yield 0.82 g, 2.1 mmol (81%), of colorless solid.

22a: ^{31}P NMR (C_6D_6) δ 38.2; ^1H NMR (C_6D_6) δ 0.45 (t, 3 H, CH_3-CH_2-); 0.8 (m, 4 H, CH_2 (butyl)), 1.6 (m, 2 H, PCH_2), 1.73 (d, ^4J(H-P) = 2.3 Hz, 3 H, CH_3), 6.8-7.8 (m, 15 H, Ph); ^{13}C NMR (C_6D_6) δ 14.00 (s, CH_3), 24.36 (d, ^3J(C-P) = 17.1 Hz, C-CH_3), 24.78 (s, CH_2 (butyl)), 26.51 (d, ^2J(C-P) = 11.0 Hz, CH_2), 35.32 (d, ^1J(C-P) = 58.6 Hz, PCH_2), 136.65 (d, ^1J(C-P) = 76.9 Hz, C), 139.71 (d, J(C-P) = 9.8 Hz, C), 142.65 (d, J(C-P) = 6.1 Hz, C), 151.67 (d, J(C-P) = 6.1 Hz, C); mass spectrum (chemical ionization) m/e (relative intensity) 391 (M + 1, 100). Anal. Calcd for $C_{25}H_{27}PS$: C, 76.89; H, 6.97; P, 7.93; S, 8.21. Found: C, 76.67; H, 7.12; P, 7.71; S, 8.24.

(2-(*p*-Chlorophenylhydroxymethyl)-1,2-diphenylvinyl)-*n*-butylphenylphosphine Sulfide (23a,b). 1,2,3-Triphenylphosphirene (0.6 g, 2.4 mmol) in THF (30 mL) was cooled to -70 °C and treated with *n*-butyllithium (1.8 mL, 2.9 mmol). After 15 min, *p*-chlorobenzaldehyde (0.41 g, 2.9 mmol) was added. After 15 min at -70 °C, the mixture was hydrolyzed (δ ^{31}P -26.62 and -29.33) and then reacted with sulfur at room temperature. The solvent was evaporated and the products purified by chromatography with ethyl acetate. **23b** (R_f ~0.5) and **23a** (R_f ~0.4) were recovered. Yield 0.86 g, 1.7 mmol (71%). Pure **23a** was obtained by crystallization in THF: mp 221 °C; colorless solid; ^{31}P NMR (THF) δ 43.38; IR (KBr) ν(OH) 3380 cm^{-1}; mass spectrum (chemical ionization) (^{35}Cl) m/e (relative intensity) 517 (M + 1, 75), 199 (100). Anal. Calcd for $C_{31}H_{30}OPSCl$: C, 72.01; H, 5.85; S, 6.20; Cl, 6.86. Found: C, 71.36; H, 5.81; S, 6.07; Cl, 6.99.

Cleavage of 14 by Naphthalene-Sodium. 1,2,3-Triphenylphosphirene (**14**) (0.75 g, 2.6 mmol) was added to a solution of 1:1 naphthalene-sodium radical anion (5.8 mmol) in THF at -70 °C. After 10 min, iodomethane (0.33 mL, 5.3 mmol) was added. The mixture was hydrolyzed and reacted with sulfur at room temperature. The solvent was removed by evaporation. The residue was chromatographed with hexane-ether (93:7). Yield of **26** (R_f ~0.3) was 0.28 g, 0.8 mmol (31%); **25** (R_f ~0.2), yield 0.3 g, 0.9 mmol (34%).

25: colorless solid; mp 98 °C (THF-hexane); ^{31}P NMR (C_6D_6) δ 36.3; ^1H NMR (C_6D_6) δ 1.67 (d, ^2J(H-P) = 13.2 Hz, 3 H, PCH_3), 6.8-7.8 (m, 15 H, Ph), 8.14 (d, ^3J(H-P) = 24.2 Hz, 1 H, CHPh); mass spectrum (chemical ionization) m/e (relative intensity) 335 (M + 1, 100). Anal. Calcd for $C_{21}H_{19}PS$: C, 75.42; H, 5.73; S, 9.59. Found: C, 75.67; H, 5.96; S, 9.60.

26: colorless solid; mp 111 °C (THF-hexane); ^{31}P NMR. (toluene) δ 32.8; ^1H NMR (C_6D_6) δ 1.25 (d, ^2J(H-P) = 12.7 Hz, 3 H, PCH_3), 1.71 (d, ^4J(H-P) = 2.4 Hz, 3 H, CH_3-C-Ph), 6.9-7.8 (m, 15 H, Ph); ^{13}C NMR. (C_6D_6) δ 24.93 (d, ^1J(C-P) = 62.3 Hz, PCH_3), 26.26 (d, ^3J(C-P) = 8.5 Hz, C-CH_3), 136.59 (d, J(C-P) = 76.9 Hz, C), 139.50 (d, J(C-P) = 11.0 Hz, C), 142.49 (d, J(C-P) = 7.3 Hz, C), 151.22 (d, J(C-P) = 7.3 Hz, C); mass spectrum (chemical ionization) m/e (relative intensity) 349 (M + 1, 100).

Registry No. 1, 74363-95-4; **2**, 82265-68-7; **3**, 64439-05-0; **4**, 90635-58-8; **5**, 83603-06-9; **6**, 96826-84-5; **7**, 96826-85-6; **8**, 96826-86-7; **9a**, 96826-87-8; **9b**, 96894-22-3; **10**, 82265-69-8; **11a**, 96826-88-9; **11b**, 96894-23-4; **12**, 96826-89-0; **12a**, 96826-90-3; **12b**, 96894-24-5; **13**, 96845-00-0; **14**, 90633-10-6; **15**, 96845-02-2; **16**, 96845-03-3; **17**, 96826-92-5; **19**, 90633-11-7; **21a**, 96826-93-6; **21b**, 96845-04-4; **22a**, 96845-05-5; **22b**, 96845-06-6; **23a**, 96845-07-7; **23b**, 96845-08-8; **25**, 96845-09-9; **26**, 96845-10-2; dimethyl acetylenedicarboxylate, 762-42-5; diphenylacetylene, 501-65-5; ethyl phenylpropiolate, 2216-94-6; morpholine, 110-91-8; dimethylbutadiene, 513-81-5; trimethyloxonium tetrafluoroborate, 420-37-1; 1:1 naphthalene sodium radical anion, 3481-12-7; 1,3-cyclohexadiene, 592-57-4; copper chloride, 7758-89-6.

Proximity as a Component of Organic Reactivity

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Abstract: Neither the S_N2 reaction of methyl iodide in 100% pyridine, nor the S_N2 reaction of triethylamine in 100% ethyl iodide, nor the elimination reaction of 4-(4-nitrophenoxy)-2-butanone in 100% piperidine displays special reactivity ascribable to the continuous bimolecular contact. It is concluded that proximity, by itself, cannot explain the fast rates characteristic of many intramolecular reactions. Two parameters, time and distance, must be incorporated into the proximity concept to make it viable.

This article addresses a question that has not yet been experimentally answered: What is the kinetic effect on a bimolecular reaction A + B → C when A is totally surrounded by B (i.e., when reactant B serves as the solvent in which solute A cannot escape contact)? Obviously, the literature describes a multitude of solvolyses in water, acetic acid, etc., where the solvent participates as one of the reactants. But the role of "total contact" (if any) has not been determined because it is impossible to reduce the concentration of a protic solvent without concurrently changing the properties of the medium. For example, a comparison of reactions in pure water with those in 0.5 M water/acetonitrile would likely entail large solvent effects that obscure all other phenomena. We have now completed a series of experiments involving bimolecular substitutions and eliminations in which the reactant-solvent is *aprotic*. Dilution of this component was then carried out, with minimal perturbations to the medium, using inert aprotic solvents of almost identical polarity. Thus, bimolecular proximity could, for the first time, be rigorously assessed.

Results and Discussion

In all previously published articles on S_N2 kinetics, low levels of both nucleophile and electrophile were invariably added to a particular solvent. We, on the other hand, studied the S_N2 reactivity of methyl iodide (1.1×10^{-3} M) dissolved in pyridine. Since pyridine served as both the nucleophile and solvent, the methyl iodide is continually "bathed" in the second S_N2 component. Moreover, dipole-dipole interactions within the solvent shell of methyl iodide would tend to place a pyridine nitrogen backside of the carbon-iodine bond[1] (where it needs to be prior to bond formation).

Formation of the *N*-methylpyridinium iodide charge-transfer band was followed at 370 nm to obtain a $k_{obsd} = 3.6 \times 10^{-3}$ s^{-1} at 25.0 ± 0.1 °C in 100% pyridine. We then obtained rate constants with systems where the pyridine concentration had been reduced stepwise to less than 1% by adding either *o*-dichlorobenzene or ethylene dichloride. In this manner we could reduce the "proximity" of methyl iodide to the pyridine. Medium effects on the rate were not a concern for several reasons. (1) The cosolvents were selected because their dielectric constants and $E_T(30)$ values[2] resemble closely those of pyridine (i.e., *o*-dichlorobenzene, 9.9 and 38; ethylene dichloride, 10.4 and 42; pyridine, 12.4 and 40). (2) We used both an aromatic and ali-

(1) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811.
(2) Reichardt, C. "Solvent Effects in Organic Chemistry"; Verlag Chemie, New York, 1979; pp 270-272.

0002-7863/85/1507-4706$01.50/0

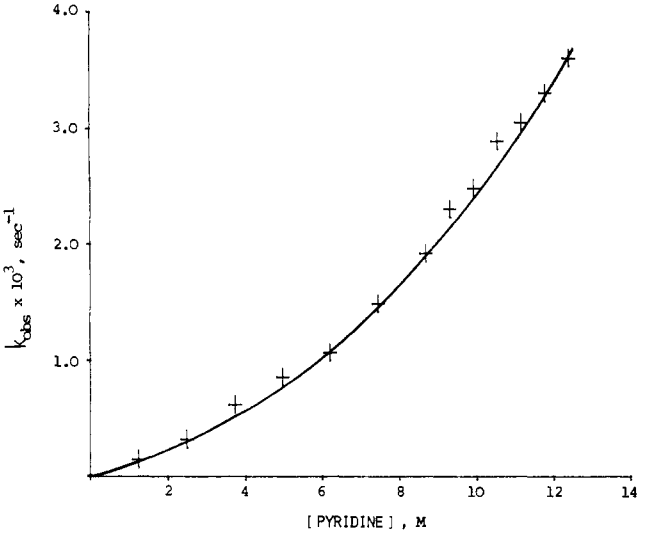


Figure 1. The observed rate at 25.0 °C of the S_N2 reaction between pyridine and 1.1×10^{-3} M methyl iodide dissolved in various pyridine/*o*-dichlorobenzene mixtures plotted as a function of pyridine concentration.

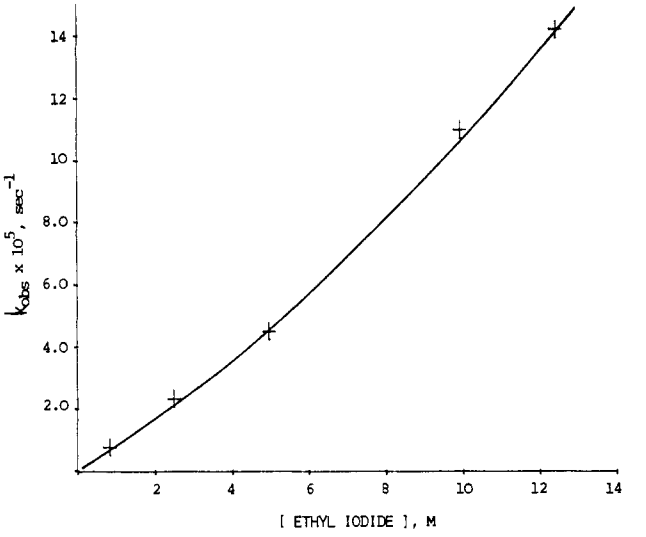


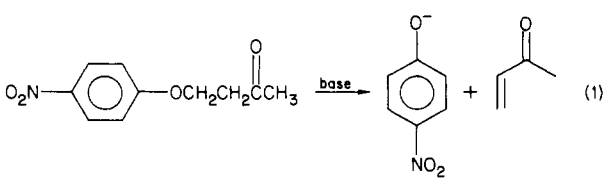
Figure 2. The observed rate at 25.0 °C of the S_N2 reaction between ethyl iodide and 6.6×10^{-2} M triethylamine dissolved in various ethyl iodide/tetrahydrofuran mixtures plotted as a function of ethyl iodide concentration.

phatic cosolvent to minimize the possibility of specific solvation and solvent-sorting effects. (3) The reaction between methyl iodide and pyridine responds only modestly to solvent changes (e.g., k_{rel} = 1.0, 2.0, and 29 in benzene, ethanol, and nitrobenzene).[3]

A plot of k_{obsd} vs. [pyridine] is shown in Figure 1. From the gentle concavity of the graph, it is clear that "bathing" methyl iodide in nucleophile up to and including 100% pyridine (equivalent to 12.4 M) imparts no special proximity effect. Since the calculated second-order rate constant at 100% pyridine differs from that at 10% pyridine by less than threefold, no significant enhancement is achieved by total nucleophile–electrophile contact.

This conclusion is supported by another series of experiments in which a nucleophile (triethylamine) was added to a solvent composed totally of electrophile (ethyl iodide). The rate of the subsequent S_N2 substitution was then determined titrimetrically. Contact between the triethylamine and ethyl iodide was reduced by adding either chlorobenzene or tetrahydrofuran, solvents with $E_T(30)$ values almost identical with those of ethyl iodide[2] (i.e., chlorobenzene, 37.5; tetrahydrofuran, 37.4; ethyl iodide, 36.5). Again, plots of k_{obsd} vs. [ethyl iodide] are almost linear up to and including 100% ethyl iodide (Figure 2); there is no dramatic upswing in rate near 100% ethyl iodide as might be expected if intermolecular proximity, by itself, were a special component of reactivity.

Since S_N2 reactions have a fairly strict angle requirement,[4] the proper angular relationship between nucleophile and electrophile might be rarely achieved even when the solvent is composed entirely of nucleophile. Hence the observed proximity effect is small. This possibility prompted us to examine a base-induced proton abstraction from 4-(4-nitrophenoxy)-2-butanone (eq 1).[5]



The elimination reaction was chosen because proton transfer is known to have a particularly broad reaction window.[6] For example, we have observed a fast C–H to B proton transfer even when the C/H/B angle departs 74° from linearity.[7] Equation 1 thus permits us to examine proximity in a reaction where angular orientation is not critical. After a small amount of ketone (3.8×10^{-5} M) was added to 100% piperidine, the rate of *p*-nitrophenolate production was measured spectrophotometrically at 393 nm as a function of time. The resulting second-order rate constant ($k_2 = 5.3 \times 10^{-3}$ M^{-1} s^{-1} at 25.0 ± 0.1 °C) was then compared with those from systems containing various amounts of cosolvent (chlorobenzene, tetrahydrofuran, or ethyl acetate). As before, no substantial proximity effect is evident (Table I). When a rate study was carried out with low levels of piperidine (0.1–0.3 M) in chlorobenzene, we obtained clean second-order kinetics with a $k = 4.4 \times 10^{-4}$ M^{-1} s^{-1}. This k_2 differs from that based on 100% piperidine by a factor of only 12 (orders of magnitude less than proximity-induced accelerations in many intramolecular systems).[8,9] The conclusion is inescapable: proximity effects manifest themselves in intramolecular reactions but *not* intermolecular reactions.

Table I. Second-Order Rate Constants for the Elimination Reaction of 3.8×10^{-5} M 4-(4-Nitrophenoxy)-2-butanone in Mixtures of Piperidine and Chlorobenzene, Ethyl Acetate, or Tetrahydrofuran at 25.0 °C[a,b]

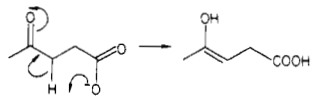
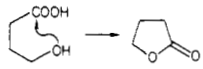
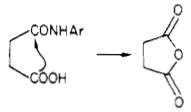
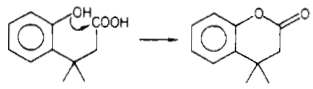
% piperidine, v/v	[piperidine], M	$k_2 \times 10^3$, M^{-1} s^{-1}		
		chlorobenzene	ethyl acetate	THF
10	1.0	1.0	0.54	0.49
20	2.0	1.4		
30	3.0	2.1	1.2	0.99
40	4.0	2.4		
50	5.1	3.2	1.6	1.9
60	6.1	3.3		
70	7.1	3.6	2.9	2.7
80	8.1	4.6		
90	9.1	5.0	3.6	4.2
100	10.1	5.3	5.3	5.3

[a] The elimination was shown to be cleanly second order in chlorobenzene containing 9.8×10^{-2} to 0.29 M piperidine. [b] The $E_T(30)$ values of piperidine, chlorobenzene, ethyl acetate, and THF are 35.5, 37.5, 38.1, and 37.4, respectively.

Differences between intramolecular and intermolecular reactivity, demonstrated in our experiments, were treated theoretically by Page and Jencks.[10] It is worthwhile to review here

(3) Leffek, K. T.; Matheson, A. F. *Can. J. Chem.* **1972**, *50*, 982.
(4) Mihel, I.; Knipe, J. O.; Coward, J. K.; Schowen, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 4349.
(5) Pohl, E. R.; Hupe, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8130.
(6) Menger, F. M. *Tetrahedron* **1983**, *39*, 1013.
(7) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996.
(8) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(9) Bruice, T. C. *Annu, Rev. Biochem.* **1976**, *45*, 331.

Table II. Variations in Effective Molarities for Several Intramolecular Reactions[a]

reaction	EM,[b] M
	0.1
	88
	5.1×10^4
	1.9×10^8

[a] Data taken from ref 8. [b] EM = "effective molarity" = k_{intra}/k_{inter}.

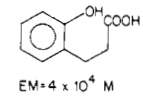
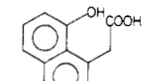
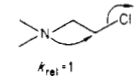
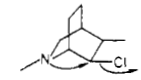
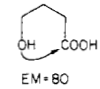
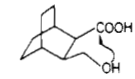
the essence of their calculations on the Diels–Alder dimerization of cyclopentadiene in the gas phase. Loss of translational and rotational entropy upon forming the dimer equals -31 and -21 eu, respectively, for a total of -52 eu. In actual fact, the observed equilibrium $\Delta S°$ value lies between -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 *not* lost 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 for 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. Thus, 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 Table II that "effective molarities" or "EM values", where EM = k_{intra}/k_{inter} in units of molarity, can equal less than unity! Page and Jencks have provided two explanations. (1) Transition states may be unusually "loose" and, as a consequence, entropy-rich. This ostensibly reduces the advantage of intramolecular over intermolecular systems.[10] The problem is, however, that a "loose" transition 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) should cancel. (2) The second explanation given for lower than expected EM values relates to unspecified 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."[10] 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,[11] 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.[12] 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 significant. 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 10 in size (Table III).

Table III. Cases in Which a Single Frozen Rotation Leads to Large Rate Increases[a]

1.	 EM = 4×10^4 M	 EM = 5×10^8 M
2.	 $k_{rel} = 1$	 $k_{rel} = 2 \times 10^5$
3.	 EM = 80	 EM = 1.4×10^5

[a] Data in 1 and 3 taken from ref 8. Data in 2 taken from Hutchins, R. O.; Rua, L. *J. Org. Chem.* **1975**, *40*, 2567.

(C) Another disturbing feature of entropy is seen in Table IV. *Entropies of activation exhibit absolutely no relationship to EM values and, hence, provide little insight into the source of intramolecularity.* DeTar and Luthra[13] (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[14] (who studied 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[15] which resemble those of Page and Jencks except that Br· recombination to Br_2 was used, instad of cyclopentadiene dimerization, as the model reaction. Dafforn and Koshland arrived at a theoretical EM which is smaller by a factor of 10^6 than the Page–Jencks value of 10^8 M. Page[16] claims that Dafforn and Koshland incorrectly ignored the internal rotational entropy of Br_2, a claim later denied by Dafforn and Koshland.[17] From our point of view, the severe model dependency of the entropy calculations constitutes only one of several reasons to shy away from Page–Jencks theory.

So the question remains: Why does proximity, so often cited to explain huge intramolecular accelerations, have no effect on intermolecular reactions? One could, of course, claim that our kinetic results are totally expected; that fast reaction rates require that proximity be coupled with favorable orientation ("orbital steering").[15] But we have argued at great length[6] that angular alignment is *not* critical to many reactions. For example, Lipscomb

(10) Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 1678.

(11) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.
(12) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(13) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505.
(14) Bird, R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1221.
(15) Dafforn, A.; Koshland, D. E. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 2463.
(16) Page, M. I. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 940.
(17) Dafforn, A.; Koshland, D. E. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 779.

Table IV. Entropies of Activation and Intramolecular Reactivity

1.[a] $Br(CH_2)_nCO_2^- \rightarrow$ lactone

ring size	ΔS^*, eu	EM
7	−14	6×10^{-2}
8	−9	6×10^{-4}
9	−14	6×10^{-4}
10	−21	2×10^{-3}

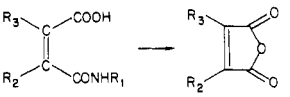
comment: no correlation between ΔS^* and EM

2.[b] $Me_2N(CH_2)_3COOAr \rightarrow Me_2N(CH_2)_3COOH + ArOH$

Ar	$-T\Delta S^*$	EM
Ph	−5.7	1260
p-Cl	−2.2	1080
m-NO_2	−4.3	1700
p-NO_2	−1.9	5400

comment: no correlation between ΔS^* and EM

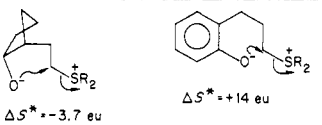
3.[c]



R_1	R_2	R_3	ΔS^*, eu	EM
CH_3	H	H	2.9	6×10^{10}
CH_3	H	*t*-Bu	2.7	1×10^{11}
Pr	Me	Me	−8	3×10^{13}

comment: the entropically *least* favorable reaction has the *highest* EM

4.[d]



comment: two related intramolecular reactions have totally different ΔS^* in water

[a] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. [b] Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1. [c] Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1206. [d] Knipe, J. O.; Coward, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4339.

and co-workers[18] have described a carbonyl addition in which *one-third* of a hemispherical surface centered at the carbonyl carbon is occupied by the "reaction funnel". We have shown experimentally that proton transfers are insensitive to large departures from linearity.[7] We cannot, therefore, ascribe our slow intermolecular kinetics to "proximity without orbital steering". Clearly, we must search elsewhere for a suitable rationale, and in this regard now stipulate the following postulate: *The rate constant for reaction between A and B is proportional to the residence time*[19] *that A spends within a bonding distance of B.* Neither of the two key components of reactivity, *time* and *distance*, is optimized in simple bimolecular reactions, thereby accounting for their sluggishness. A detailed discussion of the subject will be presented elsewhere.[20] In the mean time, two points should be emphasized. (1) It is preferable to interpret solution reactivity in terms of two Newtonian fluents, time and distance, rather than in terms of a catch-all parameter, entropy, which reflects undeterminable changes in low-frequency vibrations, solvation shell structure, conformational equilibria, etc. (2) "Proximity" by itself does not constitute a full and adequate explanation for intramolecular and enzymatic reactivity. Total "proximity" was achieved with our intermolecular S_N2 reactions, and yet no unusual rates were observed.

Experimental Section

Materials. Amines were Aldrich "Gold Label" or reagent grade materials purified by distillation over potassium hydroxide pellets. Methyl iodide and ethyl iodide were reagent grade (Aldrich) purified also by distillation. *o*-Dichlorobenzene and 1,2-dichlorobenzene were "Gold Label" grade and used as received. Chlorobenzene was dried over calcium hydride and distilled. Ethyl acetate was purified by washing with 5% sodium bicarbonate and water, drying over magnesium sulfate, and distilling. 4-(4-Nitrophenoxy)-2-butanone was prepared according to the procedure of Pohl and Hupe.[5]

Kinetics. The reaction of methyl iodide in pyridine was followed spectrophotometrically at 370 nm; the absorbance increased with time at this wavelength owing to the charge-transfer band of the product. Reactions were initiated by adding 50 μL of methyl iodide in dioxane to 3.00 mL of pyridine equilibrated at 25.0 ± 0.1 °C in the thermostated chamber of a spectrophotometer. A different strategy was adopted to follow the quaternization of triethylamine in ethyl iodide. Thus, 0.14 mL of triethylamine was added to 15 mL of ethyl iodide thermostated at 25.0 ± 0.1 °C in a constant-temperature bath. Aliquots of 1.0 mL were removed at known time intervals and added to 4 mL of standard hydrochloric acid. The excess acid was then back-titrated against standardized sodium hydroxide using phenolphthalein as the indicator. The E2 elimination of 4-(4-nitrophenoxy)-2-butanone in piperidine was observed spectrophotometrically at 393 nm in a manner similar to the methyl iodide-pyridine reaction. A product study by NMR and GLC indicated that the elimination is well behaved. The first and third reactions were followed to completion whereas the second reaction was followed only to 2 half-lives, thereby requiring the Guggenheim method for data workup.

Acknowledgment. This work was supported by the National Institutes of Health.

Registry No. Methyl iodide, 74-88-4; pyridine, 110-86-1; triethylamine, 121-44-8; ethyl iodide, 75-03-6; 4-(4-nitrophenoxy)-2-butanone, 57027-70-0.

(18) Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770.

(19) Reuben, J. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 563.
(20) To be published in *Acc. Chem. Res.*