Tetrahedron Vol. 39, No. 7, pp. 1013 to 1040, 1983
Printed in Great Britain.

0040-4020/83/071013-28$14.00/0
Pergamon Press Ltd

TETRAHEDRON REPORT NUMBER 145

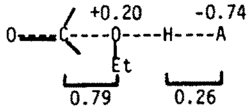
DIRECTIONALITY OF ORGANIC REACTIONS IN SOLUTION

FREDRIC M. MENGER
Department of Chemistry, Emory University, Atlanta, GA 30322, U.S.A.

(*Received in the U.S.A.* 31 *August* 1982)

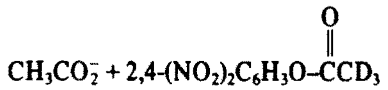
CONTENTS

The transition state is a mental construct facilitating discussion of chemical reactivity. So important is the transition state concept that organic chemists are exposed to it from the start of their training.[1] Physical organic chemistry has as one of its major objectives the detailed description of transition states. This has culminated in the construction of complex energy surfaces[2] and of pictures, often quite elaborate, showing partial atomic charges and bond orders:[3]



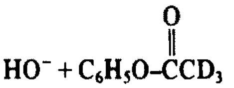
Partial atomic charges and bond orders are estimated from isotope effects and Brönsted coefficients. For example, β-deuterium isotope effects (k_{CH_3}/k_{CD_3}) were measured for the following carbonyl reactions:[4]

k_{CH_3}/k_{CD_3}



$$CH_3CO_2^- + 2,4\text{-}(NO_2)_2C_6H_3O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}CD_3$$

0.950



$$HO^- + C_6H_5O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}CD_3$$

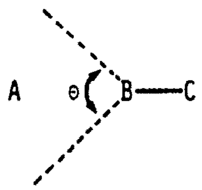
0.980

The isotope effects are consistent with "fractions of reactant progress" at the transition state of 0.37 and 0.15, respectively.[4]

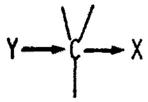
Most chemists would agree that a partial bond order or a fraction of reactant progress almost certainly represents a weighted average derived from an *array* of transition state geometries. Yet little agreement exists as to what the arrays look like. Jencks[5] has written, for example, that "...many transition states have a high degree of order and low entropy". Dunitz[6] refers to "a strongly preferred orientation for nucleophilic attack" in carbonyl additions. Koshland[7] has proposed that a 10° misalignment of reactant groups relative to an ideal orientation causes a large decrease in rate. We, on the other hand, believe (and will provide evidence) that transition states are often floppy and disordered. The fact of the matter is that chemists have only a vague notion as to the pliability of transition states in solution, and that consequently they are unable to assign significance to numbers such as "62% bond breakage". Does this value mean that most transition state contributors fall within the 62 ± 5% range? Or is the distribution curve broad so that a substantial number of contributors possess greater than 72%, or less than 52%, bond breakage? One would like to know, in short, the width of the saddle on which the transition state lies.

Transition state structure in organic chemistry is commonly described by means of computer-generated contour maps.[8] We ourselves couple theory with experiment later in the article. But a word of caution about energy diagrams is necessary. Their shapes are based on potential energy calculations in the gas phase[9-12] that have at least two major deficiencies: (i) Reactivity is related to changes in free energy, not potential energy. Since potential energy needs a kinetic energy term to give internal energy, and since internal energy needs a PV term to give enthalpy, and (most importantly) since enthalpy needs an entropy term to give free energy, the relationship between reactivity and potential energy is diffuse at best. (ii) Gas phase calculations are not always germane to solution chemistry. Anyone knowing that the gas phase basicity of pyridine is substantially greater than that of ammonia[13] appreciates the danger of extrapolating from gas to liquid. Mushiness in solvent organization surrounding the transition state precludes, apart from any other reason, a literal acceptance of energy curves. In particular, it is a mistake to endow underserved reality to the frequently-cited "saddle point" implying a single transition state with a definable degree of bond breakage and formation. Instead, the transition state undoubtedly possesses multiple bending modes of low restoring force. The transition state would thus lie in a broad energy valley and encompass a host of geometries each with characteristic partial atomic charges and partial bond lengths.

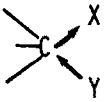
Having emphasized the flexibility of transition states, we can now consider the concept of a "reaction window". For example, the reaction A + B − C → A − B + C could occur *via* a "cone" of trajectories:



Each trajectory, linear and otherwise, is associated with a particular degree of A–B bond formation and B–C bond cleavage. Observed bond orders, determined by isotope effects as mentioned above, represent values averaged over the entire window. The larger the θ, the smaller the significance of the experimentally-determined bond order. It is as if "43" is used to describe the age of a human population; the number provides only low quality information on a population of widely divergent ages. Note that there is a finite probability that reaction succeeds with trajectories lying outside the window. The dotted lines merely indicate the approximate size and location of the window within which the bulk of the reaction occurs. Backside S_N2 displacement obviously falls inside the reaction window whereas frontside does not:



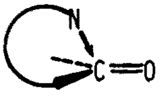
Backside

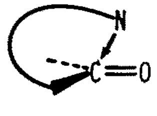


Frontside

Ideally, we would like to know if backside but ***non-linear*** trajectories are permissible and, if so, how successful they are relative to the linear geometry. In other words, we would like to define the reaction window of S_N2 substitutions, and all organic reactions, in as great a detail as possible.

Since our "cone" model places all the transition state flexibility into a single coordinate, it can be justifiably criticized as highly artificial. The hope is, however, that the model is somewhat less artificial than the one which discounts flexibility altogether. The hope is also that the model stimulates the design of interesting experiments. For example, one can inquire as to the relative rate of carbonyl addition when a nucleophile is fixed in two different loci with respect to the carbonyl:





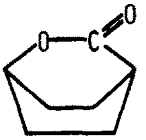
An experiment of this type requires, of course, the synthesis of rigid systems—not usually an easy task. It is for this reason, perhaps, that so little is known about the directionality of organic reactions.

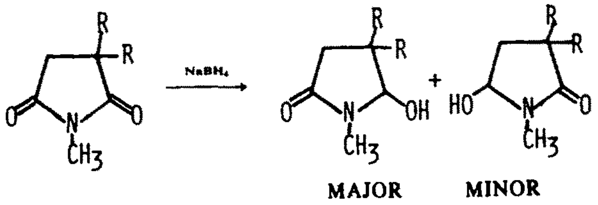
Directionality is a fundamental component of chemical reactivity. For example, backside preference in S_N2 reactions (crude as this statement of directionality might be) predominates over all other mechanistic aspects of bimolecular substitutions. *No* reaction is adequately described in the absence of information on its directional properties. The dependence of reactivity on directionality has important biochemical implications as well. If reactivity diminishes only slowly upon deviating from an optimal angularity ((i.e. if θ is large), then a set of catalytic groups at an active site need not be precisely aligned. If, on the other hand, reaction windows are narrow, then a slight misalignment causes a serious rate decrease. Transition state pliability and enzyme specificity are closely allied.

In concluding this introduction, I should point out that what follows is not a review. Directionality of organic reactions in solution is too undeveloped a subject to warrant a review at present. The reader will, instead, encounter an assorted collection of observations which bear in some manner on the question of directionality. The article is laced with theory, experiment, and conjecture (some of it unpublished) originating from the research group of the author.

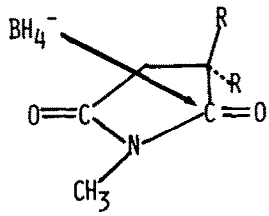
CARBONYL ADDITIONS

Bender[14] was one of the first to consider the trajectory of carbonyl additions. He pointed out that the lactone below saponifies ten times faster than an ordinary aliphatic ester. Since a backside approach colinear with the lactone carbonyl is totally blocked, nucleophiles must prefer a trajectory above or below the O/C/O plane. Along similar lines, Speckamp[15] showed that the borohydride reduction of *gem*-disubstituted succinimides takes place preferentially at the seemingly more hindered carbonyl adjacent to the *gem* substituents:

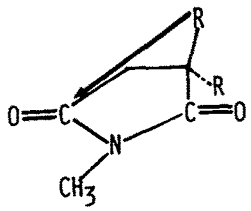




For example, the product ratio with $R = CH_3$ equals 79:21. When $R = C_6H_5$, reaction occurs *exclusively* at the carbonyl near the *gem*-diphenyls. This remarkable regioselectivity was attributed to the hydride following a trajectory that is above, but not perpendicular to, the plane of the ring:

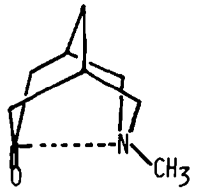


The *gem*-substituents tend to block the corresponding trajectory leading to isomeric product:[16]

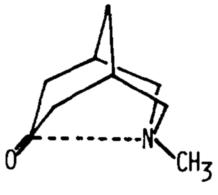


Lehn[17] carried out *ab initio* calculations on the minimum energy path taken by hydride upon adding to formaldehyde. When the H^- approaches the carbonyl up to a distance of 3 Å, it follows the H/CO/H bisector in the plane of the carbonyl (point A, Fig. 1). As the H···CO distance decreases to 2.5 Å, interactions between the H^- and the two formaldehyde protons cause the H^- to rise 55° out of the carbonyl plane (point B). Little energy change or distortion of the carbonyl planarity occurs to this point. Final approach of the H^- to the bonding distance (B to D) is guided by the π^* carbonyl orbital and is accompanied by a rapid conversion to a tetrahedral carbon. The calculations indicate a continuous energy decrease as the H^- moves toward the carbonyl. In other words, no transition state is detectable by the MO method. Despite this worrisome feature, one can examine the ease with which H^- departs from its favored path. Thus, at a H···CO distance of 2.5 Å (point B), it requires only 0.6 kcal mol^{-1} for the H^- to shift as much as 0.3 Å off the path toward the carbonyl plane. A 20° lateral angular displacement parallel to the carbonyl plane costs roughly 2 kcal mol^{-1}. Although these energy increments increase for H^- positions closer to the carbon, there is clearly a fair degree of wobble in the reaction pathway. If we could peer into the private lives of reacting atoms, they would seem intoxicated.

Dunitz[18] used a crystallographic method to describe "reaction paths" for carbonyl additions. The idea was to examine by X-rays several compounds bearing both a carbonyl and an amino group. The carbonyl carbon and amino nitrogen could in each case interact intramolecularly, thereby distorting the carbonyl's planarity, C=O bond length, etc. The hope was that by observing structural parameters in a series of increasingly deformed carbonyls, the reaction path for carbonyl addition could be mapped (as in still photographs of a moving object). Figure 2 shows three of the compounds included in the study. Underneath the compounds are four structural parameters: d_1, the N···CO distance; d_2, the C=O bond length; Δ, the distortion of the carbonyl from planarity; and θ, the N/C/O angle. It is seen that the shorter the N···CO distance, the longer the C=O bond length and the greater the deviation of the carbonyl group from planarity. Moreover, there is no doubt that the nitrogen approaches the carbonyl along a direction roughly 110° to the C=O bond rather than perpendicular to it. This agrees with the *gem*-disubstituted succinimide work mentioned earlier. The preference for an N···CO angle near the tetrahedral value is also illustrated by the aminoketone above.[19] An undistorted Dreiding model of the molecule gives an N···CO angle of 90°. In actual fact, the molecule bends so as to generate an N···CO angle of 110°.



Dreiding Model



Observed

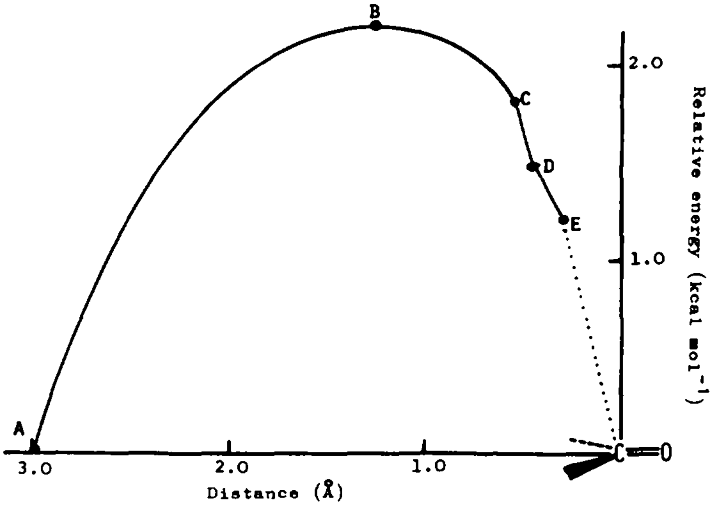
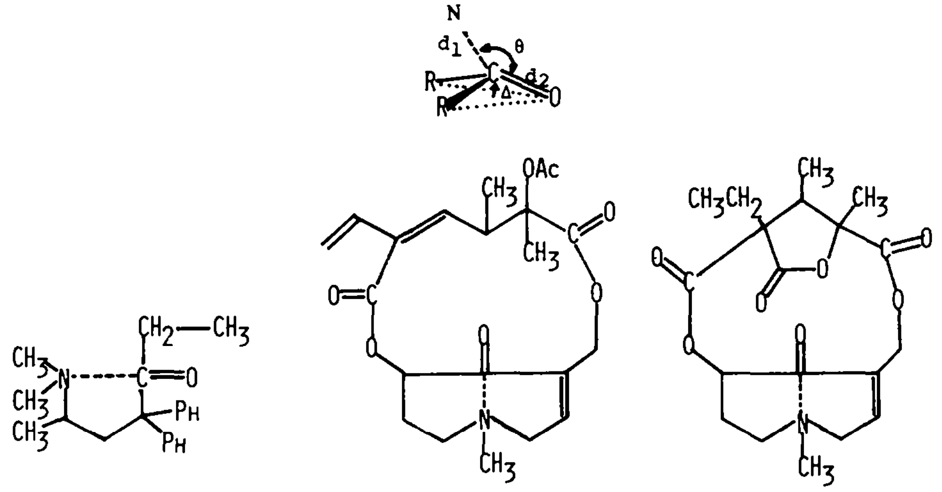


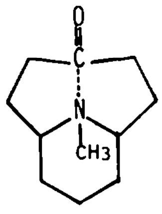
Fig. 1. Minimum energy pathway for addition of hydride to formaldehyde. The formaldehyde lies in a plane perpendicular to the page. Data are taken from Ref. 17.



d_1 = 2.91 Å	d_1 = 1.99 Å	d_1 = 1.64 Å
d_2 = 1.21 Å	d_2 = 1.26 Å	d_2 = 1.38 Å
Δ = 0.06 Å	Δ = 0.21 Å	Δ = 0.36 Å
θ = 105°	θ = 110°	θ = 111°

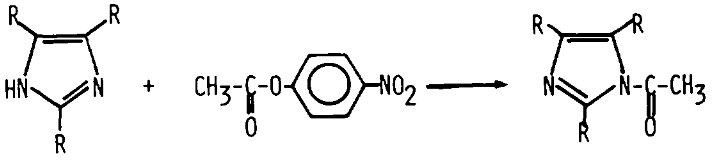
Fig. 2. Distances and angles of three compounds with intramolecular interactions between amino and carbonyl groups; d_1 = N···C distance, d_2 = carbonyl bond length, Δ = distance of C from RRO plane, and θ = N/C/O angle.

The Dunitz solid state approach to reaction trajectories does not, despite its great interest, provide information on reaction windows. X-ray structures may suggest an optimum trajectory, but they tell nothing about *other* concurrent trajectories. Collectively, an array of non-optimal geometries could well dominate a reaction pathway (similar to intermolecular hydrogen bonding where greater than half the population deviates by 20° or more from the lowest energy linear configuration[20]). Spectroscopic studies on transannular interactions in the compound below bear on this matter. Infrared data indicate a large (0.5 Å) change in the N···CO distance when the solvent is shifted from chloroform to cyclohexane.[21]



Such a susceptibility of geometry to small solvent perturbations demonstrates that the transition state for nucleophilic addition to carbonyls lies not on a saddle "*point*" beneath steep walls but rather in a shallow "glaciated" *valley* where a multitude of geometries are within reach.

We have examined the rate of nucleophilic attack on a carbonyl carbon by imidazoles having zero, one, or two methyl groups adjacent to the nitrogens.[22]



Inasmuch as the methyl groups engage in non-bonded interactions with the ester, the reaction is impeded. It is seen from Table 1 that a second methyl in proximity to a nitrogen has a much more profound effect on the rate than the first. This cannot be attributed to basicity because the pK_a values

Table 1. Activation parameters and relative rates at 25.0° for the acylation of imidazole bases with p-nitrophenyl acetate in water

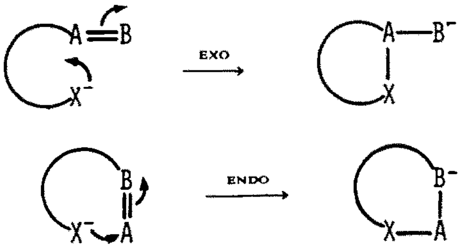
Nucleophile	pK_a	ΔH^* (kcal)	ΔS^* (eu)	k_{rel}
Imidazole	6.95	7.5	-35	151[a]
2-Methylimidazole	7.86	9.0	-33	34
2,4,5-Trimethylimidazole[b]	8.86	10.9	-33	1

[a] Second-order rate constant for this reaction equals 0.513 M^{-1} sec^{-1}.

[b] This compound was investigated because both nitrogens are banked by two methyl groups. 2,4-Dimethylimidazole has non-equivalent nitrogens and was thus avoided.

increase uniformly with methyl substitution. But the results can be explained qualitatively with the following postulates: (a) If the reaction window is narrow (a single trajectory in the extreme), then the effects of the methyl groups should be roughly additive. In other words, the ratio of $k_{H,H}$ to $k_{Me,H}$ should approximate the ratio of $k_{Me,H}$ to $k_{Me,Me}$. This presupposes little shortening of the N/C partial bond with methyl substitution in agreement with the work of Arnett[23] and of Johnson.[24] (b) If the reaction window is wide, a single methyl group should induce a relatively minor rate retardation because the nucleophile has the maneuverability to direct the methyl group outwardly and thus minimize non-bonded interactions. A second methyl group should, however, cause a more severe rate perturbation because shifting one methyl away from the ester brings the other one closer. Since the effects of the methyl groups are definitely not additive (Table 1), a single trajectory mechanism seems unlikely. Note from Table 1 that the rate differences arise mainly from changes in ΔH^* (not ΔS^*), suggesting that non-bonded interactions as opposed to solvation effects do indeed govern the behavior. In general, for a given reaction type, the following relation would be expected: the longer the partial N–C bond in the transition state, the larger the volume of space within the "cone" available to the nucleophile, the smaller the effect of the second methyl group over and beyond that of the first. This expectation has not yet been adequately tested.[25]

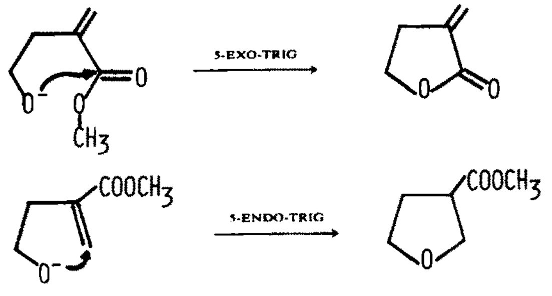
Baldwin has pointed out the importance of trajectory considerations to synthetic organic chemistry.[26,27] He devised a set of qualitative rules which are now accepted as useful guidelines. Intramolecular additions to carbonyls and other trigonal groups were classified into two types, *exo* and *endo*:



Thus , "7-*exo-trig*" signifies an *exo* addition to a trigonal system that creates a seven-membered ring. Baldwin's rules state: (a) 3,4,5,6 and 7-*exo-trig* reactions are all favored; (b) 3,4, and 5-*endo-trig* are disfavored, whereas 6 and 7-*endo-trig* are favored. The ease with which an intramolecular addition occurs seems to depend on whether or not the chain-length is sufficiently long to permit a reasonable trajectory. Favorable reactions all have larger X/A/B angles (i.e. angles closer to 110°) than disfavored ones:

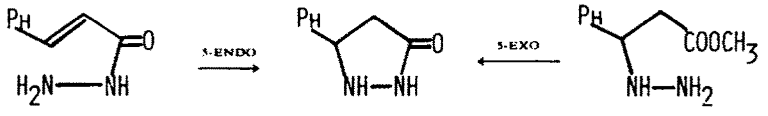
Examples are numerous:

(a) The ester below cyclizes cleanly in base to the lactone (5-*exo-trig*) with no trace of cyclic ether formation (5-*endo-trig*):

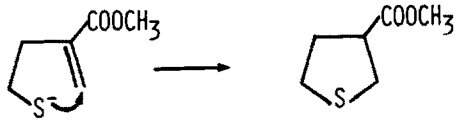


Since methoxide adds readily, Michael fashion, to the 5-*exo-trig* product, one cannot attribute the absence of cyclic ether to an inert β-carbon.

(b) 5-Phenyl-3-pyrazolidinone is formed in a 5-*exo-trig* process but not in the 5-*endo-trig* counterpart:



Note that "disfavored" does not necessarily mean "disallowed"; disfavored products can sometimes be obtained at elevated temperatures.[28,29] This is not surprising because reaction cones ought to expand with temperature. A particularly interesting exception to Baldwin's rules involves a sulfur compound that cyclizes at 65° in a 5-*endo-trig* mechanism. Sulfur, with its large size and polarizable electrons, seems better able than oxygen to accommodate a bent trajectory.



There is no questioning the utility of Baldwin's rules and the general validity of his rationale. Adherence to Baldwin's rules does *not*, however, establish the presence of *strong* directional preferences in the transition states. In this connection, the following points should be made: (i) The most impressive examples of Baldwin's rules are based on product ratios where, for example, a 5-*endo-trig* competes with a 5-*exo-trig*. Now a product ratio is a sensitive parameter. If the activation energy for a 5-*endo-trig* reaction exceeds that of a 5-*exo-trig* reaction by only 2 kcal mol^{-1}, the product of the latter will be obtained in very high yield. This fact, coupled with the inherent reactivity difference between the two reactive sites of an ambident electrophile, imparts an uncertainty to the exact magnitude of the directional preference. (ii) Whan an 5-*endo-trig* system is placed in a planar conformation (plane I, Fig. 3), then the X/A/B angle is relatively large (105°). But this must be an unreactive conformation because X lies here in the nodal plane of the double bond's π^* orbital. Rotating X out of plane I toward II, to permit orbital overlap, sharpens the X/A/B angle to less than 90°. Moreover, it is impossible, without prohibitive strain, for X to position itself in plane II above atom A (where maximum orbital overlap for addition at A would normally be achieved). Therefore, any observed reactivity differences between 5-*endo-trig* and 5-*exo-trig* reflect a severe structural impediment, not a subtle deviation from a highly preferred trajectory. (iii) Finally, Baldwin's rules say nothing about the effect of trajectory on a family of *favored* reactions within which wide angularity variations are possible. Work from our laboratory, described later, addresses this problem.

No trajectory theory has caused more controversy than Koshland's "orbital steering".[7,30,31] He proposed that a misalignment of reactant groups by as little as 10°, relative to an ideal orientation, causes a massive decrease in rate. Since there is a high probability of misalignment when atoms with small reaction windows collide randomly, bimolecular reactions in solution are often slow. Enzymes, on the

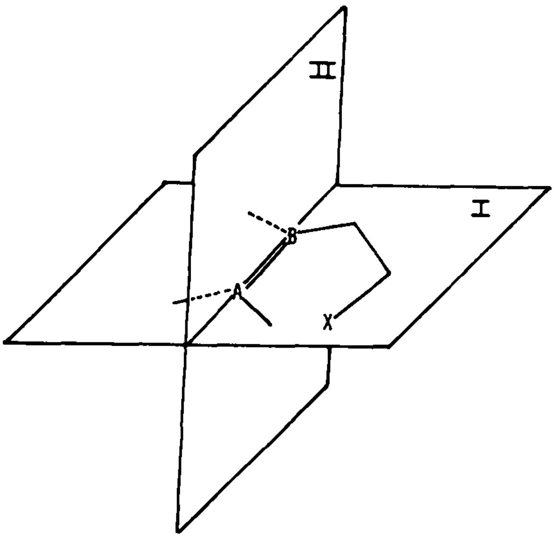
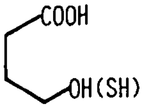
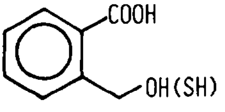


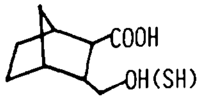
Fig. 3. A 5-*endo*-trig system in which X and the AB double bond lie in plane I. Although the X/A/B angle is relatively favorable, the conformation is unreactive.

other hand, can impose optimal orientations on interacting orbitals at active sites (orbital steering) thereby accounting for a large portion of enzymatic catalysis.[30] The evidence for an extremely sensitive dependence of reactivity on angular displacement rests mainly on differing lactonization rates found among structurally similar hydroxyacids (Fig. 4).[32] It is seen that modifying the supporting ring system from [2.2.1] to [2.2.2] in compounds **I** and **II** leads to a 10° decrease in trajectory angle (arbitrarily defined as the angle between the alcohol oxygen, carbonyl carbon, and α-carbon). A rate decrease of three orders of magnitude accompanies the angle change. Similarly, an angle difference of 7° in compounds **III** and **IV** is associated with a 21-fold rate variation. The question arises, of course, as to whether there exists a direct causal relationship between rate and trajectory angle. Koshland thinks there is because, he argues, other possible sources of rate perturbations (strain, steric effects, HO/CO distances, etc) remain constant in the [2.2.1] and [2.2.2] systems.

Koshland also carried out experiments with thiol analogs of several hydroxy-acids.[30] The reasoning was that if reaction windows are small, then substitution of oxygen by sulfur (a large atom with a totally different orbital structure than oxygen) could have a dramatic impact on cyclization behavior. We see below that replacing OH by SH affects cyclization rates differently for different systems. This suggests that sulfur and oxygen do not have the same orientational requirements, a reasonable conclusion







k_{OH}/k_{SH}: 70 110 11,500

especially if the reaction window for carbonyl addition is small and selective. Indeed, orbital steering theory states that the window is so narrow that a 10° alignment variation can produce a 10^4 rate effect.

Adverse response to the orbital steering theory was swift in coming.[33,34] Bruice,[33] for example, claimed that simple vibrational and torsional amplitudes at room temperature exceed the small but kinetically significant displacements implied by the orbital steering model. Although we clearly sympathize with this retort, it must be stated that opponents of orbital steering relied purely on theoretical arguments. No one devoted experimental effort, so impressive in Koshland's work, to provide alternate explanations of the lactonization rates or to define angular dependence more precisely. The matter was further clouded by work of Hoare.[35] He calculated the energy required to form misaligned transition states within the confines of a solvent cage. When the constraint of reaction trajectories by solvent cages is taken into account, the orbital steering theory is ostensibly upheld.

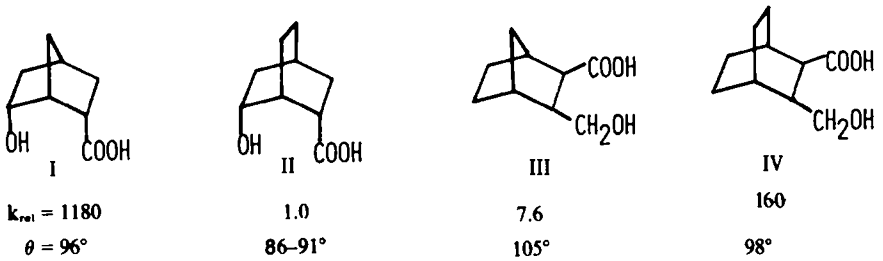
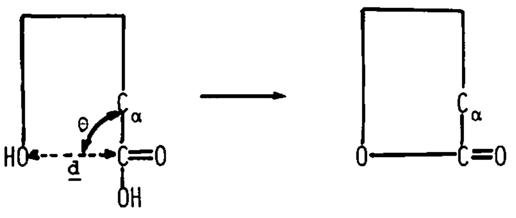
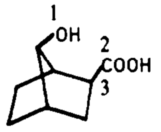


Fig. 4. Relative rates of lactonization of four hydroxyacids as a function of θ, the angle defined by the hydroxy oxygen, carbonyl carbon, and carbon alpha to the carbonyl.

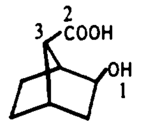
In 1980 we reported additional experimental data on the directionality of lactonization reactions.[36] The plan was to secure two hydroxyacids with the following properties: (i) The two compounds must have measurable differing angular relationships θ between their hydroxy and carboxy groups.



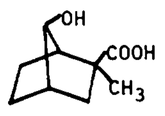
Since molecular flexibility leads to uncertainty in this regard, a rigid carbon framework is needed to support the functionalities. (ii) Despite the angular differences, the initial OH/COOH distances d must be the same so as not to introduce a second variable. (iii) The hydroxy groups must possess identical inherent reactivities (e.g. one hydroxy should not be primary and the other tertiary). (iv) The lactone products must have identical strain energies in order that product stability not influence the rates of lactonization. Obviously, these stipulations constitute a nonrealizable ideal. The ideal can be approximated, however, by a norbornyl system bearing a hydroxy and carboxy group on nonequivalent carbons as in V; interchanging the two groups to give VI modifies the alignment while keeping the other parameters relatively constant. Thus, force-field calculations on V and VI show that the compounds have



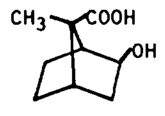
V



VI



VII



VIII

similar energies (within 1 kcal mol^{-1}) and similar O_1C_2 distances (2.83 and 2.81 Å) but contrasting $O_1C_2C_3$ trajectory angles (70° and 80°). This alignment variation should, if orbital steering theory is correct, produce a 10^4 difference in lactonization rates. A similar rate effect would be predicted for VII and VIII whose O_1C_2 distances are both 2.69 Å while their $O_1C_2C_3$ angles are 76° and 85°, respectively. Our "reversomers" would seem to be more satisfactory with respect to obeying the four stipulations than the [2.2.1] vs [2.2.2] systems of Koshland.

Syntheses of compounds V to VIII (peripheral to the discussion but not to the success of the project) are shown in Figure 5. Note the need to control the stereochemistry at carbons 2 and 7 of the norbornyl framework: the 7-hydroxy or carboxy group had to be *syn* (and not *anti*) while the 2-hydroxy or carboxy group had to be *exo* (and not *endo*). Accordingly, key steps in the synthetic scheme include a stereoselective $NaBH_4$ reduction to *syn* alcohol and a thermodynamically favored *exo* formation under equilibrating conditions.

Before discussing the orientation effects on cyclization rates of the reversomers, I should first compare the relative ring strains in the corresponding lactones. Table 2 lists their IR carbonyl stretching frequencies (a parameter which ranges from 1740 cm^{-1} for δ-lactones to 1840 cm^{-1} for β-lactones). The IR frequencies of V and VI are seen to differ by 7 cm^{-1} and those of VII and VIII by 12 cm^{-1}. These

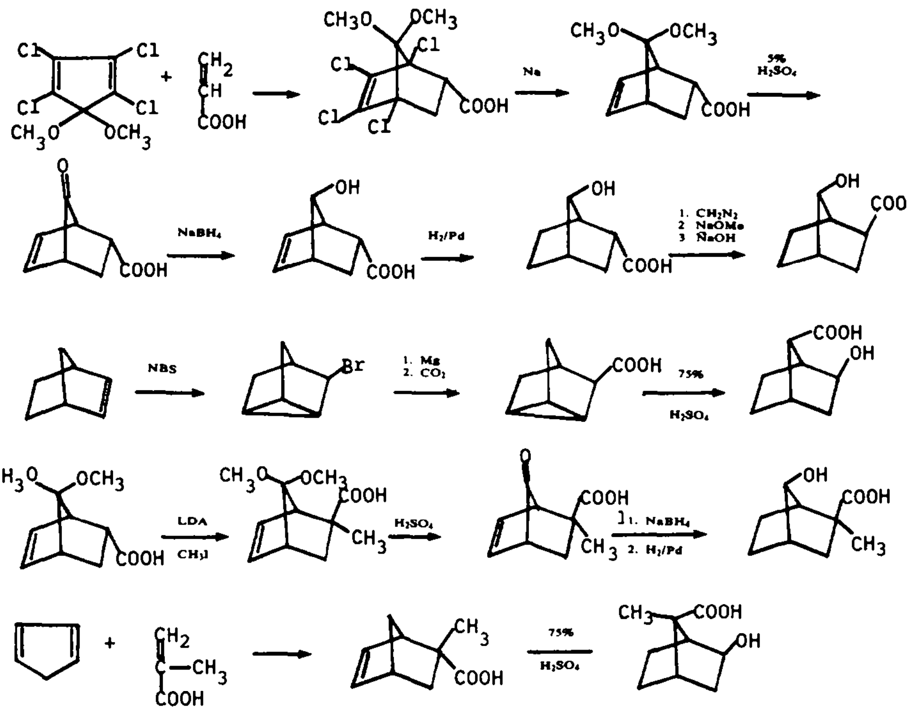


Fig. 5. Synthesis of compounds used in the studies of directionality of carbonyl additions (Ref. 36).

Table 2. 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°

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]
V	70	1778	45	0.0083	1
VI	80	1771	7	0.01	1.2
VII	76	1780	13	0.30	36
VIII	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 on the base of the column directly to the left.

differences are regarded as small and certainly not indicative of appreciable ring-strain variations. Saponification rates, another strain-sensitive parameter, are also listed in Table 2. Lactone **VI**, with a hydrolysis rate sixfold less than that of V, probably has a carbonyl somewhat more hindered from external hydroxide. But the effect is trivial relative to the 10^5 rate changes found among diverse aliphatic lactones.[37] Thus, as one might conclude intuitively from visual inspection of the compounds, interchanging hydroxy and carboxy groups of V/**VI** or **VII**/**VIII** does not create within the lactone pairs significant energy differences which could complicate comparisons of the hydroxyacids.

Acid-catalyzed lactonizations of hydroxyacids V, **VI**, **VII** and **VIII** have relative rates of 1, 1.2, 36 and

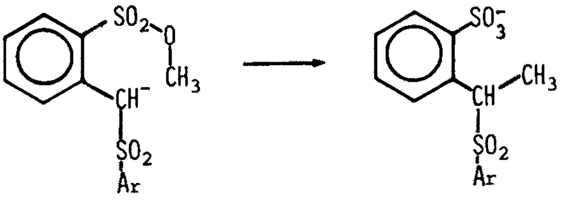
22, respectively (Table 2). The faster rates found for **VII** and **VIII** probably originate from steric acceleration of the type detected by Bunnett[38] in lactonizations of substituted aromatic hydroxyacids. The crucial observation, however, is that **V** and **VI** lactonize at nearly identical rates despite the 10° difference in alignment between the hydroxy and carboxy groups. Similarly, **VII** and **VIII** display virtually no rate dependence on orientation within the confines of a 9° variation. We have thus demonstrated experimentally for the first time that an angular displacement of a few degrees is not kinetically significant.[39] The reaction window is 10° and perhaps much larger. Of course, one would prefer to study a wide range of angles, but it is impossible to design several norbornyl derivatives encompassing a large angle spread while still obeying the four stipulations set forth above. Nonetheless, the lactonization experiment illustrates a general approach which provides information on directionality and which warrants further exploitation in the future.

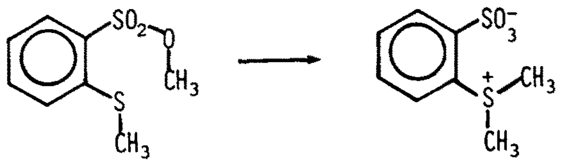
Lipscomb applied a "partial retention of diatomic differential overlap" MO method to a variety of carbonyl additions.[40] The resulting potential energy surfaces point strongly to a highly deformable transition state. For example, addition of methanol to formic acid displays a reaction "funnel" that subtends about 18% of the hemispherical surface centered at the carbonyl carbon and lying above the plane of the formic acid. This assumes a methanol oxygen/carbonyl carbon distance of 1.62 Å. When the partial bond is lengthened to 2.28 Å, fully one-third of the hemispherical surface is occupied by the reaction funnel! At a distance of 3.5 Å (a reasonable value, according to Lipscomb,[40] for a "loose" transition state), shifting methanol 20° from its preferred direction of approach costs less than 1 kcal/mol. The corresponding vibrational frequency is less than $30\,\mathrm{cm}^{-1}$. Stringent steric requirements for carbonyl addition are, therefore, not expected.

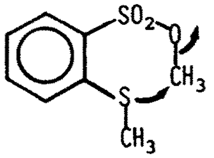
Unfortunately, matters are not as clear-cut as implied in the preceding paragraph. Calculations of Koshland based on a 1.80 Å nucleophile–carbonyl distance (almost half of the value used by Lipscomb for a "loose" transition state) lead, not surprisingly, to a much less pliable species. The role of solvent, as mentioned in the introductory paragraphs of this report, adds another uncertainty. Lipscomb freely admits that solvent effects are important to potential energy surfaces and that a high dielectric medium could dampen transition state deformations. Directionality of organic reactions in solution is, clearly, a field in its infancy.

SUBSTITUTIONS

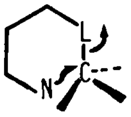
Backside S_N2 substitution represents one of the oldest and best known statements of directionality.[42,43] Eschenmoser, in a widely quoted paper,[44] invoked a directionality argument to explain the behavior of the following methyl transfers. Crossing experiments and kinetic data prove that the products arise exclusively from *inter*molecular S_N2 substitution. *Intra*molecular methyl transfer, of the type shown below, is totally absent despite the fact that reactions with 5 or 6-membered cyclic transition



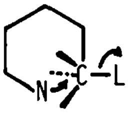




states often proceed rapidly. The lack of "endocyclic" S_N2 substitution undoubtedly stems from the unfavorable frontside trajectory:

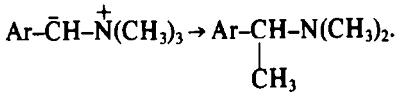


"Exocyclic" S_N2 reactions are, on the other hand, perfectly acceptable:



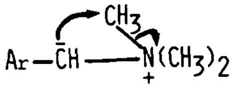
The subject of S_N2 directionality relates to an interesting family of 1,2-shifts which includes the Wittig and Stevens rearrangements:

$$Ar\text{–}\bar{C}H\text{–}OR \rightarrow Ar\text{–}CHR\text{–}O^-$$



$$Ar\text{–}\bar{C}H\text{–}\overset{+}{N}(CH_3)_3 \rightarrow Ar\text{–}\underset{CH_3}{\underset{|}{C}H}\text{–}N(CH_3)_2.$$

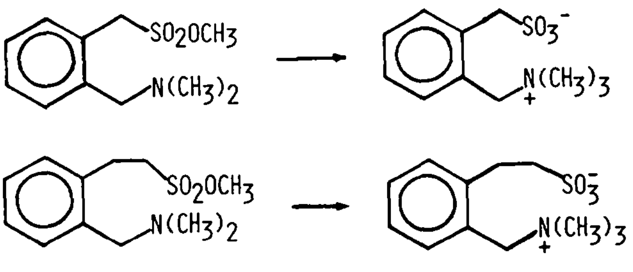
The temptation is to propose a concerted S_N2 reaction:



In actual fact, such a mechanism is disallowed by the presence of a frontside trajectory. Stated somewhat differently, the mechanism violates the principle of orbital symmetry conservation.[45] A more realistic view of the 1,2-shifts, supported by CIDNP data,[46] invokes a radical dissociation-recombination pathway.

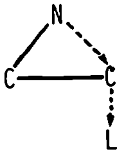
Exclusive backside substitution in $N + CH_3L \rightarrow NCH_3 + L$ indicates that acute N/C/L angles fall outside the reaction window. Yet this still leaves open the question of window size within the confines of a backside mechanism. Are 170° and 190° trajectories permissible and, if so, how do their success rates compare with the 180° angle usually assumed for S_N2 reactions? These are, of course, subtle questions. Intuitively, one would expect S_N2 substitutions to have a smaller reaction window than carbonyl additions; the antibonding MO at an sp^3 carbon is less "exposed" than at an sp^2 carbon. Hard data are, however, scarce. Investigations, described below, are among the few that pertain to the subject.

King[47] recently searched for endocyclic nucleophilic substitutions in the following reactions:



Intramolecular methyl transfer would require here an 8 and a 9-membered cyclic transition state, respectively. Initital concentrations were kept low (5×10^{-3} M) to minimize bimolecular competition. Under these circumstances, the first of the above reactions is entirely intermolecular. On the other hand, 16% of the methyl transfer in the second reaction derives from an intramolecular mechanism (the first reported endocyclic S_N2). King estimates that the intramolecular transfer has a low "effective molarity" (k_{intra}/k_{inter}) of 2×10^{-3} M. The relative inefficiency was ascribed in part to deviation from the ideal 180° orientation. Actually, an unstrained linear N/C/O geometry is attainable even with the 8-membered cyclic transition state. Perhaps non-bonded interactions in the cyclic transition states tend to favor bent, but permissible, trajectories over the linear one, thereby retarding the rate.

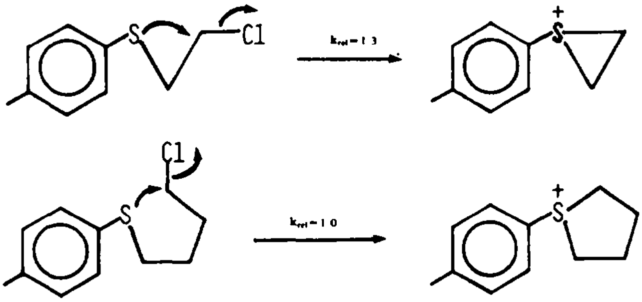
Exocyclic S_N2 substitutions leading to 3-membered rings almost certainly take place by means of non-linear backside trajectories (a supposition confirmed by recent unpublished MO calculations from our laboratory):



It is thus interesting to compare these cyclizations with the corresponding closures of 5 and 6-membered rings where linearity is possible (Table 3).[48] One sees that despite the bent trajectories and obvious strain, 3-membered rings close fairly readily (sometimes faster than the 6-membered analog!). Formation of 3-membered rings has, of course, an entropic advantage in that the reactive groups are always in close proximity. Nonetheless, their rapid rates are impressive and a good indication of transition state flexibility.[49]

Although the data in Table 3 show that O^- is a better nucleophile than neutral N, the superiority manifests itself far more with the 3-membered ring than with the 5 and 6-membered rings. Kirby[48] uses a directionality argument to explain this fact. An amine nucleophile has rather specific directional requirements owing to the orientation of the orbital containing the non-bounded electron pair. An alkoxide, on the other hand, has three pairs of electrons in degenerate orbitals any one of which can participate in nucleophilic attack. Since closing 5 and 6-membered rings places little demand on the directional properties of the nucleophile, O^- and N behave similarly. With 3-membered systems, orbital orientation becomes important and O^-, with its greater directional flexibility, displays the more potent nucleophilicity.

Usually 5-membered rings close faster than any other ring size because trajectory factors are ideal, strain is no problem, and the number of restricted rotations in the transition state is small compared with larger rings. The preference for cyclizing 5-membered rings is apparent in Table 3 for both the oxygen and nitrogen nucleophiles. Stirling[50] discovered an interesting exception to this generalization. Formation of the episulphonium ion from 2-chloroethyl p-tolyl sulfide is actually *faster* than formation of the corresponding 5-membered ring:



A remarkable 114-fold rate advantage of the 3-membered ring over the 5-membered ring was observed in $ArS(CH_2)_nCHPhCl$ where n = 1 or 3. Sulfur has polarizable non-bonded electrons that are easily distorted to accommodate the bent S_N2 trajectory involved in closing 3-membered rings. Hard nucleophiles such as N and O^- have more difficulty in this regard.

PROTON TRANSFERS

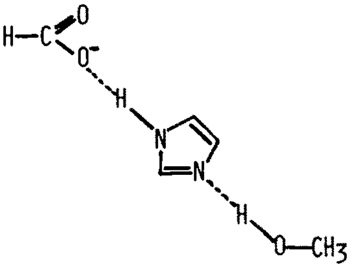
Our attention has recently focused on the directionality of the most fundamental of all reactions in solution, proton transfer. Over two decades ago, Westheimer[51] treated the A···H···B transition state as a linear entity for which low frequency vibrations can be totally neglected. This simplification persists to

Table 3. Relative effective molarities for the cyclization of ω-halogenoalkoxides and amines[a]

Ring Size, n	EM	
	$Cl(CH_2)_{n-1}O^-$	$Br(CH_2)_{n-1}NH_2$
3	2.5×10^3	15
4	4	0.2
5	6×10^4	7×10^3
6	280	100

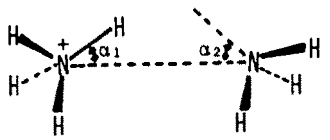
[a] Data taken from Ref. 48.

the present day. For example, Kollman[52] performed *ab initio* calculations on the energetics of proton transfer in a formate/imidazole/methanol triad. Although O–H and N–H distances were optimized, the O/H/N angles were kept fixed in a linear configuration:



The linear transition state for proton transfer has found legitimacy in the behavior of hydrogen bonds. Hydrogen bonds, which are situated on the reaction coordinate for proton transfer,[53–55] are often regarded as linear.[56,57] Calculations by the CNDO/2 method demonstrate, however, that bending a hydrogen bond by as much as 30° off the A–H···B line hardly affects the hydrogen bond energy.[58] Monte Carlo calculations suggest that linear A–H···B relationship has indeed the lowest energy but that statistical factors lead to large populations of bent hydrogen bonds.[20] For example, more than half of the intermolecular hydrogen bonds have an A/B/H angle of greater than 20°, and a 40° bend is not uncommon. Therefore, until such time that a transition state for proton transfer is proved significantly more rigid than a hydrogen bond, one can reasonably postulate a wide angular distribution of transition state geometries.

Scheiner,[59] using an *ab initio* MO method, studied the effect of angular deformation upon the energetics of NH_4^+-to-NH_3 proton transfer. He defined two deformation parameters, α_1 and α_2, to specify the rotations of the proton donor and acceptor, respectively, from a linear N/H/N geometry:



Three modes of angular deformation were considered explicitly: (i) The proton donor was held at $\alpha_1 = 0$ while the acceptor was rotated. (ii) Both acceptor and donor were bent in the same direction ($\alpha_1 = \alpha_2$), (iii) Donor and acceptor were rotated in opposite directions ($\alpha_1 = -\alpha_2$). The internitrogen distance was kept constant as the proton was being transferred. Among the three modes, the third results in the highest energy increase, followed by the second and the first:

α_1	α_2	Barrier, kcal mol^{-1}
0	+20°	1
+20°	+20°	2
+20°	−20°	3

But none of these barriers to proton transfer is large despite the substantial distortions. Moreover, if the N–N distances are permitted to optimize, then the resulting "adiabatic" barriers diminish to even lower values (about 40% less). It should be noted further that energy calculations such as these ignore statistical factors and thus underplay, if anything, the importance of bent trajectories in the real world. Since a 20° trajectory, for example, encompasses an entire "cone" of pathways, it should be entropically *favored* over the single linear geometry. Clearly, the transition state for intermolecular proton transfer is a wobbly, multi-directional entity.

We have used the MINDO/3 method to secure energies for N-to-N proton transfer in $NH_2CH_2NH_3^+$.[60] Calculations, employing a Davidon–Fletcher–Powell optimization subroutine, initially located the minimum energy position of the mobile proton when confined to the bisecting XY plane (Figure 6). The resulting transition state has its mobile proton in the N/C/N plane; an energy 21 kcal mol^{-1} greater than that of the $NH_2CH_2NH_3^+$ ground state; a partial N–H bond distance of 1.27 Å (compared to 1.01 Å for a primary amine); and a highly non-linear N/H/N angle of 103°.

Once having located the minimum energy point in the XZ plane, we moved the mobile proton in increments along the X, Y or Z axis. At each step, the bond distance and angles were optimized to achieve minimal energy for that particular proton locus. For proton movement in the Z direction, calculations were carried out in two ways: (i) Energies were determined without any geometric constraints, thereby permitting rotation about the N–C bonds to accommodate, to whatever extent it can, the proton shift. (ii) Energies were also calculated while confining the amino groups to the transition state geometry; we could thus assess transition state flexibility in the Z direction when the proton "rides the stationary orbitals". The results of these calculations are given in Table 4 and Fig. 7. The last column of Table 4 shows how proton relocation affects the energy relative to that of the transition state. There clearly exists a striking insensitivity of the energy to shifts in the mobile proton. For example, a large 0.07 Å proton shift in the XY plane along the +X direction (away from the carbon) or in the −X direction (toward the carbon) raises the energy by less than 1 kcal mol^{-1}. Similarly, moving the proton 0.20 Å out of the XY plane along the Z-axis produces an energy increase of only 1.1 kcal mol^{-1}. Stretching an N–H partial bond 0.15 Å along the N–H vector (not shown in Table 4) costs only 0.45 kcal/mol. When the proton shifts 0.20 Å toward one of the nitrogens in the Y direction, the system is stabilized by a mere 1.7 kcal mol^{-1}. We conclude that the proton has considerable motional freedom in the transition state even when the system is highly strained.

The N/H/N angle in the intramolecular transition state deviates over 76° from linearity (Table 4).This departure from linearity does not, however, seem to contribute substantially to the high 21 kcal mol activation energy. The major energy requirement must arise from compressing the N/C/N angle from 114.8° in the ground state to 87.9° in the transition state which, calculations show, requires 20 kcal mol^{-1}. Another indication that bent N/H/N geometries cost little derives from calculations on proton transfer in $NH_2CH_2CH_2NH_2^+$. The five-membered cyclic transition state, with a bent N/H/N angle of 134°, is associated with an energy only 5.3 kcal mol above the ground state. Indeed, no energy is required for proton transfer in $NH_2(CH_2)_3NH_3^+$; the six-membered cyclic transition state has an N/H/N angle deviating 47° from linearity. The important point here is that if severely bent N/H/N geometries are readily generated in intramolecular reactions, then non-linear transfer probably contributes to intermolecular reactions as well. Assumptions of linearity in the latter are therefore suspect.

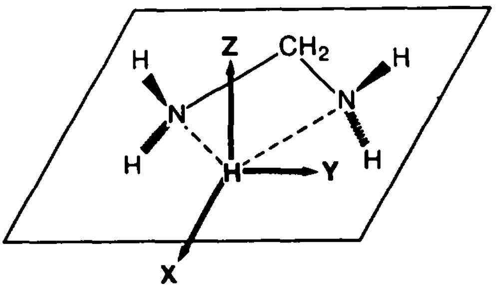


Fig. 6. Transition state for N-to-N proton transfer in $NH_2CH_2NH_3^+$.

Table 4. Transition state geometries and energies for N-to-N proton transfer in $NH_2CH_2NH_3^+$ with the proton situated at various loci

	N-H, Å	N/H/N,°	N/C/N,°	ΔE,kcal/mol
TS[a]	1.27	103	88	0.00
+X, Å				
0.05	1.30	100	88	0.46[b]
0.07	1.31	98	88	0.89
0.10	1.33	96	88	1.8
0.15	1.37	93	88	4.0
-X, Å				
0.05	1.25	107	88	0.46
0.07	1.24	109	88	0.91
0.10	1.23	112	88	1.9
0.15	1.21	116	89	4.1
Y, Å				
0.05	1.31	103	88	-0.15
0.10	1.36	104	88	-0.56
0.15	1.40	104	89	-1.13
0.20	1.44	105	90	-1.67
Z, Å				
0.05	1.28	103	88	0.07[c] (0.16)[d]
0.10	1.28	103	88	0.27 (0.61)
0.15	1.28	102	88	0.61 (1.38)
0.20	1.29	102	88	1.10 (2.45)

[a] Transition state with an energy of 163 kcal/mol compared to 142 kcal/mol for ground state.

[b] Indicates that a 0.05 Å shift in the +X direction (see Figure 1) elevates the energy relative to the lowest energy configuration by 0.46 kcal/mol.

[c] Energy when permitting complete freedom to optimize.

[d] Energy when the atoms of the NH_2 groups are confined to the transition state coordinates.

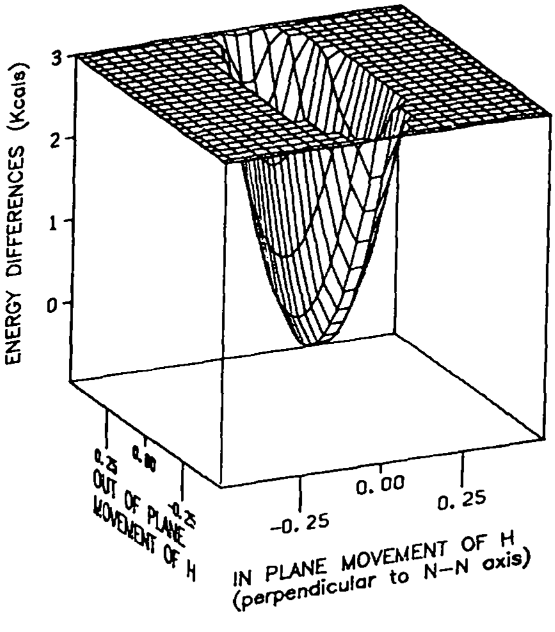
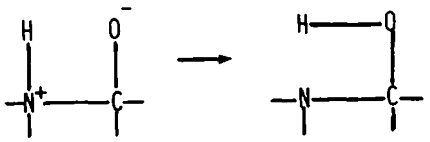
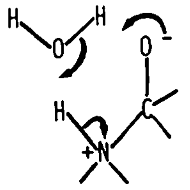


Fig. 7. Energy increases caused by proton movement in the X-direction (in plane) and in the Z-direction (out of plane) from an optimal transition state geometry.

The MINDO/3 calculations on $NH_2CH_2NH_3^+$ relate to the "proton switch" mechanism of tetrahedral intermediates:

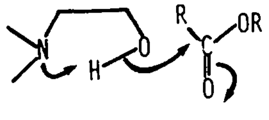


Such a mechanism has been proposed for ester aminolyses, amide hydrolyses, and enzyme-catalyzed mechanisms.[61–63] It appears from the high activation energy associated with our 1,3-shift that the mechanism, taken literally, is not favorable. If, however, one or more solvent or buffer species intervene according to a Grunwald–Meiboom mechanism,[64] then compressing the N/C/O angle would no longer be necessary, and rates of 10^6–10^8 sec^{-1} are possible.[65]

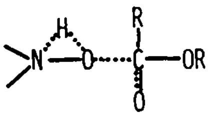


Non-linear transition states in proton transfer are not merely a figment of the theoretician's computer; they are proven fact in intramolecular reactions. Several examples are cited below. Their purpose is not so much to prove that bent transition states are present in organic chemistry; everyone is aware of this. Instead, I wish to illustrate interesting relationships between reactivity and directionality. Furthermore, I wish to advance the theme that since bent geometries are found in fast *intra*molecular reactions, bent geometries should also be important components of *inter*molecular reactions that are traditionally treated as linear. The consequences of multi-directional transition states in intermolecular reactions will be taken up in the final section of this paper.

Jencks[66] invoked an intramolecular general base catalysis to rationalize the 10^5 greater nucleophilicity of an aminoalcohol relative to that of water:

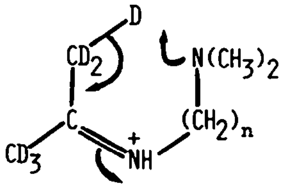


The N/H/O angle deviates about 45° from linearity. Similarly, Jencks[66] suggested that nucleophilic attack by the NH_2OH oxygen could be aided by an intramolecular O-to-N proton transfer:



Experimental proof for such an extreme form of transition state bending has yet to appear in the literature.

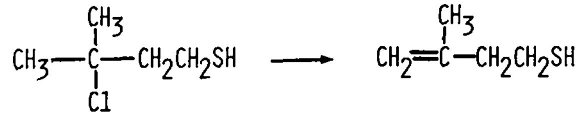
Hine[67] is one of the few who ever specifically addressed the question of directionality in proton transfer. He measured the ability of an intramolecular amino group to catalyze double bond migration in immonium ions:



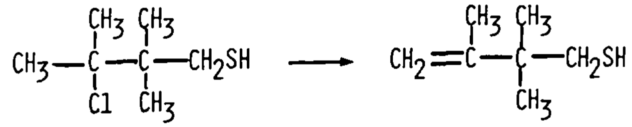
$k_{n-3} > k_{n-4}$

When n = 3, an 8-membered cyclic transition state is formed having an N/D/C angle of 150°. When n = 4, the resulting 9-membered transition state is able to attain an N/D/C angle of 180°. The *former* reaction actually proceeds at the faster rate. If directional requirements were stringent, then the reaction with a linear transition state would have exceeded in rate the reaction with a bent geometry. Apparently, a 30° variation in angularity is less vital here than an entropic factor associated with the freezing of a single extra rotation.

Grob[68] observed anchimerically assisted eliminations in 3-chloro-3-methylbutanthiol and 3-chloro-2,2,3-trimethylbutanthiol:

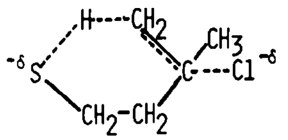


$$CH_3-C(CH_3)(Cl)-CH_2CH_2SH \longrightarrow CH_2=C(CH_3)-CH_2CH_2SH$$

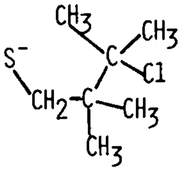


$$CH_3-C(CH_3)(Cl)-C(CH_3)_2-CH_2SH \longrightarrow CH_2=C(CH_3)-C(CH_3)_2-CH_2SH$$

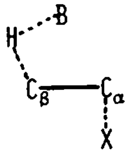
Dramatic rate increases (10^4 and 10^7-fold for the 3-methyl and 2,2,3-trimethyl compounds, respectively) occur upon ionizing the thiols to thiolates, pointing to an efficient catalysis *via* a bent S/H/C geometry:



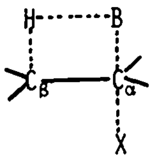
The particularly impressive value of 10^7 was attributed to the geminal methyl groups promoting a conformation favorable to intramolecular base-induced elimination:



Surprisingly, thiolate is often a more effective base in E2 reactions than alkoxide.[69] One would have expected the "soft" sulfur to have a lesser affinity for the "hard" proton. A possible explanation relates to an E2 transition state proposed by McLennan:[70]



Base attacks the proton with a non-linear trajectory and, in addition, engages in a remote interaction with the C_α. Sulfur, having polarizable electrons, would be better than oxygen in accommodating such a geometry. The so-called "E2C" mechanism of Parker and Winstein[71] demands an even greater covalent interaction between the base and C_α and, consequently, an even sharper B/H/C_β angle:



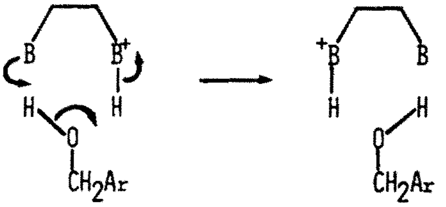
Bunnett[72] has presented strong arguments, supported by our MINDO/3 calculations mentioned earlier, against such a mechanism.

We have applied dynamic NMR methods to the study of OH proton exchange in aprotic solvents.[73] Various acid, base, intramolecular, and bifunctional catalyses were observed, but by far the most effective catalyst was a combination of amine and amine salt. Thus, the mono-$HClO_4$ salt of N,N,N',N'-tetramethylethylenediamine is a 10^4 more powerful catalyst than the free diamine:

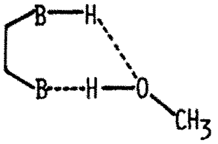
$$C_6H_5CH_2OH \xrightarrow{Me_2NCH_2CH_2NMe_2} C_6H_5CH_2OH' \quad k_{rel} = 1$$

$$C_6H_5CH_2OH \xrightarrow{Me_2NCH_2CH_2\overset{+}{N}HMe_2} C_6H_5CH_2OH' \quad k_{rel} > 10^4$$

A monamine salt will not by itself accelerate the rate of proton exchange of benzyl alcohol. The kinetics are most simply rationalized by a bifunctional catalysis which averts charge formation in the aprotic solvent:

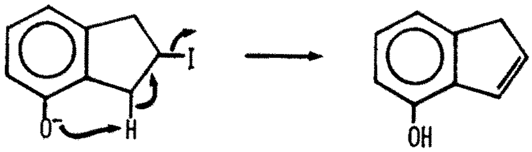


If one of the O/H/B angles is arbitrarily fixed at an "ideal" 180°, then the other O/H/B angle must deviate widely from linearity:

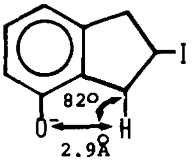


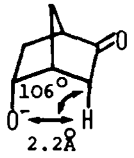
Clearly, rapid catalysis and non-linearity are compatible. One must then ask, as is done in the final section of this paper, what role non-linear trajectories might play in the kinetics, Brönsted coefficients, isotope effects, etc. of *intermolecular* reactions where an array of geometries is likely.

In most published examples of intramolecular catalysis with bent trajectories, the molecules are flexible. This leads to uncertainty as to the exact geometrical relationships among the reacting functionalities. Ideally, trajectory effects should be examined with rigid molecules where the functionalities are fixed in space and where, therefore, bond distances and angles are defined precisely. Our lactonization experiments,[36] described in the carbonyl section, illustrate the approach. We have also begun studying molecules in which an oxygen base is held rigidly with respect to a mobile proton:

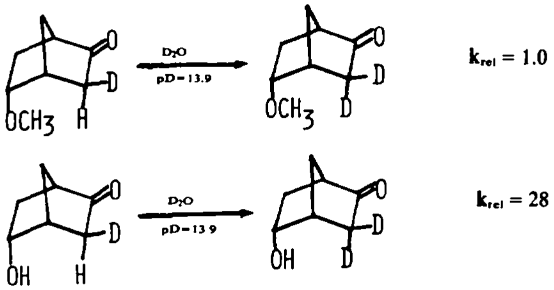


The syntheses of these compounds[74] are given in Fig. 8 while the relevant bond distances and angles are shown below:

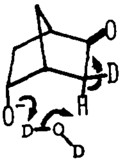




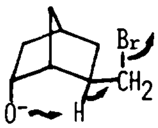
We found that although the iodophenolate does indeed eliminate in aqueous and aprotic solvents, the reaction occurs entirely *via* a bimolecular mechanism. Absence of an intramolecular transfer can be ascribed either to the sharp O⁻/H/C angle of 82° or to the long O⁻/H distance of 2.9 Å. The latter apparently constitutes the more serious impediment to reaction as shown by the enolization behavior of *endo*-5-hydroxy-2-norbornanone. Here the O⁻/H/C angle of 106° also deviates greatly from linearity, but the O⁻/H distance is only 2.2 Å. Under basic conditions ($pD = 13.9$, 70°), the hydroxyketone exchanges its *endo* proton roughly 28 times faster than does the methylated analog:



If one assumes that a general base catalysis is operating and that the pK_a of the *endo*-OH is 18, then the true catalysis (*i.e.* the observed catalysis corrected for the small O⁻/OH ratio at $pD = 13.9$) is in fact very large (3×10^5). Of course, the possibility exists that a water molecule interposes between the oxygen anion and the proton, thereby improving the trajectory angles:



Although such a mechanism has never been detected, we could avoid it even as a possibility by studying a related proton transfer:



Since the elimination can be carried out in nonaqueous media, a "through-solvent" process is of no concern. The substrate, whose synthesis is presented in Fig. 9, was mixed with an equimolar amount of potassium *t*-butoxide in *t*-butan(ol-*d*) and warmed to 53 ± 1°. Dehydrobromination was apparent in the NMR from the appearance of a vinyl signal concomitant with the disappearance of the $-CH_2Br$ multiplet. The time dependence of the vinyl peak area (relative to that of an internal standard) provided a semi-quantitative measure of the reaction time. Thus, 15 minutes were required for three half-lives. When *exo*-2-bromomethylbicyclo[2.2.1]heptane, *endo*-norborneol, and potassium *t*-butoxide were incubated at equivalent concentrations, no intermolecular base-catalyzed elimination was observed after 20 days. Fast intramolecular catalyzed elimination in *endo*-2-hydroxy-*exo*-6-bromomethyl[2.2.1]heptane is clearly indicated; a viable catalytic pathway in an E2 elimination can proceed through an O⁻/H/C transfer deviating 74° from colinearity!

Ideally one would like to construct a 3-dimensional plot which maps reactivity as a function of angularity and distance. Each point on the plot would represent a rate constant from a rigid molecule in which B and HA

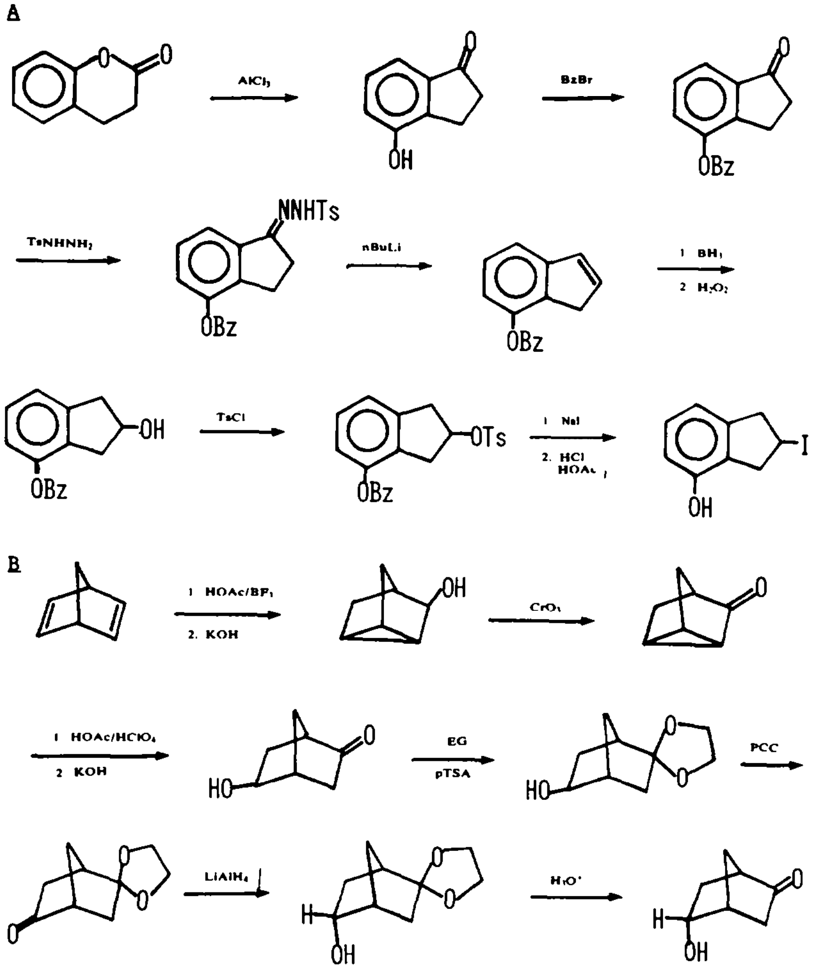


Fig. 8. Synthesis of compounds used in studies of proton transfer trajectories (J. F. Chow and P. C. Vasquez, unpublished work).

are fixed in a particular ground state geometry. The main difficulty in securing such information lies in synthesizing sets of compounds with subtle variations in the spatial relationships among intramolecular functionalities supported on rigid frameworks. But whatever the synthetic problems, the information is essential to characterize fully organic and biochemical pathways. How can one evaluate, for example, a particular arrangement of catalytic groups surrounding a substrate at the active site of an enzyme without first understanding the relationship between reactivity and alignment?

MULTI-DIRECTIONAL TRANSITION STATE THEORY

Multi-directional transition state theory claims, as its basic postulate, that the transition state for an intermolecular reaction comprises an array of trajectories each of which is associated with a characteristic degree of bond formation and bond cleavage. The question then arises as to how the properties of the reaction window, and the individual trajectories within it, affect various kinetic parameters. In attempting to answer this question, I must pass from the experiments and calculations of the previous sections to the realm of speculation. Every effort is made, however, to incorporate reasonable assumptions so that the conclusions are at least credible. Perhaps the stage will be set for more authoritative theorizing that will surely appear in the future.

The general plan is to "calibrate" the reaction window of an intermolecular reaction by using an intramolecular reaction whose efficiency and trajectory are known. Immediately one encounters a serious problem: What intramolecular reaction should serve as a standard? This is a serious problem because physical organic chemists have only a primitive understanding of intramolecular catalysis. A few sentences are necessary to elaborate on this point. The "effective molarity" or "EM" parameter has been devised to assess the efficiency of intramolecular reactions. EM is defined as k_{intra}/k_{inter} for closely related

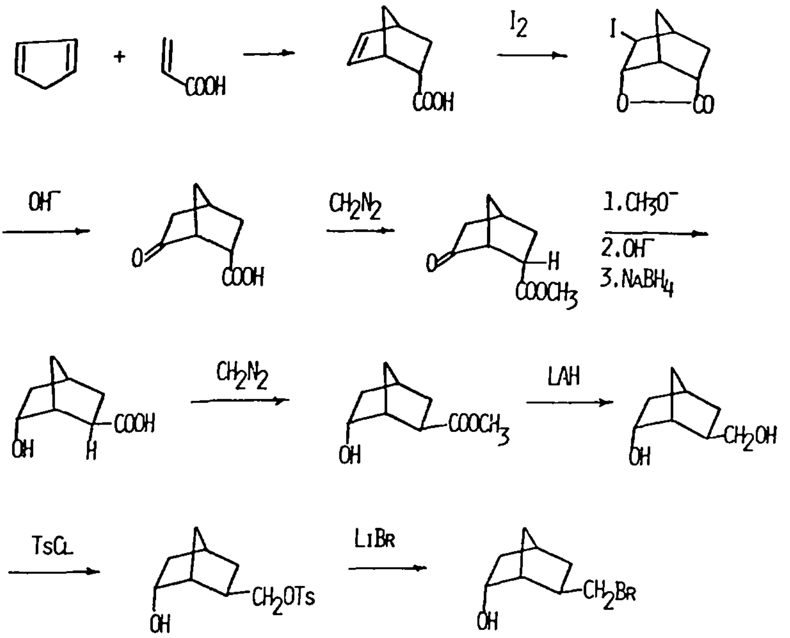
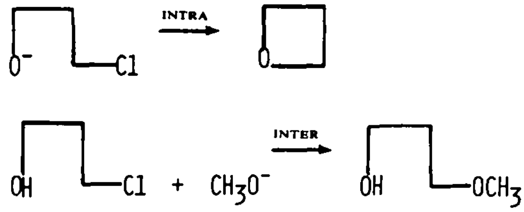
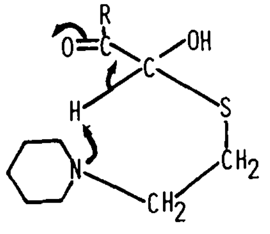


Fig. 9. Synthesis of *endo*-2-hydroxy-*exo*-6-bromomethyl[2.2.1]heptane (H. B. Kaiserman, unpublished work).

intramolecular and intermolecular reactions operating by identical mechanisms:[75]



The EM here of 4 can be regarded formally as the methoxide concentration necessary for the intermolecular reaction to go as fast as the intramolecular one. Often the efficiency of an intramolecular reaction renders such a concentration unattainable. The puzzling thing is that EM values vary widely for no rational reason. Figure 10 gives several examples.[48] Changes in substituent, solvent, and reaction type at constant ring size can produce large variations in EM. In order to provide the required calibration, I have arbitrarily selected an intramolecular proton transfer recently studied by Okuyama:[76]



The EM for this general base-catalyzed enolization is found to be 90 M. But the EM must be revised upward to account for four free rotations that permit unproductive conformations. Freezing these rotations is necessary to bring the proton and the non-bonded electrons of nitrogen into proximity. Jencks[34] and Illuminati[77] suggest a rate enhancement of 5-fold for freezing each rotation, whereas Bruice[78] prefers a factor of 230. Using the most conservative literature value of 5, one arrives at an EM of 5.6×10^4 M for an idealized reaction with roughly a 60° deviation from N/H/C colinearity.[79] If, in concert with published notions,[80] 10^8 M is accepted as the maximum EM value (corresponding here to a linear geometry), then the following conclusion arises: A linear intramolecular proton transfer proceeds 1.8×10^3 times faster than one with a 60° bend.

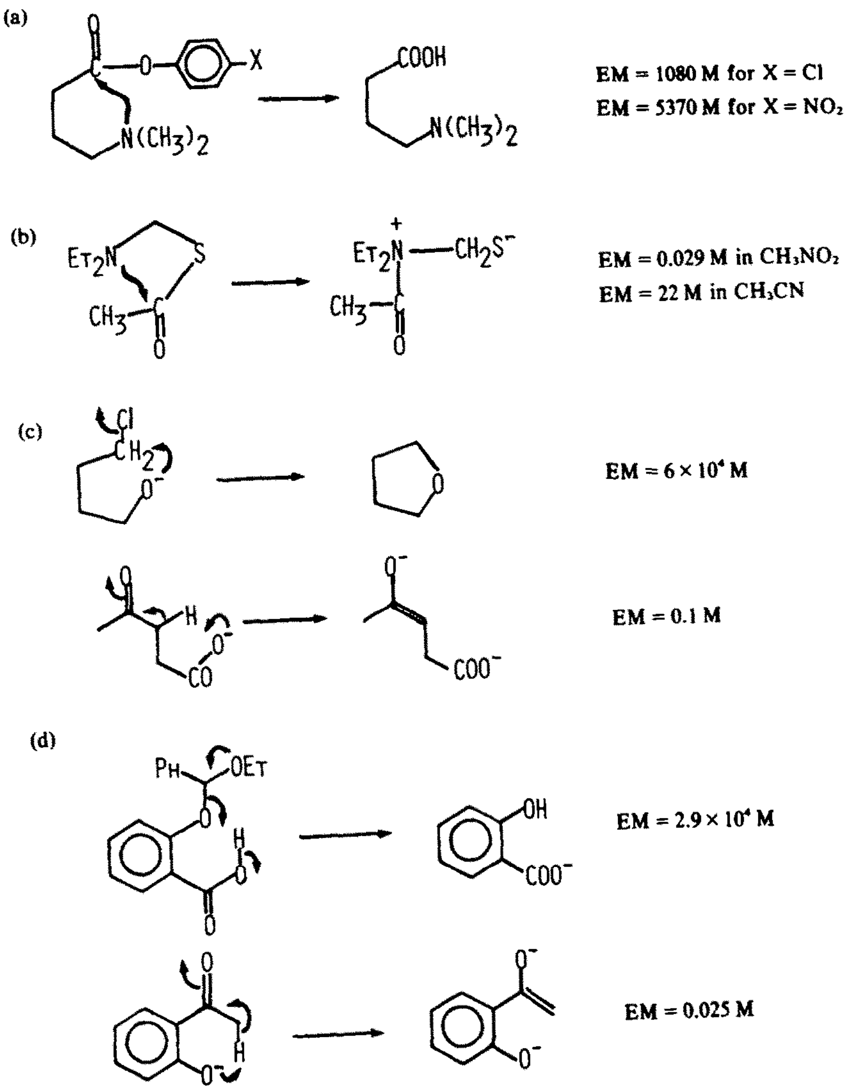
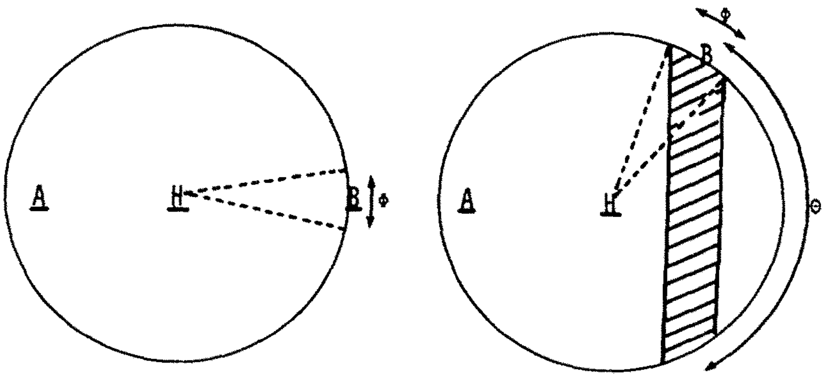


Fig. 10. Examples of effective molarities (EM) as a function of substituent (a), solvent (b), and reaction type at constant ring size (c and d). Data taken from Ref. 48.

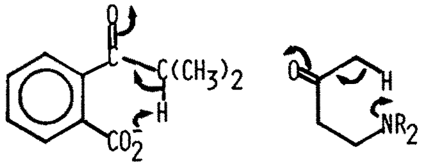
The number 1.8×10^3 represents a comparison between linear and bent *intra*molecular transition states. In order to obtain the contribution of a bent geometry to an *inter*molecular proton transfer, one must correct for the "reaction cone" available only to non-linear transition states. This is accomplished with the aid of the diagrams below:



On the left is depicted a linear A/H/B transition state with a vibrational bending amplitude Φ; the surface area available to B on the "reaction sphere" (i.e. the curved "cap" of the cone) is given by $2\pi r^2$ (1-cos $\Phi/2$) where r represents the H/B bond length in the transition state. On the right we see a bent A/H/B geometry with a reaction window θ; the surface area available to B (shaded zone) now has an area of $2\pi r^2[\cos(\theta/2-\Phi/2)-\cos(\theta/2+\Phi/2)]$. Thus the bent transition state is favored geometrically by a factor R equal to the quotient of the two areas:

$$R=\frac{\cos(\theta/2-\Phi/2)-\cos(\theta/2+\Phi/2)}{1-\cos\Phi/2}$$

The smaller the value of Φ, the greater the "probability" advantage of a bent geometry over a linear one. At a constant $\theta = 60°$, for example, R = 23 when $\Phi = 10°$ whereas R = 116 when $\Phi = 2°$. In the case of our particular proton transfer, R = 50 because $\theta = 120°$ and $\Phi = 8°$ (a reasonable value at room temperature[81]). Thus, the 60° bend is associated with a rate that is 2.8% (i.e. 50/1800) of a "linear" rate. Different but substantial percentages are also calculated for related model reactions such as the enolization of o-isobutyrylbenzoate[82] and 4-diethylaminobutan-2-one:[83]



The point here is that severely bent geometries play an important role in *inter*molecular processes, and assumptions to the contrary[51,52] are suspect, the arbitrary quality of our treatment notwithstanding.

The contribution of bent geometries to the overall rate becomes more prominent with (i) a decrease in ϕ, (ii) an increase in EM, and (iii) an increase in the rate enhancement produced by freezing a single rotation. The third component is particularly important. If, for example, I had used an "entropy factor" of 7 instead of 5, then a 60° bend would have manifested a rate greater than 10% of the linear rate! By selecting a minimal factor of 5, the per cent contribution of bent geometries is actually biased downward.

One can reasonably postulate that rate and trajectory angle are related by a bell-shaped curve. Accordingly, I have chosen a Cauchy probability distribution described by the following equation:

$$y=\frac{C}{\pi(C^2+X^2)}.$$

The variable y represents the reaction rate (with a maximum at X = 0) while X is the trajectory angle (with X = 0 representing A/H/B colinearity). The integral of the bell-shaped function from $-\infty$ to $+\infty$ equals unity. Constant C can be evaluated from the fact that y at 60° is, as described above, an ascertainable percentage of y_{max}. It should now be clear why a "calibrating" intramolecular reaction is needed: the reaction serves to define the rate vs angle distribution curve. By integrating the function between limits, one is able to calculate the percent of the total reaction occurring within various trajectory ranges. These data are given in Table 5. A substantial portion of the reaction is seen to take place with highly bent transition states. For example, 24% of the proton transfer lies outside the 0 ± 25° trajectory range. Even with a modest entropy factor of 5, a sizeable contribution to the reaction (12%) derives from transition states outside the 100° window. Although these numbers must not be accepted literally, they clearly support the plausibility of multi-directional transition state theory.

Multi-directional transition state theory can be applied to a well-known dilemma regarding primary deuterium isotope effects. Classical rate theory predicts a k_H/k_D ratio in excess of 6, whereas experimental values are often much less than this. In fact, primary isotope effects only slightly greater than unity are not uncommon. This discrepancy has been explained by a symmetric vibration which contributes zero point energy to a linear transition state thereby lowering the rate ratio.[51] Alternatively, one can describe an intermolecular proton transfer by an array of trajectories each of which is associated with a particular isotope effect; an observed isotope effect is a weighted average of the components. Thus, More O'Ferrall has calculated k_H/k_D values equal to 7.9, 3.2 and 1.7 for A/H/B angles of 180°, 120° and 90°, respectively.[84] Clearly, a reaction with a wide window, as in Table 5, would manifest a low

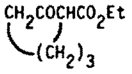
Table 5. The percent of total reaction occurring within reaction windows of different sizes[a]

Angle Range[b]	%
0 ± 10°	50
0 ± 25°	76
0 ± 50°	88
0 ± 75°	92

[a] Values are based on an intramolecular proton transfer with an EM of 90, a reaction window of 120°, 4 free rotations, and an entropy factor of 5 per free rotation.

[b] 0° represents A/H/B colinearity

Table 6. Brönsted coefficients for base-catalyzed enolization of ketones[a]

Ketone	pK_a of Ketone	β
CH_3COCH_3	20.0	0.88
CH_3COCH_2Cl	16.5	0.82
 $CH_2COCHCO_2Et$ $(CH_2)_3$	13.1	0.64
$CH_3COCH_2COO^-$	9.7	0.52
$CH_3COCHBrCOCH_3$	8.3	0.42

[a] Data taken from Ref. 92

k_H/k_D according to the contributions from non-linear geometries. Since isotope effect and angular distribution may be interrelated, particular caution is required when attempting to correlate k_H/k_D with degree of proton transfer. Future research into the possible link between multi-directional transition states and isotope effects would seem highly desirable.

Multi-directional transition state theory can also be invoked to resolve a problem which for decades has muddled the interpretation of Brönsted plots. Brönsted plots are obtained by measuring rates of a reaction catalyzed by a series of acids (or bases) with varying pK_a values. Log k vs pK_a plots are usually linear over a wide range of acidities or basicities. Thus, the general base-catalyzed isomerization of α-glucose,[85] the hydrolysis of ethyl dichloroacetate,[86] and the cyclization of 4-chlorobutanol[87] display linear Brönsted plots over pK_a ranges of 17, 9 and 17 units, respectively. For several reasons (e.g. rates approaching diffusion controlled velocities,[88] multi-step mechanisms,[89] and solvation effects[90]) the plots may deviate from linearity, but for the most part straight lines are observed over pK_a intervals of 5–10 units and sometimes as seen above, over intervals as large as 17 units. Brönsted coefficients, derived from the slopes of the straight lines, usually vary from 0 to 1. Traditionally, these coefficients are equated with the extent of proton transfer in the transition state. Thus, it is written that "Brönsted exponents do measure transition state structure in more than a qualitative way".[91]

A specific example of a Brönsted treatment is given in Table 6 which lists β coefficients for the base-catalyzed enolization of ketones.[92] As the ketone becomes more and more acidic, the β decreases substantially from 0.88 to 0.42. Such a trend is traditionally explained by the Hammond principle:[93] The most acidic ketone has the most exothermic proton transfer and therefore the most reactant-like transition state. The early transition state (i.e. the small degree of proton transfer) is reflected in the small β value.

One now arrives at a serious (and usually ignored) anomaly. The β values in Table 6 vary with the acidity of the ketone but *not* with the basicity of the catalysts used to obtain β. Indeed, the linearity of the Brönsted plots depends on this fact. It is as if the degree of proton transfer in the transition state between an acid and base depends on the acidity of the acid but not on the basicity of the base. Similarly, a linear Brönsted plot for a general acid-catalyzed reaction entails obedience to Hammond with regard to the substrate basicity but disobedience with respect to catalyst acidity. Confusion over this point abounds.

Only two reasonable assumptions within our framework are necessary to analyze the Brönsted behavior: (i) the stronger the base or acid catalyst, the wider the reaction window. (ii) The greater the angular deviation of a given trajectory from A/H/B colinearity, the more extensive the proton transfer. This first assumption is based on the reactivity-selectivity principle[94] while the second one derives from the Hammond postulate.[93] Consider now proton transfers involving a strong base with a wide reaction window (10% maximum rate at a 60° deviation from colinearity) and a weak base with a more narrow window (1% maximum rate at 60°). The corresponding Cauchy curves can then be subdivided into 10° intervals, and the percent of reaction within each interval calculated as before (Table 7). In harmony with the second assumption, I assign in column 3 of Table 7 an increasing degree of proton transfer to increasingly bent transition states. Note that for any particular trajectory interval (e.g. 10–20°) the strong base is given a *smaller* degree of proton transfer than a weak base. Thus, the Hammond postulate is obeyed *within* the reaction window of each base as well as *between* the two bases. The last column in Table 7 multiplies columns 2 and 3 to give the degree of bond cleavage contributed by each interval. By summing the last column, one arrives at the degree of bond cleavage expected for the reaction as a whole. The important point here is that the strong and weak bases hardly differ in their overall degree of bond cleavage (0.61 and 0.59, respectively). If the *same* reaction window had been used for *both* bases, then the β values would have been dissimilar (0.61 and 0.71).[95] The lesson from this highly artificial

Table 7. Multi-directional transition state theory as applied to proton transfer to a strong and weak base

Range [a]	% Reaction[b]	A···H[c]	Contribution[d]
1. Strong Base			
0-10°	30	0.4	0.120
10-20°	20	0.5	0.100
20-30°	13	0.6	0.078
30-40°	8	0.7	0.056
40-50°	5	0.8	0.040
>50°	24	0.9	0.216
			0.610
2. Weak Base			
0-10°	65	0.5	0.325
10-20°	16	0.6	0.096
20-30°	6	0.7	0.042
30-40°	3	0.8	0.024
40-50°	2	0.9	0.018
>50°	8	1.0	0.080
			0.585

[a] Colinearity is represented by 0°.

[b] Percentages are calculated assuming 10% of the maximum linear rate at 60° for the strong base and 1% for the weak base.

[c] The larger the number, the greater the A-H bond cleavage.

[d] Numbers indicate the contribution to the apparent degree of A-H bond cleavage provided by a given trajectory range.

u

numbers game is clear. Brönsted coefficients, and all kinetically based parameters, can be analyzed and dissected by means of multi-directional transition state theory. Much more work is required, of course, to assess the value of the model.

In summary, a reaction $A + B \rightarrow A - B$ in solution can be viewed in two ways: (i) Reactant A is likened to a "bullet" which strikes B to form a new bond. If the energies of A and B or their geometric relationships are inadequate, then the hit is unsuccessful and the two entities ultimately depart. (ii) Reactant A is likened to a "guided missile" which finds its way into the reaction window of B and, with suitable thermal activation, forms the A–B bond. Bond formation following a "soft" collision[96] between A and B is initiated within an array of geometries. The purpose of this report is to support the latter alternative.

I have presented a multi-directional transition state theory which, as its basic postulate, claims that reactions are comprised of a multitude of transition state geometries each with a characteristic degree of bond formation and cleavage. All kinetically-based parameters are actually weighted averages taken over the entire reaction window. At present the theory is necessarily qualitative, but this need not impact adversely on its utility.[97] Experiments designed to test the theory further are in progress, but the difficulties are severe. In particular, obtaining sets of compounds with subtle differences in the spatial relationships among the reactive functionalities (as in the lactonization experiments cited earlier[36]) requires a laborious synthetic program. Yet those willing to expend the effort will be rewarded with an understanding of organic reactivity far more detailed than now available.

Acknowledgements—Support by the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund administered by the American Chemical Society, is gratefully acknowledged. The efforts of numerous graduate students and post-doctorates, whose published and unpublished work appears in this report, are especially appreciated. Finally I must express my gratitude to Dr. George S. Hammond for several valuable discussions.

REFERENCES

[1] R. T. Morrison and R. N. Boyd, *Organic Chemistry*, 3rd Edn, p. 64. Allyn and Bacon, Boston, Mass. (1973).

[2] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*) 274 (1970).

[3] J. L. Palmer and W. P. Jencks, *J. Am. Chem. Soc.* **102**, 6472 (1980).

[4] I. M. Kovach, J. P. Elrod and R. L. Schowen, *Ibid.* **102**, 7530 (1980).

[5] "Chemical Approaches to Understanding Enzyme Catalysis", *Proc. 26th OHOLO Conf.*, Zichron Yaacov, Israel (Edited by B. S. Green, Y. Ashani and D. Chipman), p. 152. Elsevier, New York (1982).

[6] H. B. Bürgi, J. D. Dunitz and E. Shefter, *J. Am. Chem. Soc.* **95**, 5065 (1973).

[7] D. R. Storm and D. E. Koshland, Jr., *Ibid.* **94**, 5815 (1972).

[8] R. D. Gandour and R. L. Schowen, *Transition States of Biochemical Processes*, Chap. 1-3. Plenum Press, New York (1978).

[9] H. Eyring, *Chem. Rev.* **10**, 103 (1932).

[10] R. N. Porter and M. Karplus, *J. Chem. Phys.* **40**, 1105 (1964).

[11] K. Fukui, *J. Phys. Chem.* **74**, 4161 (1970).

[12] B. Liu, *J. Chem. Phys.* **58**, 1925 (1973).

[13] M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz and R. W. Taft, *J. Am. Chem. Soc.*, **94**, 1369 (1972).

[14] M. L. Bender, *Chem. Rev.* **60**, 53 (1960).

[15] J. B. P. A. Wijnberg, H. E. Schoemaker and W. N. Speckamp, *Tetrahedron* **34**, 179 (1978).

[16] For a molecular mechanics approach to carbonyl additions utilizing congestion functions and cones of preferred approach see W. T. Wipke and P. Gund, *J. Am. Chem. Soc.* **98**, 8107 (1976).

[17] H. B. Bürgi, J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.* **96**, 1956 (1974).

[18] J. D. Dunitz, *X-ray Analysis and the Structure of Organic Molecules.* Cornell University Press, Ithaca, New York (1979).

[19] M. Kaftory and J. D. Dunitz, *Acta Cryst.* **B32**, 1 (1976).

[20] W. L. Jorgensen and M. Ibrahim, *J. Am. Chem. Soc.* **102**, 3309 (1980).

[21] G. I. Birnbaum, *J. Am. Chem. Soc.* **96**, 6165 (1974).

[22] F. M. Menger and D. Y. Williams, *Tetrahedron Letters* **23**, 3879 (1982).

[23] E. M. Arnett and R. Reich, *J. Am. Chem. Soc.* **102**, 5892 (1980).

[24] C. D. Johnson, *Tetrahedron Letters* **23**, 2217 (1982).

[25] Compare, however, the effect of substituents on an S_N2 reaction with that of a borderline S_N1-S_N2 process. J. I. Seeman, R. Galzerano, K. Curtis, J. C. Schug and J. W. Viers, *J. Am. Chem. Soc.* **103**, 5982 (1981). R. F. Hudson and R. J. Withey, *J. Chem. Soc.* 3513 (1964).

[26] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* 734 (1976).

[27] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun* 736 (1976).

[28] J.-P. Anselme, *Tetrahedron Letters* 3615 (1977).

[29] K. R. Fountain and G. Gerhardt, *Tetrahedron Letters* 3985 (1978).

[30] D. R. Storm and D. E. Koshland, Jr., *J. Am. Chem. Soc.* **94**, 5805 (1972).

[31] D. R. Storm and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci. U.S.A.* **66**, 445 (1970).

[32] As pointed out by R. M. Moriarty and T. Adams, *J. Am. Chem. Soc.* **95**, 4070 (1973), three of the hydroxyacids studied in Ref. 30 had incorrect structures. This problem does not, however, invalidate the arguments because most of the compounds, including the four shown here, were correctly assigned.

[33] T. C. Bruice, A. Brown and D. O. Harris, *Proc. Nat. Acad. Sci. U.S.A.* **68**, 658 (1971).

[34] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U.S.A.* **68**, 1678 (1971).

[35] D. G. Hoare, *Nature* (*London*) **236**, 437 (1972).

[36] F. M. Menger and L. E. Glass, *J. Am. Chem. Soc.* **102**, 5404 (1980).

[37] E. T. Kaiser and F. J. Kézdy, *Prog. Biorg. Chem.* **4**, 239 (1976).

[38] J. F. Bunnett and C. F. Hauser, *J. Am. Chem. Soc.* **87**, 2214 (1965).

[39] Alternatively, one might conclude that the angles of 70° and 80° for V and VI bracket an optimal angle near 75°. This seems unlikely since it requires a *different* optimal angle for VII and VIII (near 81°). Furthermore, 75° is smaller than the optimal angle suggested by the work of Dunitz and Lehn mentioned in the text.

[40] S. Scheiner, W. N. Lipscomb and D. A. Kleier, *J. Am. Chem. Soc.* **98**, 4770 (1976). See also A. J. Stone and R. W. Erskine, *J. Am. Chem. Soc.* **102**, 7185 (1980).

[41] A. Dafforn and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci. U.S.A.* **68**, 2463 (1971).

[42] P. Walden, *Chem. Ber.* **32**, 1855 (1899).

[43] E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley and J. Weiss, *J. Chem. Soc.* 1525 (1935).

[44] L. Tenud, S. Farooq, J. Seibl and A. Eschenmoser, *Helv. Chim. Acta* **53**, 2059 (1970).

[45] T. L. Gilchrist and R. C. Storr, *Orbital Reactions and Orbital Symmetry*, 2nd Edn. Cambridge University Press, Cambridge, England (1979).

[46] A. R. Lepley, *J. Am. Chem. Soc.* **91**, 1237 (1969).

[47] J. F. King and M. J. McGarrity, *J. Chem. Soc., Chem. Commun.* **175** (1982).

[48] A. J. Kirby, *Adv. Phys. Org. Chem.* **17**, 183 (1980).

[49] One could as an alternative to a bent transition state visualize a linear transition state with a severely distorted carbon center that brings L in line with N. Both descriptions speak to the floppiness of transition states.

[50] R. Bird and C. J. M. Stirling, *J. Chem. Soc., Perkin II* 1221 (1973).

[51] F. H. Westheimer *Chem. Rev.* **61**, 265 (1961).

[52] P. A. Kollman and D. M. Hayes, *J. Am. Chem. Soc.* **103**, 2955 (1981).

[53] F. Strohbusch, D. B. Marshall and E. M. Eyring, *J. Phys. Chem.* **82**, 2447 (1978).

[54] R. Scott and S. Vinogradov. *J. Phys. Chem.* **73**, 1890 (1969).

[55] W. P. Jencks, *Catalysis in Chemistry and Enzymology*, p. 338. McGraw-Hill, New York (1969).

[56] W. Adam, A. Grimison, R. Hoffmann and C. Zuazaga de Ortiz, *J. Am. Chem. Soc.*, **90**, 1509 (1968).

[57] R. E. Jones and D. H. Templeton, *Acta Cryst.* **11**, 484 (1958).

[58] A. Goel, A. S. N. Murthy and C. N. R. Rao, *J. Chem. Soc.* (*A*) 190 (1971).

[59] S. Scheiner, *J. Phys. Chem.* **86**, 376 (1982).

[60] F. M. Menger, J. Grossman and D. C. Liotta, to be published in *J. Org. Chem.*

[61] A. S. A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.* **89**, 3020 (1967).

[62] T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 2nd Edn, p. 646. Harper and Row, New York (1981).

[63] M. Komiyama and M. L. Bender, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 557 (1979).

[64] E. Grunwald and S. Meiboom, *J. Am. Chem. Soc.* **85**, 2047 (1963).

[65] W. P. Jencks, *Acc. Chem. Res.* **9**, 425 (1976). See eqn (5).

[66] W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.* **82**, 1778 (1960).

[67] J. Hine. M. S. Cholod and R. A. King, *J. Am. Chem. Soc.* **96**, 835 (1974).

[68] C. A. Grob, B. Schmitz, A. Sutter and A. H. Weber, *Tetrahedron Letters* 3551 (1975).

[69] D. S. Bailey and W. H. Saunders, Jr., *J. Org. Chem.* **38**, 3363 (1973).

[70] D. J. McLennan, *Tetrahedron* **31**, 2999 (1975).

[71] A. J. Parker, M. Ruane, G. Biale and S. Winstein, *Tetrahedron Letters* 2113 (1968).

[72] J. F. Bunnett, S. Sridharan and W. P. Cavin, *J. Org. Chem.* **44**, 1463 (1979).

[73] F. M. Menger, H. K. Rhee and J. U. Rhee, *J. Am. Chem. Soc.* **98**, 792 (1976).

[74] P. C. Vasquez and J. F. Chow, submitted for publication.

[75] W. H. Richardson, C. M. Golino, R. H. Wachs and M. B. Yelvington, *J. Org. Chem.* **36**, 943 (1971).

[76] T. Okuyama, S. Komoguchi and T. Fueno, *J. Am. Chem. Soc.* **104**, 2582 (1982).

[77] G. Illuminati and L. Mandolini, *Acc. Chem. Res.* **14**, 95 (1981).

[78] T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.* **82**, 5858 (1960).

[79] The angle estimate suffices for this analysis.

[80] M. I. Page, *Chem. Soc. Rev.* **2**, 295 (1973).

[81] H. S. Johnston, *Gas Phase Reaction Rate Theory*, p. 223. Ronald Press, New York (1966).

[82] E. T. Harper and M. L. Bender, *J. Am. Chem. Soc.* **87**, 5625 (1965).

[83] R. P. Bell and B. A. Timimi, *J. Chem. Soc., Perkin II* 1518 (1973).

[84] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*) 785 (1970). See also H. Kwart, *Acc. Chem. Res.* **15**, 401 (1982).

[85] H. Schmid, *Chem. Zeitung* **90**, 351 (1966).

[86] W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.* **83**, 1743 (1961).

[87] C. G. Swain, D. A. Kuhn and R. L. Schowen, *J. Am. Chem. Soc.* **87**, 1553 (1965).

[88] M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, p. 81. Wiley-Interscience, New York (1975).

[89] M. M. Kreevoy and S. Oh, *J. Am. Chem. Soc.* **95**, 4805 (1973).

[90] D. J. Hupe and D. Wu, *J. Am. Chem. Soc.* **99**, 7653 (1977).

[91] A. J. Kresge Jr., *Proton Transfer Reactions* (Edited by E. Caldin and V. Gold), Chap. 7. Wiley, New York (1975).

[92] R. P. Bell, *The Proton in Chemistry*, p. 172. Cornell University Press, Ithaca, New York (1959).

[93] G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955).

[94] A. Pross, *Adv. Phys. Org. Chem.* **14**, 69 (1977).

[95] The larger of the two windows was used for *both* the strong and weak bases.

[96] R. A. Firestone and B. G. Christensen, *Tetrahedron Letters* 389 (1973).

[97] R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.* **1**, 17 (1968).