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 $T^{\pm}$ ($k^{\pm}$, eq 1) must be rate determining for many such reactions.

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

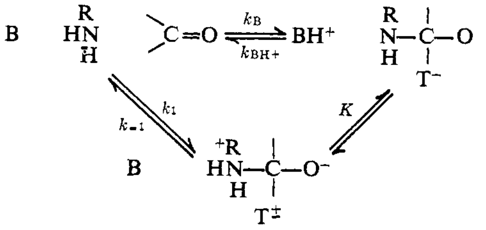
*Sir:*

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 p$K_a$ of the adduct $T^{\pm}$ and of $RNH_3^+$ are not very different[8] so that the equilibrium for proton transfer from $T^{\pm}$ 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 $T^{\pm}$ in a second step, as long as $T^{\pm}$ has a sufficient lifetime to exist. The breakdown of $T^{\pm}$ through the concerted pathway would require a thermodynamically unfavorable proton transfer from $T^{\pm}$ 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



(1)

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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).

expulsion of a partly protonated amine, the nonconcerted mechanism ($k_1 - k_{-1}$) will be the lowest energy path in both directions. General base catalysis has not been reported for the addition of basic amines to simple carbonyl compounds and even for the addition of 2-methylthiosemicarbazide ($pK_a(RNH_3^+) = 1.2$) the Brønsted plot is nonlinear, suggesting a stepwise mechanism.[10]

(b) Base catalysis of two-step acyl aminolysis reactions will ordinarily proceed through a stepwise mechanism. Although proton transfer is required in the overall reaction to form a stable product, the difference in p$K$ between the addition intermediate $T^{\pm}$ and the catalyzing base is generally small so that concerted catalysis is not expected. Thus, the rule provides an explanation for the nonlinear Brønsted plots observed for several such reactions, as described in the preceding communication.[11] In the case of methyl formate aminolysis[12] the leaving group is sufficiently poor that the expulsion of methoxide ion from $T^-$, the immediate product of the proton abstraction step, becomes rate-determining when the pH is decreased. The rule requires amplification of a previously proposed concerted mechanism for catalysis[12] into a fast amine addition and a rate-determining proton transfer step; the "water" reaction may be assigned to a proton switch in $T^{\pm}$ to form the neutral addition intermediate.

(c) The addition of hydrogen peroxide to the carbonyl group gives an extremely unstable initial product, $H_2O_2^+{-}CR_2{-}O^-$, so that concerted general base catalysis by weak bases is possible; however, catalysis by strong bases is not expected because of the favorable equilibrium to form the hydroperoxide anion ($pK_a(HOOH) = 11.6$). In general, when the p$K$ of the catalyst is changed so that the requirements of the rule are no longer met, a concerted will change to a stepwise mechanism of catalysis; this may appear as a positive deviation of the "water" or "hydroxide-catalyzed" point in a Brønsted plot. The observed[13] $\beta$ value of 0.66 for catalysis by carboxylate ions of hydrogen peroxide addition and the positive deviation of the "hydroxide" point, interpreted as an uncatalyzed attack of $HOO^-$, agree with these predictions. Base catalysis by hydroxide ion of other addition reactions of ROH is likewise expected to involve specific base catalysis.

(d) "Acid catalysis" by water of addition reactions to the carbonyl group and, in the reverse reaction, hydroxide ion catalysis of the breakdown of addition compounds $HOCR_2X$ involve a small or unfavorable $\Delta pK$ and does not occur through a simple concerted mechanism.

(e) Fully concerted bifunctional acid-base catalysis is rare or nonexistent because of the improbability of meeting the conditions of the rule simultaneously at two sites on the reactant and catalyst. Enhanced reactivity of bifunctional catalysts may represent proton transfer alone[14] or a mechanism in which a separate proton transfer step permits product formation, but need not be rate determining, as suggested for catalysis by carboxylic acids of hydrogen peroxide addition to aldehydes.[13]

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[10] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3262 (1972).

[11] J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *ibid.*, **94**, 4729 (1972); see also references therein.

[12] G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

[13] E. Sander and W. P. Jencks, *ibid.*, **90**, 4377 (1968).

[14] R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969). Other examples may be interpreted in the same way; *e.g.*, B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

## Generation of a Stable Spiro Dihydroaromatic Anion

*Sir:*

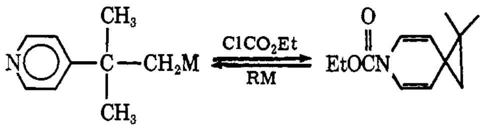
While the intermediacy of bridged arylalkyl cations in rearrangement reactions is well established[1] and stable salts of such cations have been prepared and studied,[2,3] the corresponding anions (**1**) have been comparatively neglected. Such anions have been implicated in the rearrangements of polyarylethyl metal compounds.[4,5]

**1**

**2**

Herein we describe the preparation and properties of several stable spiro aromatic organometallic compounds and show how 4-(4-pyridyl)butyl metal compounds exist in the 4,4-spirodihydropyridine structure rather than the open form as is the case for 2-(4-pyridyl)-2-methylpropyl metal compounds.[6]

Pyridylalkyl metal compounds are more likely to exist in the spiro structure (**2**) due to the great electron-withdrawing power of the pyridine ring. We have already reported how 2-(4-pyridyl)-2-methylpropyl metal compounds (**3**) close to the spirourethane (**4**) with ethyl chloroformate. We have now synthesized two new *N*-carbethoxydihydropyridines and converted them to organometallic compounds by a reaction analogous to eq 1, right to left.



(1)

**3** **4**, M = Li, Na, K, MgCl

Conversion of dimethyl 3,3-tetramethyleneglutarate *via* the acyloin[7] reaction to 4,4-tetramethylene-2-hydroxycyclopentanone (**5**), bp 85–86° (0.17 mm), $M^+ = 154$, followed by sodium borohydride reduction gave *trans*-1,2-dihydroxy-4,4-tetramethylenecyclopentane (**6**), mp 102–103°, $M^+ = 156$. The diol **6** was cleaved with aqueous sodium metaperiodate to give 3,3-tetramethyleneglutaraldehyde (**7**). Treatment of the dried ether extract of this reaction mixture with dry gaseous ammonia at 0° afforded 4,4-tetramethylene-1,4-dihydropyridine (**8**), as evidenced by nmr analysis,

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[1] D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3863, 3875, 3883 (1949); **74**, 2159 (1952); **86**, 3767 (1964).

[2] L. Eberson and S. Winstein, *ibid.*, **87**, 3506 (1965).

[3] G. Olah, E. Namanworth, M. Comisarow, and B. Ramsey, *ibid.*, **89**, 711 (1967).

[4] H. E. Zimmerman and F. J. Smentowski, *ibid.*, **89**, 5455 (1957); H. E. Zimmerman and E. Zweig, *ibid.*, **83**, 1196 (1961).

[5] E. Grovenstein, Jr., *ibid.*, **79**, 4895 (1957); E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963); **89**, 1852, 2348 (1967).

[6] G. Fraenkel and J. W. Cooper, *ibid.*, **93**, 7228 (1971).

[7] H. Kwart and J. A. Ford, *J. Org. Chem.*, **24**, 2060 (1959). This procedure is the fastest and most efficient of several tried.