36	9.96
O2-C1-O3	0.23	0.43
O2-C1-O4	0.23	0.32
O3-C1-O4	0.46	0.88

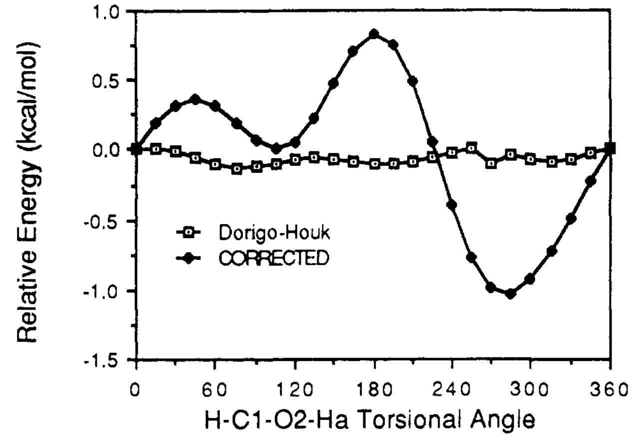

Figure 5. 3-21G-based torsional energies about the $H_2O\cdots C{=}O$ partial bond in Figure 3 compared with the Dorigo–Houk treatment.[4]

calculations, into a molecular mechanics framework.

Following Allinger's recommendations,[12] we secured force constants for our 3-21G structure in the following manner: Changes in energy were computed as a function of small incremental perturbations in the 3-21G bond lengths. The resulting energy vs distortion data were then fit by a nonlinear least-squares method to the MODEL bond-stretching potential function. This yielded numbers that, after scaling by the suggested value of 0.9, were inserted into the force field as the bond-stretching parameters. Similarly, the bond-bending constants were derived by measuring the 3-21G energy as a function of angle distortion. Since distorting one angle usually deforms one to three angles elsewhere in the molecule, all energy data from bent 3-21G structures were curve-fit *simultaneously* to the MODEL potential function for bending interactions. Table IV provides sample comparisons between our 3-21G-derived force constants and those assumed by Dorigo and Houk.

Table IV indicates that the stretching constant for the $H_2O\cdots C{=}O$ partial bond is much weaker according to 3-12G than when estimated as half the normal C–O value. On the other hand, 3-21G discloses that the C1–O3 and C1–O4 bonds are stiffer than previously assumed because the central carbon retains carbonyl character in the transition state (in contradistinction to the sp^3 geometry imposed on the structure by Dorigo and Houk). By the same token, 3-21G rigid-rotor calculations for H–C1–O3–H and H–C1–O4–H torsions in Figure 3 show minima at 0 and 180°, indicating that the C1–O3 and C1–O4 bonds possess lactone-like barriers to rotation (rather than ether-like barriers assumed previously). Figure 5 proves that imparting a zero barrier to rotation about the $H_2O\cdots C{=}O$ partial bond, as done in the past, 4 is in error by 1 kcal/mol.

All new force constants were entered into the force field along with approximate dipole moments derived from the methyl acetate model. When the force field was applied to the 15 lactonizations, the correlation between ln k_{obs} and *Ea*(calc) degenerated into a scatter diagram (Figure 6) with an $r = 0.14$. *Thus, increasing the accuracy of the parameterization completely destroys the predictive power of the transition-state model*! Stated another way, the past success of transition-state modeling relies on unrealistic force constants arbitrarily assigned to the transition state.

In order to define exactly which force constants in the Dorigo–Houk (D–H) procedure gave rise to the impressive predictive ability, we created 16 different force fields containing various combinations of D–H parameters and MODEL default values for the stretching, bending, torsion, and van der Waals components. For example, a force field using the entire D–H parameterization gave the expected $r = 0.95$. A force field in which only the van der Waals constants or only the stretching constants were supplied by D–H (the remainder coming from MODEL) gave unsatisfactory r values of 0.64 and 0.71, respectively. Using both the D–H torsional and bending parameters, along with MODEL values for stretching and van der Waals interactions, reestablished the high correlation ($r = 0.94$). In other words, the correlation in Figure 2 stems largely from a fortuitous combination of sp^3-like bending and torsional parameters. But, as already mentioned, these parameters are suspect because the central carbon in the transition state does not in fact assume a fully tetrahedral geometry and, for this reason, the assumed force constants do not agree with our calculated values.

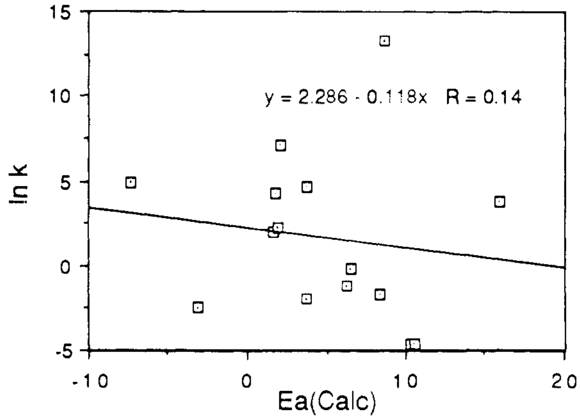

Figure 6. Scatter diagram (correlation coefficient 0.14) obtained when ab initio derived force constants are used in the transition-state modeling.

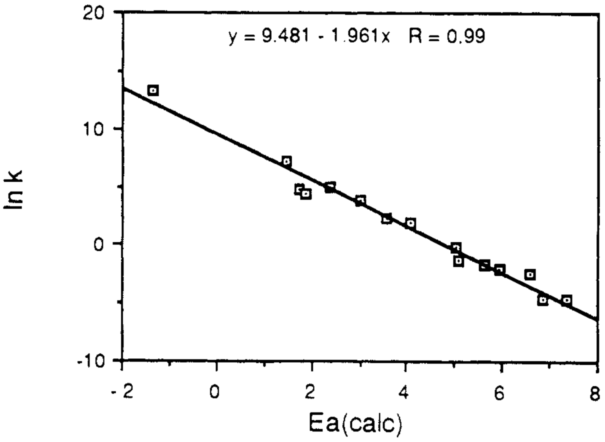

Figure 7. FUDGIT-derived correlation between ln k_{obs} and calculated activation energies. The correlation coefficient is 0.99.

FUDGIT Software. Since authentic parameter sets were not necessarily required for high rate correlations, the possibility existed of using a computer to predict rate constants by having it locate suitable force fields while ignoring physical reality. A procedure developed for the purposed worked as follows: A correlation coefficient for ln k_{obs} vs E_a(calc) was computed with use of an initial file of parameters as already discussed. Small incremental changes were then made in certain structural or force constants, and the correlation coefficient was calculated again. If the correlation improved, the changes were retained. The cycle was executed repeatedly and the force field scanned in its entirety until the correlation coefficient did not further improve. In essence, this method corresponds to a trial and error steepest ascent search for a parameter set that gives the highest correlation.

"Nonsense" force fields were shown to give higher correlations than any yet reported for transition-state modeling. For example, an $r = 0.99$ was obtained with a force field in which bond angles deviated by over 30° from their unstrained values and stretching constants were in error by over a factor of 2 (Figure 7). Details here are unimportant. The key point is that it is not necessary to "model" a transition state accurately to achieve high correlations.[13] High correlations can be achieved by a variety of parameter sets, including some that are absurd. Thus, the published Dorigo–Houk force field is neither uniquely successful nor

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(12) Allinger, N. L. *Brief Guidelines for Obtaining Parameters for the MM2 System*. Obtained by personal correspondence.

(13) It has been shown that a large portion of the energy requirements of an intramolecular hydride transfer entails a carbon skeleton distortion that delivers a hydrogen to a recipient carbon. Only after a critical distance is reached does actual chemical reaction begin. Sherrod, M. J.; Menger, F. M. *Tetrahedron Lett.* **1990**, *31*, 459.

particularly informative from a mechanistic point of view.

FUDGIT has another advantage aside from improved correlations. Suppose experimental data from another lactonization became available. It would be a simple matter for FUDGIT to reoptimize with *all* compounds and thereby improve predictive power if this were the primary goal. But since the Dorigo–Houk procedure, being burdened with assumptions, lacks such flexibility, data from this compound could cause a deterioration in the correlation. It would be possible, of course, to arbitrarily modify the parameter set (e.g., assume that force constants are 30% of their normal value rather than 50%), but then the method becomes equivalent in philosophy to the intellectually vacuous FUDGIT approach.

Conclusion

The claim by Dorigo and Houk that they have found an empirical method for predicting lactonization rates has been verified (although FUDGIT will do the job even better). Predictions do not depend, however, on the accuracy of the transition state, but rather on how closely the associated parameters coincide with one of many parameter sets (even "nonsense" sets) that happen to provide a good correlation.[11,14] Caution is advised in deducing from transition-state modeling any notions about chemical reactivity including transition-state structure and the relationship between rate and distance.

Acknowledgment. This work was supported by the National Science Foundation.

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(14) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

Effect of Cyclodextrin Complexation on the Photochemistry of Xanthone. Absolute Measurement of the Kinetics for Triplet-State Exit[1]

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Abstract: The photochemistry of xanthone aqueous solutions has been examined in the presence of cyclodextrins (α-, β-, and γ-CD). From spectrophotometric measurements it is concluded that xanthone forms 1:1 inclusion complexes with all cyclodextrins and that association is most favored in the case of β-cyclodextrin. Laser flash photolysis studies provide valuable information on the association/dissociation kinetics of the inclusion process. Following excitation, the xanthone triplet relocates from the cyclodextrin cavity into the aqueous phase with exit rate constants of the order of 10^7 s^{-1}; we propose that this relocation is triggered by a change in dipole moment that leads to solubility changes between the ground and triplet states. The effect is most dramatic with β-cyclodextrin, reflecting the strong ground-state association between xanthone and this oligosaccharide.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides of α-D-glucose units produced by enzymatic degradation of starch; three distinct CDs are commonly available, consisting of six (α-CD), seven (β-CD), or eight (γ-CD) sugar units. Cyclodextrins have doughnut shapes and a relatively hydrophobic cavity. The most important property of these molecules is the ability to form inclusion complexes with organic or inorganic guests.[4-8] Thus, inclusion in the hydrophobic cyclodextrin cavity can affect photoprocesses that are sensitive to solvent polarity or dielectric properties.

While there is a large volume of data available on the complexation equilibrium between various cyclodextrins and numerous substrates, very little is known about the dynamics for the association/dissociation process.[9-12] Aromatic ketones are known to form complexes with cyclodextrins in aqueous media; in the case of benzophenone, the complex with β-cyclodextrin has a substantially higher association constant than in the cases of α- and γ-cyclodextrins.[13]

Dielectric loss experiments have shown that ketones with low-lying π,π^* triplet states frequently show large increases (e.g., $\Delta\mu$ = 1.35 D for fluorenone and 4.9 D for 4-(dimethylamino)benzaldehyde) in dipole moment upon excitation into the triplet state.[14] We reasoned that such a triplet molecule would be more hydrophilic than its ground state and therefore excitation should promote dissociation of the complex. It is not sufficient to identify a ketone with a π,π^* triplet state, but in addition, the triplet state must have some property that changes significantly with changes in the media. Xanthone meets all the criteria mentioned above. Thus, in moderately polar media its triplet state has π,π^* character and has a relatively long lifetime as a result of the low reactivity frequently associated with $^3\pi,\pi^*$ states. Further, the triplet–triplet absorption spectra are quite intense and show considerable de-

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