are now new, but in order to keep this Account within bounds, I have had to restrict severely the number of references to previous reviews and earlier work. Most of these can be traced via refs 1, 2, and 25. Much of the earlier work on vibrational adiabaticity was concerned with its relationship to transition-state theory, especially as applied to the prediction of thermal rate constants. In the present Account, I have tried to emphasize three aspects of vibrational adiabaticity, illustrating them by reference to a variety of reacting systems. The first point is that colliding systems are likely to remain in the same state, that is, behave adiabatically, as they pass across regions of a potential energy surface where the MEP curves only slightly and where the frequencies of motions orthogonal to that along the MEP change relatively little. Secondly, the region of low MEP curvature frequently includes the path from the separated reagents to the adiabatic maximum for species in a given vibrational state. In consequence, and finally, VA-TST can be used to predict or explain the effects on reactivity of selectively exciting vibrations of the reagents. In general, any rate enhancement will be most pronounced in simple atom transfers when the bond that is broken in the reaction is excited vibrationally. The degree of enhancement will depend on the details of the potential energy surface between the configuration space of the separated reagents and the saddlepoint on the surface.

I am grateful to SERC and Shell Research for their support of my research on vibrational effects in chemical reactions. I also thank those members of my group who have contributed to this work: J. Brunning, B. D. Cannon, D. W. Derbyshire, M. J. Frost, R. J. Frost, J. S. Robertshaw, I. R. Sims, and M. D. Williams.

Quantitative Modeling of Proximity Effects on Organic Reactivity

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Understanding the dramatic catalytic power of enzymes is one of the most challenging and exciting chemical problems of our time. In 1948, Pauling[1] proposed that enzymes are complementary to the transition states of the reactions that they catalyze, and that enzymatic catalysis results from stabilization of the transition state by attractive interactions with the enzyme. The close analogy between enzymatic and intramolecular reactions was recognized subsequently and exploited to develop chemical models for enzymatic reactions. Subsequently, a number of theories based on structure–reactivity relationships in intramolecular reactions have been advanced to account for the rates of enzyme-catalyzed reactions. Our successful use of force-field transition-state modeling to rationalize the stereochemistry of organic reactions[2] led us to investigate a similar approach for the understanding and prediction of the relative rates of intramolecular reactions. This Account describes our development of force-field models to provide quantitative predictions of intramolecular reaction rates and to compare these with intermolecular reactivities.

Bruice's[3] pioneering studies of intramolecular nucleophilic catalysis led him to conclude that enzymes accelerate chemical reactions primarily by bringing the reactants into close proximity. This argument can be cast in free energy terms as shown in Figure 1. In a bimolecular or higher order reaction, the free energy costs that are incurred in the early part of the reaction coordinate consist largely of the enthalpic and entropic costs of bringing the reactants together. Enzyme catalysis results in part from the fact that the gathering of reactants, an entropically unfavorable act, occurs as an integral part of the complexation process, which is enthalpically favorable. Various versions of this principle have been proposed.[4-9]

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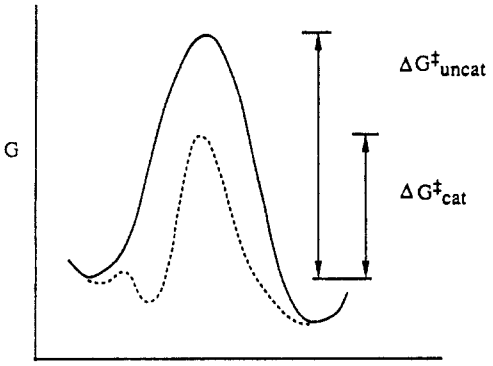

Figure 1. Schematic of bimolecular reaction in solution (solid line) and catalyzed by an enzyme (dashed line).

Page and Jencks[10] estimated that there is a 35-eu entropic advantage enjoyed by intramolecular reactions over their intermolecular analogues. This sets an approximate upper limit of 10^8 for the rate enhancement expected for intramolecular reactions due to entropic effects alone (at 25 °C, $\Delta\Delta G^{\ddagger} = -T\Delta\Delta S^{\ddagger} = 10.5$ kcal/mol). This entropic rate factor may be reduced somewhat in reactions having "loose" transition structures (such as radical recombinations) or in cases where one or more bond rotations must be frozen in the intramolecular transition structure. Furthermore, because the free energy of activation includes enthalpic as well as entropic terms, the effects of steric strain in the starting material and in the rate-determining transition state must be considered. An intramolecular reaction may be accelerated by steric compression in the ground state or retarded by steric effects (such as eclipsing interactions) which inhibit formation of a cyclic transition structure.

Menger has proposed that "the rate of reaction between two functionalities A and B is proportional to the time that A and B reside within a critical distance".[11] A lively discussion has ensued.[12-15]

In order to be useful as a predictive tool, indeed to qualify as a testable theory at all, any hypothesis must be cast in a quantitative form. Predictions of relative reactivities require explicit consideration of the enthalpic and entropic changes that occur upon conversion of the ground state into the transition state.[16]

Modeling of Transition States of Organic Reactions. The rate of a reaction is determined by the difference between reactant and transition-state free energies. Unfortunately, detailed knowledge of transition structures cannot be obtained directly from experimental techniques.[17] Mechanistic evidence can provide at best some qualitative transition-state characteristics. Ab initio molecular orbital calculations permit the structural characterization of any number of points on the potential surface, and even calculations of rates as well as spectroscopic properties and lifetimes of transition states.[18] Unfortunately, such calculations are currently feasible only for reactions of molecules that are much smaller than many of those that are of interest to organic chemists. Semiempirical MO methods may be applied to much larger systems, but these are often unreliable for predictions. Empirical force-field calculations, such as those using Allinger's MM2 program,[19] are readily applied to molecules of up to several hundred atoms but have been parametrized extensively only for ground-state molecules. Force-field calculations have been performed on reactions such as the solvolysis of alkyl halides and benzoates,[20] S_N2 reactions,[9] ester hydrolyses,[21] diimide reductions,[22] oxidation of alcohols,[23] and reductions of ketones,[24] mostly employing the structures of products or metastable intermediates (such as carbocations) as models for transition states. Our approach to this problem has been applied successfully to stereochemical studies of hydroborations, carbonyl reductions, radical and nucleophilic additions, and other reactions.[2] We locate the transition structure for a prototype reaction by ab initio molecular orbital calculations. The bond lengths and angles involving partially formed bonds which are determined by these calculations are incorporated into Allinger's MM2 force field as minimum energy values for these parameters. Stretching, bending, and torsional parameters for these bonds are determined by further ab initio calculations or are estimated. The resulting force field is then tested both for its ability to reproduce experimental results and for the sensitivity of the predictions to variations in the value of the estimated

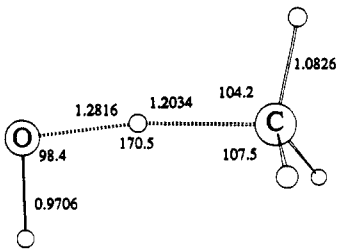

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Table I
MM2 Steric Energies of Radicals and Transition States, Predicted Activation Energies and Rate Constants, Calculated C• • •O Distances in Radicals and Transition States, and Experimental Reaction Yields for Oxidative Cyclization of Alcohols 1–7

alcohol	E_{rad}	E_{ts}	ΔE_a[a]	k	$r_{C\cdots O(rad)}$	$r_{C\cdots O(ts)}$	yield, %
1	58.4	56.3	−0.1	3.0×10^{11}	2.96	2.43	90
2	31.4	32.4	2.9	2.4×10^{9}	3.07	2.44	0
3	20.9	24.3	5.4	3.6×10^{7}	3.05	2.44	31
4	20.1	28.9	10.8	4.5×10^{3}	4.17	2.40	0
5	20.7	16.8	1.1[b]	3.0×10^{11}	4.59	2.45	86
6	21.3	24.3	5.0	7.2×10^{7}	3.02	2.43	61
7	25.5	27.3	3.8	5.4×10^{8}	3.53	2.44	38

[a] $E_{ts} - E_{rad} + 2.0$ kcal/mol. [b] See text.

parameters. Such a quantitative transition-state model is generally applicable only to a narrow range of reactions. It can be used to test various hypotheses, to explore the origin of reactivity differences, and to make interesting and testable predictions about reactivities. Future force fields of this type will be tested on more sophisticated force fields, like MM3, and will include entropy calculations as well.

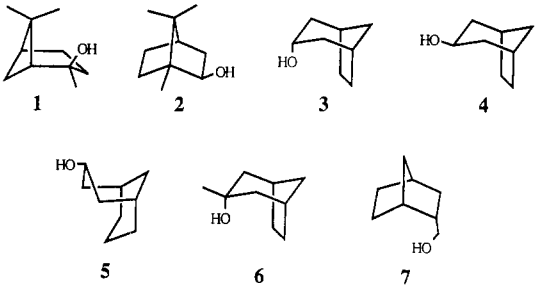
Intramolecular Hydrogen Abstractions by Alkoxyl Radicals. An early study in our laboratories involved the study of intramolecular hydrogen abstractions by alkoxy radicals.[13] To define the transition structure we chose the abstraction of hydrogen from methane by hydroxyl radical. Figure 2 shows the transition structure[29] for this reaction calculated at the MP2/6-31G** level.[25-27] The energetic effects of varying two geometrical features from their minimum energy values was studied at the MP2/6-31G**//3-21G level[26,27] of theory. An increase or decrease in the C···O distance by 0.1 Å causes the activation energy to increase by 1.2 kcal/mol, which corresponds to a 7-fold decrease in reactivity at room temperature. When the distortion is 0.3 Å, the activation energy increases by 9.0 kcal/mol, corresponding to a decrease in reactivity of about 3×10^6. Compared to similar distortions in ground-state molecules, stretching or compressing the partial C···H and O···H bonds is about three-fourths as difficult.

Heuster and Kalvoda[28] have proposed that a C···O distance of less than 2.8 Å must be attainable in order for the reaction to have preparative utility. Our calculations indicate that the preferred transition-state geometry has a C···O distance of 2.48 Å and that the activation energy increases dramatically if the C···O distance is constrained to be greater than ca. 2.7 Å.

Angular distortions have a smaller but not negligible influence on transition-state stability. For example, a 20° deviation from the ideal C···H···O angle destabilizes the transition state by 1 kcal/mol. This is the same change caused by a 0.1-Å change in the C···O distance. A 5° distortion of the H–C···H or H–O···H angle increases the activation energy by 1.5–1.8 kcal/mol. A change in the distance between reacting centers is more important than a change in attack angle.[7]

The information obtained from this study was incorporated into the MM2 force field along with reasonable estimates for other parameters.[13] The change in electronic energy associated with converting one unstrained C–H bond into one "unstrained" partial C···H bond and one unstrained partial O···H bond was found to be approximately 2.0 kcal/mol by comparing the experimental activation energies[30] of the reactions of hydroxyl radical with ethane and propane with the change in steric energies calculated by our force field. Reaction rates were calculated by using the Arrhenius equation. The A value is approximately 3×10^3 L mol^{-1} s^{-1} for the reaction of $CH_3O^\bullet$ with alkenes[30] and was estimated to be 3×10^{11} s^{-1} for intramolecular reactions.

Unfortunately, kinetic data concerning the relative rates of intramolecular hydrogen abstractions of this type are generally lacking. The lead tetraacetate induced cyclization of alcohols[28,31] is known to proceed via an intramolecular hydrogen atom transfer of this type, however, and facile side reactions of the intermediate alkoxyl radical represent an internal clock of sorts. We have compared our calculated rates to the cyclization yields of some bicyclic alcohols[32] in Table I, assuming that the yield of the reaction is a crude measure of the rate.[32]



1 2 3 4 5 6 7

Table I gives the experimental yield of the lead tetraacetate induced cyclization of seven bicyclic alcohols, calculated activation energies and rate constants for the hydrogen-abstraction step, and the calculated C···O distance in the radical ground state and in the transition state for hydrogen transfer. There is correspondence between the order of increasing ΔE_a values

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and the order of decreasing yields of cyclized product. However, compound **2** fails to give detectable amounts of cyclized product in spite of its relatively low calculated activation energy for hydrogen transfer, because its strain and tertiary bridgehead carbon make β-scission unusually facile. The calculated activation energy for the hydrogen atom transfer in **5** is −1.7 kcal/mol, so that the rate-determining step is the conversion from the boat to the chair conformer of **5**. The lower limit for the activation energy of this process is given by the difference in the stability of the two conformers, which is 1.1 kcal/mol.

There is no simple relationship between the reaction yield and the distance between the reacting centers in the ground state. The molecular flexibility of different compounds varies widely, making ground-state separation a relatively unreliable predictor of the energy required to obtain a viable transition-state geometry. Similar results were obtained in a study of the Barton reaction in steroids.[13]

In each transition structure, the C···O distance is similar to the ideal value of 2.48 Å. The relative invariance of this distance suggests that a "critical distance" for reactivity should be defined as the ideal unstrained distance between partially bonded atoms in the transition state. The C···H···O angle, on the other hand, varies significantly. The deviation from the ab initio value ranges from 8° for alcohol **5** (the most reactive) to 26° for alcohol **4** (the least reactive). In all the other substrates, the deviation is about 20°. Smaller distortions are observed for the C–C···H and C–O···H bond angles, as expected from the larger force constants for these bond angles.[13] We find that differences in rates of δ-hydrogen abstraction by alkoxy radicals arise largely from the differences in the steric strain which must be overcome to convert the ground-state geometry to the transition-state geometry.

In addition to the rigid bicyclic alcohols listed in Table I, we have also investigated the oxidative cyclization of some acyclic aliphatic alcohols. The cyclization of acyclic aliphatic alcohols under various conditions (lead tetraacetate, lead tetraacetate plus iodine, nitrite ester photolysis) generally yields tetrahydrofurans as the major or exclusive cyclic products. Only the formation of tetrahydropyrans is sometimes competitive. However, our force-field model predicted that the seven-membered transition state (leading to the tetrahydropyran product) is 0.8 kcal/mol lower in energy than the six-membered. This surprising result led us to investigate these same reactions at the ab initio level.

The structures of the butoxy and pentoxy radicals were determined at the UHF/3-21G[25,26] level. Transition states for δ-hydrogen abstraction in the butoxy radical and for ε-hydrogen abstraction in the pentoxy radical were located at the same level of theory. Figure 3 shows the calculated transition structures. The activation enthalpy for the seven-membered transition state was calculated to be 0.7 kcal/mol lower than that for the six-membered transition state.

The six-membered transition state resembles a five-membered ring of heavy (non-hydrogen) atoms, having an envelope shape like that of cyclopentane, but with a long C···O bond. The seven-membered ring has a "chair" form like that of chair cyclohexane, but again

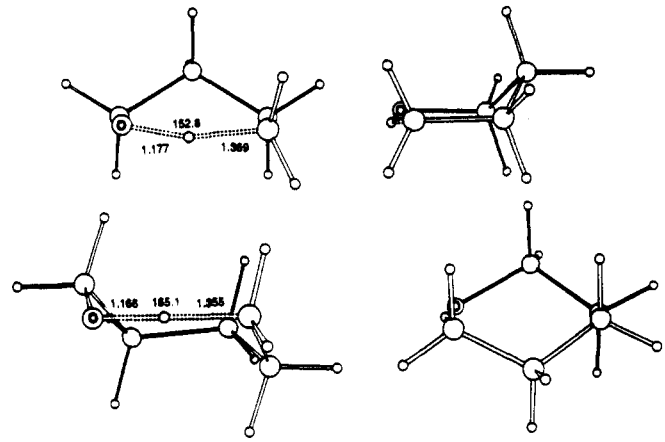

Figure 3. Two views of the UHF/3-21G transition structures for intramolecular hydrogen abstraction in the *n*-butoxy (six-membered transition state, top) and *n*-pentoxy (seven-membered transition state, bottom) radicals.

with one long bond. The O···H···C angle is slightly distorted from linearity in the seven-membered transition state (O···H···C = 165°) and distorted to a larger extent in the six-membered transition state (O···H···C = 153°). The C···H and O···H bond lengths, on the other hand, are unstrained.[26]

These results indicate that the preference for δ-hydrogen abstraction does not originate from enthalpic effects. Our calculations predict instead that there is a significantly less negative entropy of activation involved in the hydrogen atom transfer in the butoxy radical than in the pentoxy radical. The entropy differences between the reactants and transition states were computed to be −6 eu for the six-membered transition structure and −14 eu for the seven-membered transition structure. The difference in entropies of activation is therefore 8 eu, which is similar to the 9 eu more favorable entropy change for conversion of pentane to cyclopentane as compared to conversion of hexane to cyclohexane. The 8 eu advantage of the six-membered transition state corresponds to 2.5 kcal/mol at 300 K. Our calculations therefore predict that the free energy of activation is 1.8 kcal/mol lower for the six-membered transition state than for the seven-membered at room temperature. The conclusion that this preference is primarily the result of entropic factors is supported by the experimental observation that the δ-hydrogen/ε-hydrogen-abstraction ratio varies little with temperature in the corresponding reaction of carbon radicals.[33]

It might seem alarming that entropy controls reactivity here, whereas our MM2 model neglects entropy. We can only compare processes that have similar entropies of activation using our force-field model, or else calculations of activation entropies must be carried out. This can be done from moments of inertia plus vibrational frequencies and will be a feature of future models. The entropy differences should be small for the many relatively rigid polycyclic systems that we have treated here in detail.

The potential utility of force-field models in the design of multistep synthetic routes is illustrated by the following study.[34] During Corey's[35] recently reported

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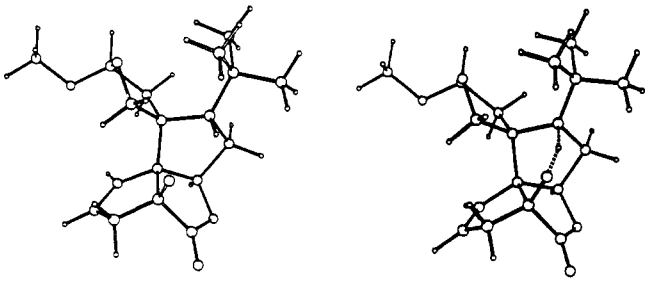
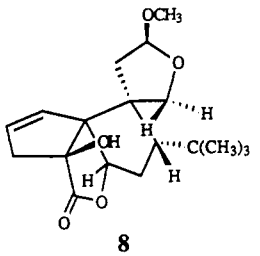


Figure 4. The ground-state conformation of 8 and the transition structure leading to 10.

synthesis of ginkgolide B, treatment of alcohol 8 with lead tetraacetate was found to give none of the desired cyclization product 9, but gave instead product 10.



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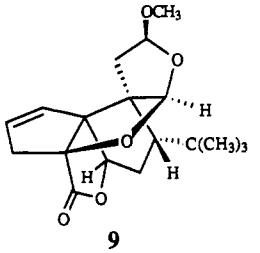

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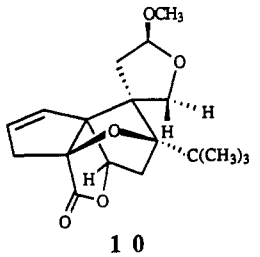


10

Examination of Dreiding models suggests that 9 should be formed, opposite to the experimental results. Our force-field model correctly predicts the observed product and provides an explanation for its formation. The lowest energy transition structure leading to formation of 9 was calculated to be 5.8 kcal/mol higher than the lowest energy transition structure leading to 10. This difference in steric energies needs no correction for electronic effects, as tertiary and α-alkoxy C–H bonds are known to have similar reactivities toward alkoxyl radicals.[36] The transition state leading to 10 (Figure 4) has a geometry similar to that of the lowest energy conformation of the alkoxyl radical corresponding to 8, in which unfavorable steric interactions of the *tert*-butyl group are minimized. The *tert*-butyl adopts a quasi-equatorial conformation, which is shown by MM2 calculations, but not by Dreiding models. When the *tert*-butyl group was replaced by a hydrogen atom, the transition state leading to 9 was favored by 1.9 kcal/mol. Similar calculations, in conjunction with experimental data for the electronic effect of different α-substituents on rates of hydrogen abstraction,[36] suggest that replacing the *tert*-butyl group with a nitrile, acetyl, or methoxycarbonyl group should give good selectivity for the product corresponding to 9.

Acid-Catalyzed Lactonizations. In contrast to the cyclization of alkoxyl radicals, acid-catalyzed lactonization of hydroxy acids has been the subject of numerous kinetic studies, and scores of rate constants are available for structurally very diverse species.[37] Because the mechanism of this reaction involves charged intermediates, it might be argued that the explicit inclusion of solvation effects would be necessary in any model with which one hoped to reproduce experimental trends. Nevertheless, we have found that a simple force-field model of the type described above for hydrogen-abstraction reactions is sufficient to reproduce experimental rates.[5,7c,38] Emboldened by our success, we have made a number of predictions for hydroxy acids that have not yet been studied experimentally.

Table II
Comparison of Calculated Activation Energies (ΔE_S for ϵ = 80), C• • •O Distances in the Starting Materials (r_{CO}), Angles of Attack (∠O• • •C—C and ∠O• • •C=O), and Experimental Rate Constants (k) for Lactonizations of Acids 11–25

hydroxy acid	ΔE_S, kcal/mol	r_{CO}, Å	∠O···C—C	∠O···C=O	k, M^{-1} min^{-1}
11	16.5	3.02	69	78	0.01
12	15.7	2.95	79	102	0.01
13	12.9	2.89	74	79	0.3
14	13.7	2.87	82	103	0.18
15	10.4	2.86	77	75	1200
16	13.0	2.98	72	74	0.95
17	11.5	4.23	(57)[a]	(61)[a]	7.2
18	10.5	2.98	80	84	10
19	9.9	2.93	75	69	71
20	10.7	2.84	78	76	107
21	10.9	4.27	(63)[a]	(117)[a]	152
22	15.5	4.38	(18)[a]	(116)[a]	0.09
23	14.4	4.37	(18)[a]	(116)[a]	0.13
24	11.0	4.60	(36)[a]	(110)[a]	45[b]
25	4.2	2.93	69	75	6.0×10^5 [b]

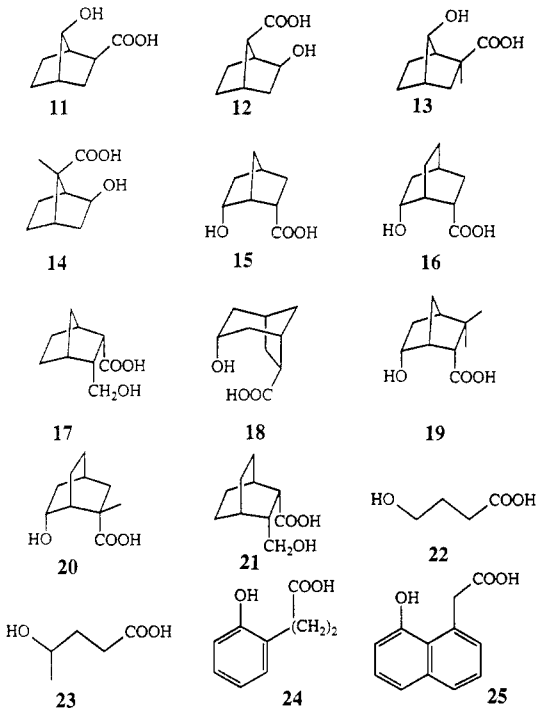
[a] Angles are given in parentheses when r_{CO} is large and the conformation does not allow direct nucleophilic attack on the carbonyl. [b] Observed rate constant multiplied by a correction factor of 7.5×10^6 to account for the lower reactivity of a phenolic hydroxyl group in acid-catalyzed esterification. See refs 5a and 38.

The steric energies of reactants 11–25 were calculated with MM2 and are shown in Table II. The ground-state C···O distances and the angles formed by the alcoholic oxygen and the C—C and C=O bonds of the carboxyl group (O···C—C and O···C=O respectively) are also listed, along with the experimental rate constants.

The rates of lactonization correlate poorly with the separation between reacting sites or angles of the functional groups in the ground states of the reactants. For example, the calculated C···O distance for compounds 14 and 15 is virtually the same, yet 15 is more than 10^4 times more reactive than 14. Similarly, in 12 and 19 the interatomic distances vary by only 0.002 Å, but 19 reacts about 7000 times faster. On the other hand, some pairs of compounds with very different C···O distances like 11 and 12, or 19 and 20, exhibit similar reactivities. There is also no correlation of reactivity with the angle formed between the hydroxyl oxygen and the carboxyl group.

Our model[39] for the acid-catalyzed lactonization transition state was developed from an ab initio calculation[25] of the reaction of water with protonated formic acid in the gas phase. The ion–dipole complex having a C···O separation of 2.05 Å, shown in Figure 5, was used. Other calculations on nucleophilic additions[40–42]

(35) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651. We thank Professor Danishefsky for pointing out this result and Professor Corey for discussion of the results and his independent force-field calculations.
(36) Walling, C.; Mintz, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 1515–1519.
(37) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.
(38) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158–9165.
(39) For an alternative method of assessing steric effects in acid-catalyzed lactonizations, see: DeTar, D. F. *J. Am. Chem. Soc.* **1974**, *96*, 1255–1256.



led us to conclude that the ion–dipole complex shown in Figure 5 is a reasonable model for the corresponding transition state in solution. The bond lengths and angles shown in Figure 5 were the minimum energy values used in our MM2 model. Simple choices of parameters were made to develop a model. As before, model calculations revealed a lack of sensitivity of the results to wide variations in the values of these parameters.[12,14]

Comparison of our calculated ΔE_S values for attack of alcohol on protonated acid with the experimental values of ln k revealed only a low degree of correlation (R = 0.62). These poor results could arise from the crudeness or incorrectness of our force-field model or from misidentification of the rate-determining step. In fact, others proposed that the rate-determining step is the loss of water from the tetrahedral intermediate, not attack of the alcohol.[37,43,44] We performed calculations to model this reaction step as well. A much better correlation (R = 0.97) between ln k and these new calculated ΔE_S values was found, as shown in Figure 6. We used this model to predict the rate constants for lactonizations of hydroxy acids that have not yet been studied experimentally. These predictions are shown in Figure 7.

Compounds **32** and **33** are predicted to lactonize at extraordinarily high rates because of the large release of steric compression that occurs in the rate-determining transition state. Compounds **28**, **30**, and **31** all have larger reactant C···O separations than compound **27**, but are predicted to react 6–180 times faster due to less unfavorable changes in bond and torsion angles upon conversion to the transition state. Compound **26**, which has a substantially smaller reactant C···O separation

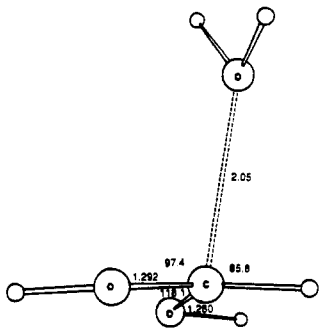


Figure 5. Transition-state model used for acid-catalyzed lactonization modeling.

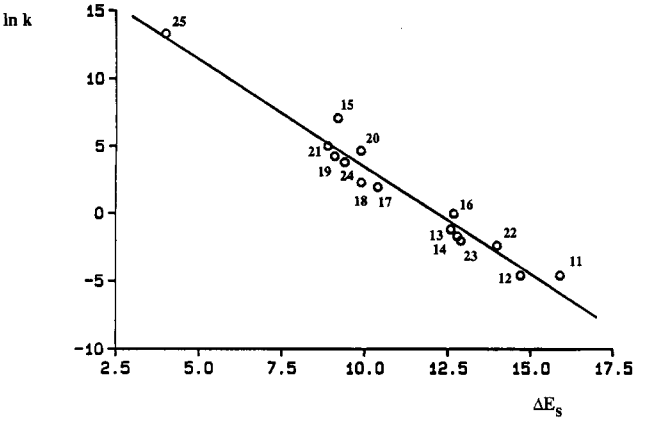


Figure 6. Plot of ln k vs the calculated change in steric energy for conversion of hydroxy acids **11–25** into the transition state for loss of water from the tetrahedral intermediate.

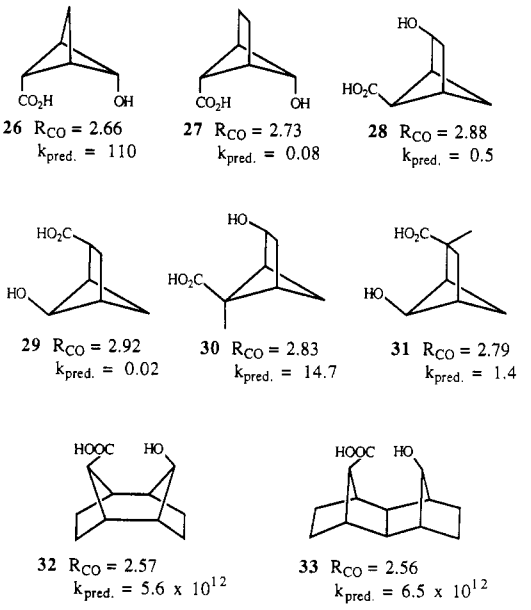


Figure 7.

than any of the compounds listed in Table II, is predicted to react at a rate that is less than or similar to that of several compounds listed therein. The results of our calculational study of acid-catalyzed lactonization reactions may be summarized as follows: (1) The relative rates of lactonization of a series of hydroxy acids can be reproduced with a simple and economical force-field model. Our calculational results support the notion that solvation effects are not an important determinant of relevant rates of lactonization[45] and that

(40) Madura, J. D.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 2517–2527.
(41) Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31–40.
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(44) Gandour, R. D. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; p 537.
(45) Bruice, T. C.; Turner, A. *J. Am. Chem. Soc.* **1970**, *92*, 3422–3428.

entropic effects are roughly similar in the series of reactants included in the study.[46] Both will have substantial effects on absolute rates, but appear not to differ much for these closely related reactions. (2) Our results indicate that breakdown of the tetrahedral intermediate is the rate-determining step of other reactions. (3) No simple relationship was found between experimental reaction rates and reactant geometries such as the distances or angles between reacting functional groups. Indeed, one would not expect such a correlation in acid-catalyzed lactonization, in which bond formation between the reacting groups does not correspond to the rate-determining step.

Conclusions. The last 25 years have witnessed the development of a plethora of theories intended to rationalize the enhanced rates of enzymatic and intramolecular reactions. Our investigations into the nature of intramolecular reactivity were designed to demonstrate that the rates of intramolecular reactions can be understood in terms of the well-established thermodynamic principles of entropy and enthalpy, combined with transition-state theory. Page and Jencks have provided a semiquantitative evaluation of the rate enhancement expected for intramolecular reactions relative to intermolecular reactions due to entropic effects (up to 10^8). Our calculations demonstrate that, in a series of reactants for which entropic effects are expected to be similar, relative reaction rates which vary over an enormous range can be reproduced by consideration of enthalpic effects alone. These differential enthalpic effects can be simply and economically evaluated by using a modified MM2 force field.

The transition structure may be profitably considered an entity with a preferred arrangement of the reacting atoms, deviations from which cost energy and slow the rate of reaction. In order to form a viable transition-state geometry involving the reacting functional groups, it may be necessary to introduce torsional or other types of strain in the connecting molecular framework. Even then it may not be possible to obtain an ideal, "strainless" arrangement of the atoms that are undergoing bonding changes.

The critical determinant of reactivity is the free energy required to convert the ground-state molecule into the corresponding transition structure. This includes contributions both from the induction, or relief, of strain in the connecting framework and from distortion away from the ideal transition-state geometry. This conclusion finds support in a recent paper in which relative rates of intramolecular hydride transfers were shown to be dependent upon the increase in strain that occurs upon conversion of the ground-state to the transition-state geometry.[47] These strain changes could be estimated in a variety of different ways.[47]

Finally, we return to the question of how enzymes catalyze chemical reactions. The energetic ground state for the substrate of a turnover catalyst is the free substrate in solution. Enzymes must reduce the free energy cost of converting ground states into transition states by stabilizing the transition states. Much of this transition-state stabilization is undoubtedly related to the gathering and orienting of reactants, which compensates for the unfavorable entropy through binding. Our investigations into the nature of intramolecular reactivity revealed little dependence of reaction rate on the detailed orientation of reacting centers in the ground state, but demonstrated instead a strong dependence on the enthalpy changes that occur as the reactant structure is converted into that of the transition state. Extension of these conclusions to enzymatic reactions suggests that the large rates of enzymatic reactions do not result from extremely precise juxtaposition of reacting atoms in the enzyme–substrate complex, but arise from an increase in stabilizing enthalpic interactions between enzyme and substrate in the corresponding reaction transition structure.[48] Intramolecular reactions are fastest when the scaffolding on which the reacting functional group is perfectly complementary to the transition state; enzyme-catalyzed reactions are fastest when the active site of the enzyme best complements the transition state of the catalyzed reaction.

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(46) Page and Jencks (ref 10c) have estimated that, for each freely rotating single bond that is frozen in a cyclic transition state, the rate decreases by a factor of 5 due to entropic effects alone. In the series of reactants included in this study, the number of "freely rotating" bonds being frozen varied over a range of 2 (rate factor 25).

(47) Sherrod, M. J.; Menger, F. M. *J. Am. Chem. Soc.* **1989**, *111*, 2611–2613.

(48) Warshel has suggested that enzymes may be viewed as "supersolvents" which are highly organized for stabilizing electrostatic interactions with transition states having a high degree of charge separation. Warshel, A. *Biochemistry* **1981**, *20*, 3167–3177.