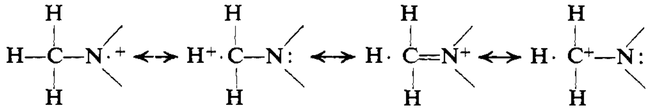
$$\mathrm{BH^+} \longrightarrow \mathrm{B\cdot^+} + \mathrm{H\cdot} \quad \Delta H^\circ_{(3)} = \mathrm{HA(B\cdot^+)} \tag{3}$$

$$\mathrm{PA(B:)} - \mathrm{HA(B\cdot^+)} = \mathrm{IP(H\cdot)} - \mathrm{IP(B:)} \tag{4}$$

The values of HA and literature IP are included in Table I (columns 6 and 5, respectively).

Methyl substituent effects in both series I and II are dramatically different between heterolytic (PA) and homolytic (HA) dissociations. In reaction 2, series I bases show increased stability of BH^+ relative to dissociated B: with increased Me substitution. These Me effects are large and distinctly nonadditive (columns 1 and 2, Table I). In reaction 3 series I bases show even larger and less additive effects of Me substitution, but here, in contrast, it is the dissociated cation radical $B\cdot^+$ which is stabilized relative to BH^+ (column 3, Table I). Series II bases show little or no effect of Me substitution on α-C in reaction 3 but a nearly additive BH^+ stabilizing effect of ~2.5 kcal in reaction 2.

The results for series I and II bases in reaction 2 may be ascribed to predominant inductive and polarization stabilizing effects[8] of Me on cationic BH^+ compared to neutral B. In series I bases, stabilization of $B\cdot^+$ relative to BH^+ may be expressed in terms of delocalization of charge and spin into Me.



The inductive, polarization, and hybridization effects probably make only minor contributions to relative HA's, since BH^+ and $B\cdot^+$ are of the same charge type. This interpretation is consistent with the fact that series II bases show nearly additive effects on PA (reaction 2) but little or no effect of Me substitution on HA (reaction 3). The latter result is expected as a consequence of nearly equal delocalizations into C–H and C–C bonds.[9] It is also of interest to note that Me substituent effects for series I in reaction 3 are about 2.5 times greater than for the corresponding isoelectronic (homolytic) C–H bond dissociation energy.[10]

Our quantitative values of $\delta_{\mathrm{R}}\Delta G^\circ_{(1)}$, which are in accord with Munson's earlier qualitative results,[11] may be combined with solution thermodynamic properties to obtain a complete analysis for the transfer of the ammonium ions from the gas phase to aqueous solution. The results and a preliminary discussion are given in a companion paper.[12] Tests of molecular orbital theories are also provided by present results. Thus, for example, the preliminary *ab initio* calculations of proton affinities for series I amines are on the order of 50 kcal larger than the experimental results.[13] It should also be noted that the nearly constant HA values for series II amines (as well as other series involving similar structural changes) are of important practical utility in experimental determination of PA values.[14]

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(8) *Cf.* J. I. Brauman, J. M. Riveros, and L. K. Blair, *J. Amer. Chem. Soc.*, **93**, 3914(1971).

(9) R. W. Taft and I. C. Lewis, *Tetrahedron*, **5**, 210 (1959).

(10) (a) J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966); (b) W. Tsang, *Int. J. Chem. Kinet.*, **2**, 311 (1970)

(11) M. S. B. Munson, *J Amer Chem. Soc.*, **87**, 2332 (1965).

(12) E. M. Arnett, F. M. Jones III, M. Taagepera, W. G. Henderson, D. Holtz, J. L. Beauchamp, and R. W. Taft, *ibid.*, **94**, 4724 (1972).

(13) (a) W. J. Hehre and J. A. Pople, *Tetrahedron Lett.*, **34**, 2959 (1970). (b) More recent calculations using geometries from minimization of energy give much closer agreement; private communication, Professor J. A. Pople.

(14) (a) M. C. Caserio and J. L. Beauchamp, *J. Amer. Chem. Soc.*, **94**, 2638 (1972); (b) J. L. Beauchamp, D. Holtz, S. D. Woodgate, and S. L. Patt, *ibid.*, **94**, 2798 (1972); (c) D. Holtz, J. L. Beauchamp, W. G. Henderson, and R. W. Taft, *Inorg. Chem.*, **10**, 201 (1971).

(15) Contribution No. 4377.

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Nonlinear Brønsted Relationships for General Acid–Base Catalysis of Aminolysis Reactions[1]

Sir:

We wish to report that the Brønsted plots for general acid–base catalysis of several acyl aminolysis reactions with nitrogen or oxygen leaving groups are nonlinear. We interpret this as evidence that there is a change in rate-determining step and an intermediate in the reactions and that the reactions are not at equilibrium with respect to transport processes involving proton transfer.[2–6]

Experimental studies of general acid–base catalysis of aminolysis have usually been limited to catalysis by a second molecule of the attacking or leaving groups (or their conjugate acids) in order to avoid interference by a nucleophilic reaction with the catalyst. We have avoided this problem by the use of reactive "α effect" nucleophiles and have examined the reactions of hydrazine with acetylimidazole and of methoxyamine with 1-acetyl-1,2,4-triazole in the presence of a series of relatively unreactive catalyst molecules, using previously described spectrophotometric techniques.[7] We have also examined the partitioning of *p*-tolyl *N*,*N*-dimethylacetimidate to ester and amide; formation of ester from this imidate is thought to involve the breakdown of a tetrahedral addition intermediate with amine expulsion, the reverse of the first step of ester aminolysis,[8] and is subject to catalysis by general acids whose conjugate bases are not effective nucleophiles toward the imidate.

The claim for nonlinearity of the Brønsted plot for general base catalysis of the hydrazinolysis of free

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(2) A. Moffat and H. Hunt, *J. Amer. Chem. Soc.*, **81**, 2082 (1959).

(3) R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969).

(4) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970).

(5) W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, **93**, 1419 (1971); J. M. Sayer and W. P. Jencks, *ibid.*, **94**, 3262 (1972).

(6) L. D. Kershner and R. L. Schowen, *ibid.*, **93**, 2014 (1971).

(7) D. G. Oakenfull and W. P. Jencks, *ibid.*, **93**, 178 (1971). Reactions of acetyltriazole were followed at 222 nm.

(8) (a) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965); (b) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967); (c) G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 2638 (1968); (d) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

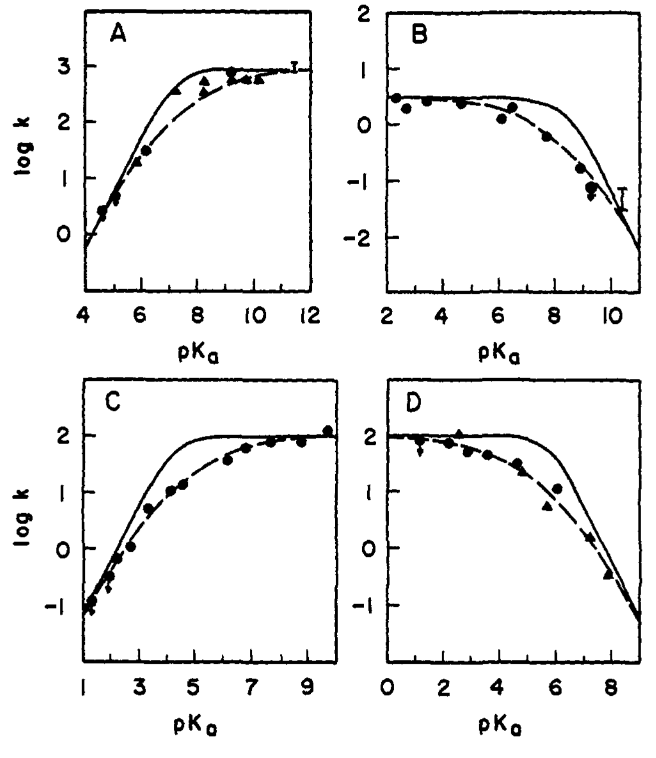
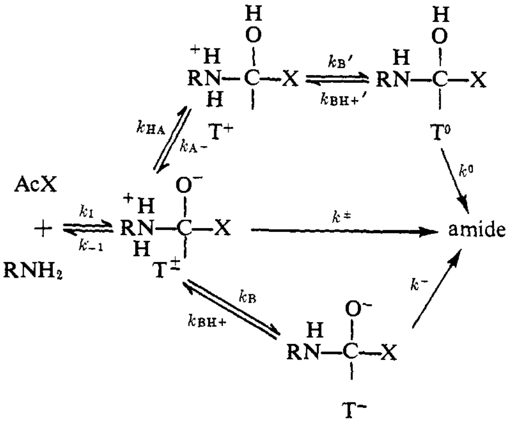


Figure 1. Brønsted plots for general acid or base catalysis of acyl aminolysis reactions by oxygen (●) and amine (▲) catalysts at 25°, ionic strength 1.0: A, hydrazinolysis of free acetylimidazole; B, ester formation upon hydrolysis of *p*-tolyl *N*,*N*-dimethylacetimidate (rate constants are relative values based on the slopes of plots of (% ester)/(% amide) against [HA]); C and D, general base and general acid catalysis of the methoxyaminolysis of *N*-acetyltriazole (rate constants in units of M^{-2} sec^{-1}).

acetylimidazole (Figure 1A) is based upon (a) the small slope ($\beta < 0.2$) for catalysis by basic amines compared to the steep slope ($\beta > 0.7$) for catalysis by weaker bases, oxyanions in particular, and (b) the curvature for the series of amine catalysts (the arrows in Figure 1 refer to upper limits for the catalytic constants in cases in which no definite catalysis was observed). The solid lines in Figure 1 show the behavior expected for a system in which proton transfer in one or the other direction occurs at every encounter of two reactants and the dashed lines show the type of curvature actually observed for simple proton transfer reactions between electronegative atoms.[9] The data are consistent with a rate-determining step of this kind. Statistical corrections do not change the shape of the curves significantly. Negative deviations were observed for some N-substituted morpholines (not shown) which may undergo slow proton transfer reactions because of steric or conformational effects.[10]

Nonlinearity in the imidate reaction (Figure 1B) is based upon catalysis of ester formation by a series of oxygen acids (carboxylic and cacodylic acids and fluorinated alcohols and acetone hydrates). Nonlinearity for general base catalysis of the reaction of methoxyamine with acetyltriazole is based upon the steep slope ($\beta \geqslant 0.6$) for catalysis by carboxylate ions and the leveling off ($\beta \leqslant 0.2$) for cacodylate, phosphate, ethylphosphate, methylarsonate, and carbonate (Figure 1C); a limiting rate constant of $\leqslant 7 \times 10^3$ M^{-2} sec^{-1} for hydroxide ion is also 10^4–10^5 below the Brønsted line established by the carboxylate ions. General acid catalysis of the same reaction shows a shallow slope ($\alpha \leqslant 0.2$) for catalysis by carboxylic acids and a negative deviation ($\alpha \geqslant 0.6$) for catalysis by ammonium ions (Figure 1D). The similar reactivity of carboxylic acids and of methoxyammonium and triazolium ions shows that the smaller rate constants for less acidic ammonium ions do not reflect an enhanced reactivity of carboxylic acids acting as bifunctional catalysts, as has been suggested to account for similar behavior in the methoxyaminolysis of *p*-nitrophenyl acetate.[11]

The shape of these curves demonstrates that there is a change in the nature of the transition states of these reactions for strong and weak base catalysts. Since the curvature is sharper than expected for a one-step reaction,[9,12] we believe that these reactions undergo a change in rate-determining step with different catalysts and, hence, proceed in a stepwise manner with an intermediate. The simplest interpretation is that an initially formed unstable dipolar intermediate (T$^\pm$, eq 1) breaks down rapidly to starting materials unless it is trapped by encountering a molecule of acid or base catalyst with subsequent proton transfer (k_{HA} and k_B). The imidate first gives the cationic and neutral intermediates T$^+$ and T^0, which can break down to ester *via* T$^\pm$ only after proton transfer steps which are diffusion controlled in the thermodynamically favored direction. More complex mechanisms are possible in which one step involves covalent bond formation or cleavage at carbon and/or preassociation of catalyst and reactant, but all mechanisms we have proposed that are consistent with the data involve (a) at least one intermediate, (b) a stepwise reaction course, and (c) a kinetically significant transport process involving the catalyst for proton transfer.[2-6] It appears that this situation is more common than we had previously believed, although we do not believe it is universal for general acid–base catalysis of acyl and carbonyl group reactions.



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The conclusion that a transport step is rate determining in these reactions means that k_1 is not rate determining: *i.e.*, the formation and breakdown of T$^\pm$

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(9) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(10) J. Hine and J. Mulders, *J. Org. Chem.*, 32, 2200 (1967).

(11) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *J. Amer. Chem. Soc.*, 89, 3537 (1967).

(12) M.-L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, 74, 380 (1970); A. Streitwieser, Jr., W. B. Hollyhead, A. H. Pudjaatmaka, P. H. Owens, T. L. Kruger, P. A. Rubenstein, R. A. MacQuarrie, M. L. Brokaw, W. K. C. Chu, and H. M. Niemeyer, *J. Amer. Chem. Soc.*, 93, 5088 (1971); A. Streitwieser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *ibid.*, 93, 5096 (1971), and references therein.

must be fast (eq 1). This holds for both the catalyzed and the uncatalyzed ("water") reactions (the rates of both are similar, since they are observed simultaneously). Since the similar reactivities of primary, secondary, and tertiary amines with phenyl acetates mean that proton transfer is not required for these uncatalyzed reactions,[8d] the uncatalyzed breakdown of the tetrahedral addition intermediate T± ($k_{\pm}$, eq 1) must be rate determining for many such reactions.

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Requirements for General Acid–Base Catalysis of Complex Reactions[1]

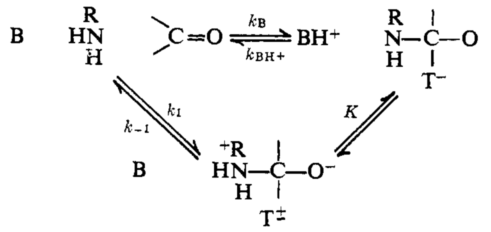
Sir:

The following simple rule is proposed as an approach to the questions (a) what determines whether an acid- or base-catalyzed reaction occurs by a stepwise or concerted reaction path, (b) what is the site of catalysis in these often kinetically ambiguous reactions, and (c) what is the nature of the driving force for such catalysis. The rule states that: *concerted general acid–base catalysis of complex reactions in aqueous solution can occur only* (*a*) *at sites that undergo a large change in pK in the course of the reaction and* (*b*) *when this change in pK converts an unfavorable to a favorable proton transfer with respect to the catalyst, i.e., the pK of the catalyst is intermediate between the initial and final pK values of the substrate site.*[2] Complex general acid–base catalyzed reactions are those in which proton transfer to or from O, N, or S atoms accompanies other processes, such as the making or breaking of bonds to carbon in carbonyl and acyl group reactions.

The rule is based on the concept that the driving force for general acid–base catalysis of complex reactions should be regarded as arising ultimately from the free energy of the proton transfer process itself, rather than from stabilization of the transition state by hydrogen bonding to the catalyst.[3] Intermolecular hydrogen bonds have small or negligible stability (relative to bonds to solvent molecules) in water and the rule avoids the assumption that there is some special stabilization energy of hydrogen bonds in the transition state.[4] Catalysis occurs simply in order to avoid the formation of high-energy intermediates, such as a protonated carbonyl group or an amine anion, and the structurally similar[5] transition states for the formation of such intermediates; concerted catalysis can be significant only when the free-energy requirements for the formation and breaking of several bonds and for the inclusion of a properly oriented catalyst molecule in the transition state of the concerted reaction are more than compensated by the extreme instability of the transition states for stepwise mechanisms. Three-dimensional transition-state diagrams, with separate axes for the heavy atom and proton transfer processes, are useful in visualizing and interpreting these situations.[6] The rule follows simply from the assumption that if the free energy of proton transfer to or from a catalyst molecule is unfavorable for the starting material and product it will also be unfavorable for the transition state.[7] Although this point appears simple, almost trivial, it has broad application and requires a reexamination of proposed mechanisms for a number of reactions catalyzed by acids, bases, and enzymes.

Applications and predictions of the rule include the following.

(a) Most additions of amines to the carbonyl group will not be subject to concerted general base catalysis. Such catalysis (k_B, eq 1) might be expected to facilitate the reaction by increasing the effective basicity and nucleophilicity of the attacking amine. However, the pK_a of the adduct T± and of RNH_3^+ are not very different[8] so that the equilibrium for proton transfer from T± to most buffer bases will be small or unfavorable. In the latter case the reverse reaction will proceed through a stepwise pathway involving a proton transfer from BH^+ to T^- at a close to diffusion-controlled rate,[9] followed by breakdown of T± in a second step, as long as T± has a sufficient lifetime to exist. The breakdown of T± through the concerted pathway would require a thermodynamically unfavorable proton transfer from T± to B that converts a good leaving group to a poor one, followed by partial reprotonation in the transition state. Since the nonconcerted expulsion of a fully protonated amine is easier than the concerted



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[2] (a) The rule does not apply to certain diffusion-controlled reactions in which separate proton transfer steps are not possible. It does apply to the separate steps of reactions proceeding through intermediates so long as these intermediates have a significant lifetime; if there are no such intermediates it should be applied to the overall reaction. (b) This rule is an extension of the *anthropomorphic rule* which states that bases will react with protons which become more acidic in the transition state (and products).[3] We were forced to propose this rule some time ago in response to some critical comments about the motivation of electrons.[4] In view of the prevailing custom of providing at least one name for all rules and explanations and since the rule here described deals with the basic driving force for acid–base catalysis, the name *libido rule* seems inescapable. However, we would not dare to advocate the adoption of such a name and trust that more ingenious name-coiners will come up with a more profound title.

[3] J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3973 (1966).

[4] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *ibid.*, **87**, 1553 (1965).

[5] G. S. Hammond, *ibid.*, 77, 334 (1955).

[6] R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970); W. P. Jencks, *Chem. Rev.*, in press.

[7] This assumption is reasonable for nearly all reactions of this type, in which the acidity (or basicity) of the transition state for the uncatalyzed reaction is intermediate between that of the starting material and product, but exceptions are possible. For example, in a (hypothetical) one-step acyl transfer reaction the carbonyl oxygen atom could be more basic in the transition state than in either the starting material or products and could be a site for general acid catalysis.

[8] J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970).

[9] M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964); E. Grunwald, *Progr. Phys. Org. Chem.*, 3, 317 (1965).