On the Source of Intramolecular and Enzymatic Reactivity

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Intramolecular reactions often proceed much faster than their intermolecular counterparts.[1] This fact pervades the thinking of organic chemists whether they be oriented synthetically, physically, or biologically. The source of the acceleration (often several powers of ten in magnitude) is not well understood as the rather tumultuous history of intramolecularity demonstrates.

At one time, Jencks[2] believed that holding two reactants in proximity would result in a 55 maximum rate enhancement. "It is clear that the large rate constants for many intramolecular reactions, compared with their intermolecular counterparts, cannot be accounted for by a local concentration effect." Several alternate explanations were offered: steric desolvation, the overcoming of van der Waals repulsions, and the changing of orbital overlap in the ground state. Bruice,[3] on the other hand, felt that both intramolecular and enzymatic reactions owe their facility to proximity effects ("propinquity"). Koshland,[4] an advocate of the 55 figure, proposed that fast intramolecularity arises from a severe angular dependence of organic reactions ("orbital steering"). Bruice[5] attacked orbital steering on grounds that it requires unreasonably large force constants. Bruice's retort ignores, however, the role of solvent. When solvent effects are included, as in the calculations of Hoare,[6] the orbital steering concept is ostensibly upheld. Delisi and Carothers[7] used Monte Carlo methods to deduce, in support of Koshland, that "drastic changes in activity can arise from minute changes in geometry"; yet at the same time they felt that Koshland substantially underestimated entropic loss in bimolecular reactions. Jencks[2] ultimately reversed his position and was "forced to the conclusion that entropic contributions to rate accelerations in intramolecular reactions must be larger than generally believed". The "Circe effect" was born.[8] Using the entropy loss in a cyclopentadiene dimerization, Jencks estimated that the proximity factor could reach a maximum of 10^8. Koshland[4] preferred a different model reaction from that of Jencks (the coupling of bromine atoms) and arrived at a factor of only 55. Cohen,[9] in a study of lactonizations, concluded that freezing a molecule into a productive rotamer could lead to huge rate enhancements ("stereopopulation control"). Others later argued that the fast lactonizations observed by Cohen are in fact driven by relief of strain.[10] Page and Jencks[11] calculated that freezing a single rotation in an intramolecular process enhances the rate by a factor of 5; the value of 230 given by Bruice[12] was considered much too high. And here the matter rests.

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If intramolecular catalysis produced a mere 10^2-fold rate increase (typical of, for example, micellar and general-base catalyses), then one might be satisfied with current levels of understanding. But intramolecular systems often lead to accelerations of $\geq 10^8$, thus rivaling enzymes in efficiency. Obviously, chemistry must resolve the discordant views on the principles that govern intramolecular processes.

An "effective molarity" (EM) parameter has been devised to quantify intramolecularity. EM is defined as k_{intra}/k_{inter} for corresponding intramolecular and intermolecular reactions operating under identical mechanisms. Kirby's recent and scholarly compilation of EM values[13] shows that they can range from very small (<0.3 M) to very large (>10^{10} M). EM values depend critically on ring size, substituent, solvent, and reaction type.[14] No existing theory can rationalize—let alone predict—these wild fluctuations. Kirby's list of EM values represents one of the largest and most variant body of unexplained data in physical organic chemistry.

The present Account focuses on one central question: Why are certain intramolecular reactions characterized by extremely large EM values? Experimental and theoretical data of our own will be coupled with work of others in an attempt to answer this question. The goal is to clarify a situation in which the idea of the past,[2-12] wrapped in an excess of terminology, seemingly conflict and overlap at one and the same time.

Previous Notions

Over a decade ago, Koshland[15] attributed fast intramolecular and enzymatic reactions to a severe angle dependence of organic reactions. Accordingly, misalignment of two reactant groups by as little as 10°, relative to an ideal orientation, causes a 10^4 decrease in rate. Since there is a high probability of misalignment when atoms with 10° "reaction windows" collide randomly, intermolecular reactions are often slower

(1) Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45.
(2) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; p 16.
(3) Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331.
(4) Dafforn, A.; Koshland, D. E. *Proc. Natl. Acad, Sci. U.S.A.* **1971**, *68*, 2463.
(5) Bruice, T. C.; Brown, A.; Harris, D. O. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 658.
(6) Hoare, D. G. *Nature (London)* **1972**, *236*, 437.
(7) Delisi, C.; Crothers, D. M. *Biopolymers* **1973**, *12*, 1689.
(8) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219.
(9) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. Hillery, P. S.; Cohen, L. A. *J. Org. Chem.* **1983**, *48*, 3465.
(10) Karle, J. M.; Karle, I. L. *J. Am. Chem. Soc.* **1972**, *94*, 9182. Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275.
(11) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678.
(12) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.
(13) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(14) Menger, F. M. *Tetrahedron* **1983**, *39*, 1013. See Figure 10.
(15) Storm, D. R.; Koshland, D. E. *J. Am. Chem. Soc.* **1972**, *94*, 5805.

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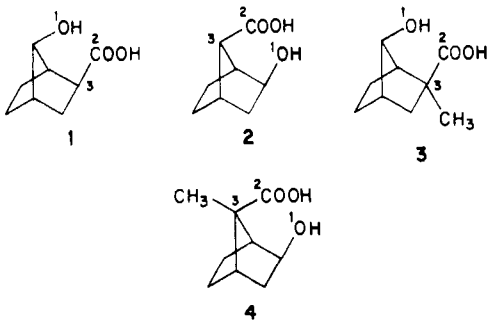
Table I
Effect of Structure on the IR and Saponification Rates of Lactones and on the Rates of Acid-Catalyzed Lactonization of Hydroxy Acids at 25.0 °C

compd	angle,[a] deg	IR, cm^{-1} (lactone)[b]	k_{OH^-}, M^{-1} min^{-1} (lactone)	k_{H^+}, M^{-1} min^{-1} (hydroxy acid)	k_{H^+} (rel)[c]
1	70	1778	45	0.0083	1
2	80	1771	7	0.01	1.2
3	76	1780	13	0.30	36
4	85	1768	1	0.18	22

[a] Represents the angle between the hydroxy oxygen, carbonyl carbon, and α-carbon as determined by force field calculations. [b] IR carbonyl stretching frequency of lactones in $CHCl_3$. [c] Relative rate of acid-catalyzed lactonization of hydroxy acids based on the column directly to the left.

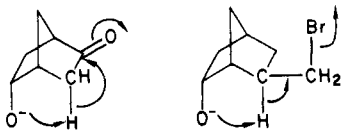
than their intramolecular counterparts where optimal orientations are imposed. Rebuttal to the Koshland idea came swift and harsh.[5] No one denied that small reactions windows could lead to large EM values; the criticism rested mainly on the contention that most functionalities *do not have* small reaction windows. Thus, simple vibrational and torsional amplitudes at room temperature exceed the kinetically significant displacements required by the Koshland model. Although the criticisms appear justified, they unfortunately relied solely on theoretical arguments. It therefore became absolutely necessary, in our view, to define reaction "angularity" with hard experimental data. If reactivity were found insensitive to angular relationships, then one would have to search elsewhere for the source of intramolecularity.

Our plan was to examine intramolecular reactivity between two functional groups held by a rigid carbon framework at well-defined angles and distances. Compounds 1–4 illustrate the approach.[16] Force field



calculations on 1 and 2 show that the compounds have similar energies (within 1 kcal/mol) and similar O_1C_2 distances (2.83 and 2.81 Å) but dissimilar $O_1C_2C_3$ trajectory angles (70° and 80°). If carbonyl additions are strongly angle dependent, then the alignment variation of 10° could produce a 10^4 difference in lactonization rates.[15] A similar rate difference would be observed for 3 and 4 whose O_1C_2 distances are both 2.69 Å but whose $O_1C_2C_3$ angles are 76° and 85°, respectively. Yet as seen from Table I, lactonization rates of 1 and 2 are almost identical, as are those of 3 and 4. Clearly, an angular displacement of 10° at constant distance is not kinetically significant. This contradicts the Koshland explanation for fast intramolecular and enzymatic reactions.

We observed an even more striking angular independence with two rigid compounds, 5 and 6, each



5 6

possessing a hydroxyl in close proximity to a mobile proton. Although intramolecular proton transfer in 5 and 6 requires severely bent $O^-/H/C$ angles of 106°, both compounds undergo such reactions rapidly. Intramolecular proton transfer, with a bent transition state, totally supersedes intermolecular competition where a linear transition state presumably dominates.[14] The point here is that angle does *not* appear to be a critical parameter in the dynamics of these and other reactions. One cannot, therefore, accept theories of intramolecularity based on a severe angle dependence.

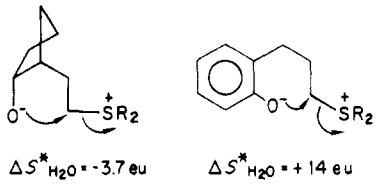
Let us now turn to an alternate view of intramolecularity, namely, that of Page and Jencks.[11] They claim that entropic factors account solely for large intramolecular rate accelerations, and they support this claim with theoretical calculations on the Diels–Alder dimerization of cyclopentadiene in the gas phase. Thus, loss of translational and rotational entropy upon forming the dimer equals −31 and −21 eu, respectively, for a total of −52 eu. In actual fact, the observed equilibrium $\Delta S°$ value lies between −31 and −39 eu. The discrepancy arises from the fact that the calculations do not include residual entropy originating from low-frequency internal motions in the dimer. A surprising amount of entropy is apparently retained even in the fairly rigid product. What does all this mean in terms of rate? If an intramolecular reaction avoided a −52 eu loss associated with the corresponding intermolecular reaction, an acceleration of about 10^{11} would result. Since compensatory internal motions in the product or transition state reduce the entropy loss of an intermolecular reaction to −35 eu, an intramolecular reaction has only a 10^8 advantage over its intermolecular counterpart. Of course, even 10^8 represents a colossal acceleration approaching that of many enzymatic catalyses. In summary, Page and Jencks believe there is nothing wonderful about an extremely fast intramolecular reaction; it is a simple entropic consequence of covalently linking two reactive entities.

Unfortunately, the preceding entropic argument does not in fact provide a highly satisfactory rationale for the difference between *inter* and *intra* reactions. Four features of the theory are particularly troublesome:

(A) If the Page–Jencks analysis is correct, then the dilemma becomes—curiously—one of understanding why intramolecular reactions are often too *slow* (i.e., why some of them display accelerations orders of magnitude less than the "expected" 10^8). One sees from Kirby's list of EM values[13] that EM can be less than unity! Page and Jencks have offered two explanations. Transition states may be unusually "loose" and, as a consequence, entropy-rich. This ostensibly reduces the advantage of intramolecular over intermolecular systems.[11] The problem is, however, that a "loose" tran-

(16) Menger, F. M.; Glass, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 5404.
(17) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996.
(18) Recent work presented in: Cotsaris, E.; Paddon-Row, M. N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1487 strongly corroborates this statement. See their "note added in proof" on p 1496.

Chart I



$\Delta S^*_{H_2O}$ = -3.7 eu $\Delta S^*_{H_2O}$ = +14 eu

sition state should be "loose" for *both* the intramolecular reaction and its intermolecular counterpart. Since EM values reflect a *comparison* between the two, residual entropic effects (as might exist in "loose" intermolecular and intramolecular general-base catalyses[19]) should cancel. The second explanation given for lower EM values relates to solvation phenomena (which are, no doubt, critical to all reactions in solution). However, "solvation" is a vague concept devoid of predictive power or testability.

(B) The Page–Jencks treatment gives rise to an important and widely quoted corollary: *Freezing a single rotation in an intramolecular process enhances the rate by a factor of only 5.* Page and Jencks state specifically that "loss or rotational entropy upon ring closure of a system containing a double bond is not significantly different from that of a saturated system which initially has one more internal rotation".[11] If there exist exceptions to the factor of 5 per frozen rotation, certainly none are mentioned. An alternate value of 230, proposed earlier by Bruice,[12] is discounted by Page and Jencks as unacceptably large. The factor of 5 has received support from a variety of sources including an article by Illuminati and Mandolini.[20] In essence, Page and Jencks conclude that intramolecularity stems from entropic differences between bimolecular and unimolecular processes and that, therefore, minor structural variations between two intramolecular systems (such as a double bond) are not kinetically significiant. The general validity of this conclusion is suspect as indicated by well-known cases where a single frozen rotation leads to a rate increase many powers of ten in size. Such cases will be examined in the next section because they hold, in my opinion, the key to the intramolecularity problem.

(C) Page–Jencks theory is further undermined by the fact that *entropies of activation exhibit absolutely no relationship to EM values and, hence, provide little insight into the source of intramolecularity.* One example of erratic entropic behavior is given in Chart I, while a table of uncorrelated entropy–EM data is presented elsewhere.[22] DeTar and Luthra[23] who evaluated quantitatively a series of S_N2 ring closures wrote, "There is no simple way to summarize the idiosyncratic contributions of individual structures to the enthalpies and entropies of activation." Bird and Stirling[24] who studied the cyclizations of ω-halogenoalkyl sulfides wrote, "Activation parameters...do not accord with any simple ideas of the factors which control rates of cyclization."

(D) Finally, mention should be made of the Dafforn–Koshland calculations[4] which resemble those of Page and Jencks except that recombination of Br· to Br_2 was used (instead of cyclopentadiene dimerization) as the model reaction. Dafforn and Koshland arrived at a theoretical EM which is 10^6 times smaller than the Page–Jencks value of 10^8 M. Page[25] claims that Dafforn and Koshland incorrectly ignored the internal rotational entropy of Br_2, a claim later denied by Dafforn and Koshland.[26] From my point of view, the severe model dependency of the entropy calculations constitutes only one of several reasons to shy away from quasi-thermodynamic rationales.

Bruice[27] referred to "proximity" in intramolecular and enzymatic reactions as the "common-sense phenomenon." Thus, when two functional groups are held near each other in an intramolecular system, but not in the corresponding intermolecular reaction, high EM values should be possible. The idea is simple and appealing. Unfortunately, it is also misleading. Proximity alone does *not* suffice to explain rapid rates as we demonstrated recently with a delightfully "low-tech" study of bimolecular S_N2 kinetics.[22] All previously published articles on S_N2 kinetics invariably employed dilute solutions of both nucleophile and electrophile. We, on the other hand, studied the S_N2 reactivity of methyl iodide (1.1 mM) dissolved in pyridine. Since pyridine served as both nucleophile and solvent, the methyl iodide was continually "bathed" in the second S_N2 component. Total proximity was assured. Moreover, dipole–dipole interactions within the solvent shell of methyl iodide would tend to place a pyridine nitrogen backside of the carbon–iodine bond[28] where it needs to be prior to bond formation. After the rate was measured in pure pyridine, we secured rates with systems in which the pyridine concentration had been reduced in stages to less than 1% by adding either *o*-dichlorobenzene or ethylene dichloride (two cosolvents having almost identical dielectric constants and $E_T(30)$ values as pyridine). From the near linearity found for plots of k_{obsd} vs. [pyridine] up to and including 100% pyridine, it is clear that total contact between methyl iodide and nucleophile imparts no special proximity effect. Similar results were obtained with the S_N2 reaction of triethylamine in 100% ethyl iodide[22] and with the elimination reaction of 4-(4-nitrophenoxy)-2-butanone in 100% piperidine.[22] In no case is there enchanced reactivity ascribable to continuous proximity.

One could, of course, claim that our S_N2 kinetics are predictable; that fast reactions are found only when proximity is coupled to favorable orientation ("orbital steering").[15] But we have argued at great length here and elsewhere[14] that angular alignment is *not* critical to many reactions. For example, Lipscomb and coworkers[29] have described a carbonyl addition in which *one-third* of a hemispherical surface centered at the carbonyl carbon is occupied by the "reaction funnel" for addition. As already mentioned, we have shown experimentally that proton transfers are insensitive to large departures from linearity. Our "substrate–solvent"

(19) Kirby, A. J.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1753.
(20) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(21) Knipe, J. O.; Coward, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4339.
(22) Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.*, in press.
(23) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505.
(24) Bird, R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1221.
(25) Page, M. I. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 940.
(26) Dafforn, A.; Koshland, D. E. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 779.
(27) Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331.
(28) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811.
(29) Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770.

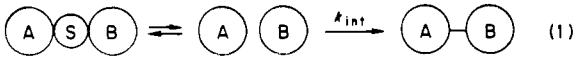
reactions are slow, therefore, *not* because of unsuitable orbital orientations among juxtaposed molecules. Instead, it appears that the reactants do not attain, despite their proximity, optimal time and distance relationships (discussed in detail below). Thus, "proximity" is a necessary but deficient component of reactivity.

In view of the difficulties with the angularity, entropy, and proximity concepts, it became necessary to develop another approach to intramolecularity. The remainder of this account deals with such an approach.

The Postulate

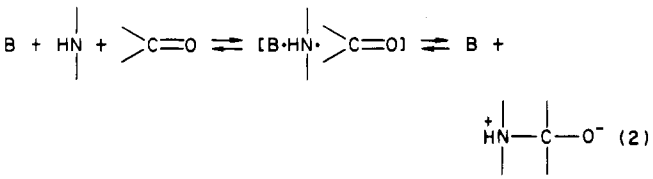
A simple postulate forms the basis of the ensuing discussion: *The rate of reaction between functionalities A and B is proportional to the time that A and B reside within a critical distance.* This postulate requires a number of explanatory comments: (1) *Time* and *distance* constitute the key components of reactivity. These fluents (as Newton called them) are embodied only obliquely in the aforementioned theories of intramolecularity. Although time is indeed related to entropy, there exist a number of obvious distinctions. The most important of these relates to the possibility of keeping time a constant by attaching A and B to rigid carbon frameworks. Entropy, on the other hand, remains an uncontrollable and intractable parameter for most reactions in solution. (2) Whereas the A/B distance is critical, angular latitude can be quite extensive (as our experiments demonstrated[14,16,17]) so that precise orientation is not a requirement for fast reactions. (3) The magnitudes of the time/distance parameters are reaction dependent and, consequently, are not specified in the postulate. More will be said about the nature of the distance variable in the next section. (4) The postulate provides nothing new or unusual. Since it takes more energy to stretch a bond than bend one, the emphasis on distance rather than angle should arouse no surprise. Others have, on occasion, proposed time as an element of reactivity.[30,31]

Our "spatiotemporal postulate" can also be viewed in terms of an equilibrium formalism (eq 1). Sol-



(1)

vent-separated A and B generate a complex in which the components reside at a critical distance. Product is formed in a second step characterized by an *intrinsic rate constant*, k_{int}. Again, a number of amplifying comments are necessary: (1) Preassociation mechanisms are reasonable in that they have been detected in carbonyl additions (eq 2),[32] nucleophilic aromatic



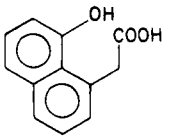
(2)

substitutions,[33] electrophilic aromatic substitutions,[34] Diels–Alder additions,[35] free radical chlorinations[36] etc. Indeed, all bimolecular reactions (even S_N2 substitutions) probably involve preassociation whether or not the complexes have as yet been detected experimentally. (2) Recent and important work of Benesi[37,38] is consistent with eq 1 in that the observed rate constant is assumed to equal the local steady-state concentration of B at the "reactive spot" of A multiplied by an intrinsic rate constant. Benesi finds that "molecules do not have to be separated very far or for very long to get lost". If A and B within a complex "take a walk" longer than 1.37 times the sum of their radii, they escape each other forever. (3) In a statistical treatment of intramolecular reactions, Sisido[39] obtained reasonable agreement with experiment by assuming that the rate constant is proportional to the number of A/B pairs in which the A/B separation is less than 2.3–2.7 Å.

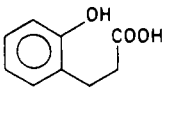
Let us now briefly discuss our postulate in terms of energy. Pritchard,[40] Polanyi,[41] and others proposed long ago that reactions take place via vibrational, not translational, activation. This means that reaction between A and B within a complex will take place the moment the complex acquires sufficient vibrational energy to surmount the intrinsic rate barrier.[30] The longer the time that A and B spend poised in a position to react, the greater the probability of thermal activation, the faster the rate. As will be shown below, large accelerations (EM > 10^6 M) occur when anchoring of A and B to a carbon framework (or to an active site of an enzyme) prevents A and B from "taking a walk" beyond the critical bonding distance. Considerable emphasis will be placed on defining the term "bonding distance".

Examples

Introducing a frozen rotation into an arylpropionic acid enhances the EM for lactonization in **7** and **8** by 10^4. Note the shear size of the rate effect (far ex-



7
EM = 5 x 10^8 M



8
EM = 4 x 10^4 M

ceeding, for example, the acceleration associated with σ participation in norbornyl systems). Note also the disparity between the observed value of 10^4 and the theoretical value of 5 per frozen rotation calculated by Page and Jencks.[11] Electronic effects are an unsuitable explanation because the carbonyls are in both cases insulated from the aromatic rings by a saturated linkage; the phenolic hydroxyl should, if anything, be *more* nucleophilic than the naphtholic hydroxyl. Relief of strain ("steric compression") likewise fails to provide a satisfactory explanation for the 10^4-fold enhancement. Compound **7** possesses a free rotation and, in the words of Page and Jencks,[11] "The presence of one or more free rotations ensures that a reacting group can move out of an unfavorable conformation so that the fraction of starting material in the high-energy, strained or desolvated form will be negligible."

(30) Firestone, R. A.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 389.
(31) Reuben, J. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 563.
(32) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.
(33) Ainscough, J. B.; Caldin, E. F. *J. Chem. Soc.* **1956**, 2528.
(34) Gold, V.; Satchell, D. P. N. *J. Chem. Soc.* **1955**, 3609.
(35) Berson, J. A.; Reynolds, R. D. *J. Am. Chem. Soc.* **1955**, *77*, 4434.
(36) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 2977.
(37) Benesi, A. J. *J. Phys. Chem.* **1982**, *86*, 4926.
(38) Benesi, A. J. *J. Phys. Chem.* **1984**, *88*, 4729.
(39) Sisido, M. *Macromolecules* **1971**, *4*, 737.
(40) Pritchard, H. O. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 779.
(41) Mok, M. H.; Polanyi, J. C. *J. Chem. Phys.* **1969**, *51*, 1451.

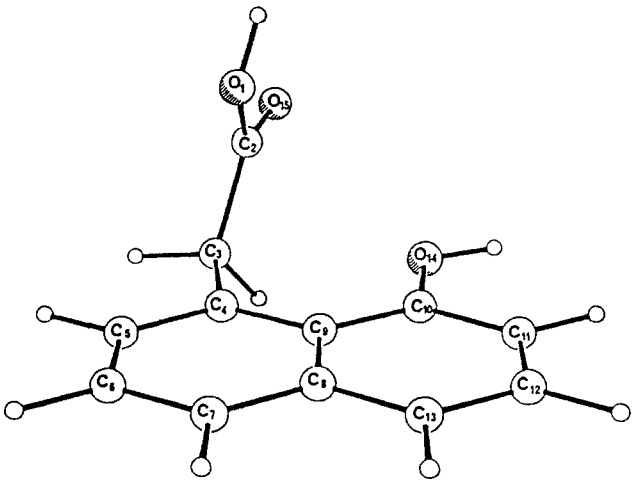


Figure 1. Minimum-energy conformation of compound **7**. The O_{14}–C_2 distance equals 2.78 Å, and the O_{14}–C_2–O_1 angle equals 97°.

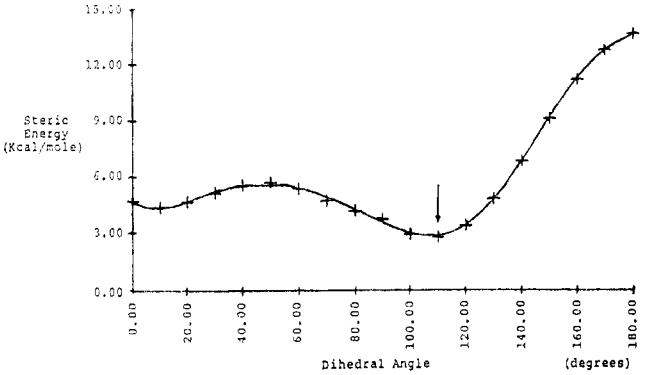


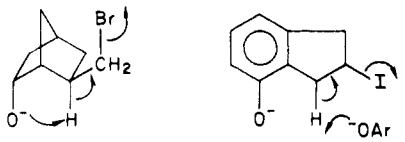
Figure 2. Steric energy of **7** as a function of the C_2–C_3–C_4–C_5 dihedral angle (see Figure 1 for numbering system). The value of 180° represents the conformer having C_2 in the plane of the aromatic ring near O_{14}. The arrow points to the conformer pictured in Figure 1.

A clue to the possible source of the 10^4 acceleration comes from MM2 dihedral driver calculations carried out by Dr. Graham Whitesell of this department. He found that the lowest energy conformation of **7** has the structure, geometric parameters, and energy relations shown in Figures 1 and 2. The hydroxy group (situated near the local mirror place containing the π-orbital of the carbonyl) lies only 2.78 Å from the carbonyl carbon. This distance approximates (a) the lower limit found for intermolecular HO/C=O contacts in the crystalline state,[42] (b) the sum of the van der Waals radii for the two groups, (c) the presumed "critical distance" cited in our postulate. Thus, the enzyme-like acceleration for cyclization of **7** stems from the two groups being held at an interactive distance within a potential well. In contrast, compound **8** was shown to lie in a potential well where the HO/C=O distance equals 4.3 Å (greatly exceeding the critical distance and sufficiently long to allow an intervening water molecule). Conformers **8** with separations less than 4.3 Å have only transient existences, and the rate of ring closure diminishes 10^4-fold.

The extra frozen rotation in **7** relative to **8** leads to a rate enhancement 10^3 times greater than that predicted by Page and Jencks.[11] Although never stated as such by Page and Jencks, their rate factor of 5 per frozen rotation seemingly applies *only* to flexible system (e.g., precursors of large rings) where locking a single rotation has no substantial effect on the distance and residence times. Too much floppiness remains. If, on the other hand, the frozen rotation enforces a critical distance upon two functionalities A and B, then enormous accelerations are possible. This is not a "strain mechanism" in the classical sense because the critical distance often approximates the sum of the van der Waals radii. Enforced proximity does, of course, prevent A and B from having an intervening solvent molecule, a factor which no doubt markedly accelerates the ensuing rate step (k_{int} in eq 1). Note in this regard that the potential energy surface for a *gas-phase* S_N2 reaction has all its points *below* the energy level of the reactants.[43]

It is legitimate to ask, "How sharply defined is the critical distance?" I do not know the answer to this question (and there is no point apologizing for my ignorance every time it surfaces). One *can* say this however: There are growing indications that reaction rate is strongly associated with small changes in distance. A prime example comes from 4-31G calculations of Scheiner[44] on proton transfer from hydronium ion to water. He finds that the barrier to proton transfer equals 1.4, 7.5, and 16.8 kcal/mol for O–O distances of 2.55, 2.75, and 2.95 Å, respectively. In other words, decreasing the O–O distance from 2.75 to 2.55 Å increases the rate 10^4-fold. And decreasing the separation from 2.95 to 2.55 Å increases the rate 10^{11}-fold!

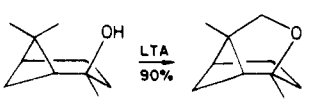
Our experimental work[17] supports the general conclusions derived from Scheiner's calculations. Compounds **9** and **10** both undergo E2 elimination. Yet **9** (with an O–H distance of 2.2 Å) does so exclusively in an intramolecular fashion, whereas **10** (with an O–H distance of 2.9 Å) reacts by an intermolecular mechanism. Apparently, 2.9 Å (but not 2.2 Å) exceeds the distance necessary for an efficient intramolecular proton transfer in these systems.



	9	10
O^-–H distance:	2.2 Å	2.9 Å
reaction mode:	intramolecular	intermolecular

Paddon-Row[18] recently determined the kinetics of intramolecular proton transfer from a hydroxyl to anion radicals generated by Birch reduction of olefins. As shown in Chart II, the efficacy of the reaction depends markedly on the distance between the proton and the olefinic carbon.[45]

Distance can also have a decisive effect on hydrogen transfer to alkoxy radicals as seen with alcohols **11** and **12** where the O/δ-C distances are 2.3 and 2.9 Å, re-



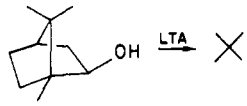
11

(42) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *Acta Crystallogr., Sect. B* **1974**, *B30*, 1517.

(43) Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672.

(44) Scheiner, S. *J. Am. Chem. Soc.* **1981**, *103*, 315.

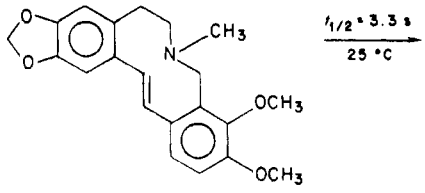
(45) Angular relationships, which also differ among the compounds, should have (as already pointed out) much less impact on the kinetics than the distances.



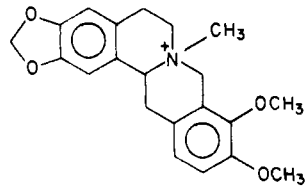
12

spectively.[46] Only the oxygen radical corresponding to **11** (generated with lead tetraacetate) is capable of intramolecular hydrogen transfer. Brun and Waegell[46] claim outright that hydrogen transfer does not occur when the distance exceeds 2.8 Å, but more experimentation is required to test this assertion.

Spectacular rate effects are observed when a molecular framework holds two groups at bonding distances. Kirby[47] found, for example, that juxtapositioning an amino group and a carbon–carbon double bond in **13**



13



leads to rapid addition; no electron-withdrawing substituent on the double bond is required. Although the EM value cannot be measured accurately (the corresponding intermolecular reaction is too slow), the EM certainly exceeds 10^8 M. Even a relatively small degree of mobility in an intramolecular amino olefin (as in **14**)

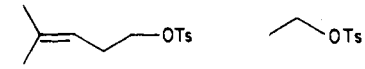
14

permits the groups to "take a walk" and escape contact. This has a highly deleterious effect on the rate (an effect not incorporated in Page–Jencks theory[11]). In terms of my postulate, the amino group and double bond must spend sufficient *time* at a bonding *distance* to ensure enzyme-like rates.

The benefit of confining one functional group inside the "reaction window"[14] of another is no better illustrated than by the work of Winstein et al.[48] who found an anchimeric assistance worth 10^{11} in a 7-norbornenyl derivative, **15**. Compare this value to the 10^2-fold ac-

15 $k_{rel} = 10^{11}$ $k_{rel} = 1$

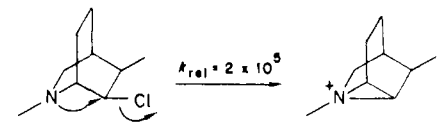
celeration associated with homallylic participation in



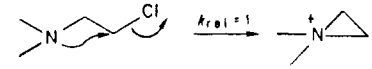
16 $k_{rel} = 10^2$ $k_{rel} = 1$

16. According to our MM2 calculations, the *gain* in "inherent strain" upon forming a tricyclene is *greater* than that for a simple three-membered ring. Therefore, the 10^9 difference between **15** and **16** cannot be attributed to steric compression. Enforced residency at a bonding distance seems like the most viable explanation for a large portion of the 10^9 rate improvement.

The huge rate effect created when a molecular framework holds two reactive groups at bonding distances was beautifully demonstrated by work of Hutchins and Rua.[49] They found that an azabicyclic chloride **17** solvolyzes in aqueous ethanol 2×10^5 times faster than an acyclic analogue **18**. If one adjusts for



17



18

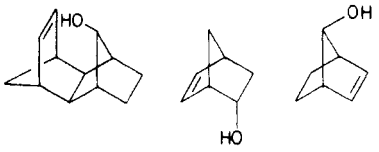
the fact that **17** is a secondary halide (inherently less reactive toward displacement than a primary one) and for the relative strain enhancements as the transition states are formed, then the 2×10^5-fold rate difference enlarges even further. Since the nitrogen in **17** is held rigidly antiperiplanar to the departing chloride for an infinite time period, the conditions for a fast reaction (as delineated in my postulate) are met. An enzyme-like rate ensues.

To summarize briefly the main points thus far: I have (a) postulated that the rate of reaction between functionalities A and B is proportional to the time that A and B reside within a critical distance, (b) presented evidence that the postulate is reasonable, (c) provided information on the magnitudes of the critical distances, and (d) cited examples of intramolecular reactions attaining enzyme-like rates when a critical distance is imposed on A and B.

Obviously, we need to know more about the nature of the distance parameter for organic reactions in solution. Such information is best obtained by studying a series of rigid molecules possessing identical pairs of intramolecularly reactive groups at gradually increasing distances. But such an approach (utilized by Paddon–Row[18] and ourselves[14]) is a costly proposition. The compounds generally require fairly lengthy syntheses; stereochemical control is essential because the two functional groups on the rigid framework must "point" toward one another; and each such synthesis provides only a single rate constant. Small wonder that organic chemists know little about the spatial requirements of their reactions! This does not mean, however, that the "spatiotemporal hypothesis" is untestable and thus useless. Given the willingness to construct elaborate molecules with subtle variations in geometric relationships between interactive substituents, the intramo-

(46) Brun, P.; Waegell, B. In "Reactive Intermediates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, p 378.
(47) Kirby, A. J.; Logan, C. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 642.
(48) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.
(49) Hutchins, R. O.; Rua, L. *J. Org. Chem.* **1975**, *40*, 2567.

Chart II



C-H distance:	1.8 Å	2.2 Å	2.5 Å
EM:	2.3×10^4 M	35 M	0.85 M

lecularity problem is solvable.

Enzymes

Consider chymotrypsin, an enzyme which hydrolyzes amides with a 10^8 acceleration.[50] Now if there is one perplexing feature of this enzyme, it is the strikingly *dull* structure of its active site. The only catalytic groups present are a poor nucleophile (the serine hydroxyl) and a notoriously weak general base (the imidazole ring).[51] Why does this unimposing duo ravage amides so effectively? The answer seems simple if the behavior of the organic systems mentioned in the previous section is any guide: Chymotrypsin holds its catalytic groups and the amide carbonyl at bonding distances; this, plus a small general-base catalysis, more than suffices to explain the 10^8 acceleration. Work of Gerig and Reinheimer[52] agrees with this picture; they found that chymotrypsin binds cinnamic acid tightly enough so that "it does not have any freedom of motion independent of the motion of the enzyme". The construct is also consistent with the $>10^8$ rate increase observed in Winstein's norbornenyl tosylate (**15**). The main difference between the source of reactivity in **15** and that at an active site lies in the nature of the forces constraining the functional groups prior to reception of vibrational energy. In one case, the forces are covalent; in the other, noncovalent.

Holding two functionalities at a bonding distance requires energy, the largest portion of which relates to the need for "extruding" solvent. From where does this energy come? Clearly, there is only one source: binding energy. Stated in another way, the association constant between the enzyme and substrate is in actuality *smaller* than it would be if functional group proximity were not enforced upon the system. But once the critical distances are secured, the ensuing rate step can be extremely fast. *This, above all, is the lesson that organic chemistry gives to enzymology.* Alternative enzyme mechanism (electrostatic stabilization,[53] rack effects,[54] transition-state stabilization,[55] etc.) are intriguing but unnecessary.

This work was supported by the National Institutes of Health and the Army Research Office. The author would also like to thank Dr. George Hammond for provocative discussions. It was he who wisely advised, "Do not argue the physical truth; argue only as to whose model is the better aid to thinking."

(50) Bender, M. L.; Kézdy, F. J.; Gunter, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 3714.
(51) An aspartate carboxyl is also near the active site, but its role in catalysis is uncertain. The main purpose may be to preclude the rotational freedom of the imidazole ring.
(52) Gerig, J. T.; Reinheimer, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 3146.
(53) Warshel, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5250.
(54) Reference 2, p 282.
(55) Pauling, L. *Nature (London)* **1948**, *161*, 707.

Chemical Aspects of UV-Induced Cross-Linking of Proteins to Nucleic Acids. Photoreactions with Lysine and Tryptophan

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UV irradiation is known to have profound effects on a number of cellular functions. Until recently, photobiology has been primarily concerned with the photochemistry of pure DNA. However, as DNA does not exist in a cell in pure solution but in intimate contact with proteins and other biomolecules, it is conceivable that DNA–protein cross-links induced by UV light are important contributors to the deleterious effects of UV light on cells. Since the reports of Smith[1] and Alexander and Moroson[2] in the early 1960s showing that UV light induces cross-linking of proteins to DNA in living systems, there has been a substantial amount of evidence indicating that DNA–protein cross-linking is a major cause of UV-induced damage in biological systems.[3] The importance of these cross-links in aging, carcinogenesis, and radiation biology has been reviewed.[4] The tendency of proteins and nucleic acids to form specific covalent adducts as a result of UV irradiation is also used as a valuable tool for probing structural aspects of native protein–nucleic acid com-

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(1) Smith, K. C. *Biochem. Biophys. Res. Commun.* **1962**, *8*, 157.
(2) Alexander, P.; Moroson, H. L. *Nature (London)* **1962**, *194*, 882.
(3) For reviews: (a) Shetlar, M. D. *Photochem. Photobiol. Rev.* **1980**, *5*, 105. (b) Kornhauser, A. *Photochem. Photobiol.* **1975**, *23*, 457. (c) Smith, K. C. *Photochem. Photobiol. Nucleic Acids* **1976**, *2*, 187.
(4) Smith, K. C. Ed. "Aging, Carcinogenesis and Radiation Biology: The Role of Nucleic Acid Addition Reactions"; Plenum Press, New York, 1976.

0001-4842/85/0118-0134$01.50/0