J. Am. Chem. Soc. **1980**, *102*, 5286–5293

Energetic Restrictions on the Allowed Range of Catalyst pK_as for General-Acid- or General-Base-Catalyzed Reactions of Carbonyl Compounds

J. Peter Guthrie[1]

Contribution from the Department of Chemistry, University of Western Ontario,
London, Ontario, Canada N6A 5B7. *Received December 4, 1979*

Abstract: A simple model for concerted general acid/base catalysis leads to a clarification of much chemistry and the ability to make approximate predictions. In this model hydrogen-bond formation from catalyst to reactant occurs in a preequilibrium step. Reaction begins along the reaction path corresponding to uncatalyzed reaction, but proton transfer along the preformed hydrogen bond occurs when the progress of the reaction has led to matching of pK_as, and reaction then proceeds along the reaction path corresponding to the specific-acid/base-catalyzed path. (This will be seen to be an elaboration on the "libido rule" of Jencks.) This more complex motion, involving progression partway along one reaction path, proton jump, and progression along another reaction path, will lead to catalysis if and only if both of the maxima in the simpler paths can be avoided. This simple model can be used for semiquantitative predictions by fitting a quartic expression, $\Delta G = ax^2 + bx^3 + cx^4$, to the known points (starting material, $x = 0.0$, $\Delta G = \Delta G_i$; product, $x = 1.0$, $\Delta G = \Delta G_f$; transition state, $\Delta G = \Delta G^*$). Algebraic manipulation gives the coefficients for the quartic and x^*, the position of the transition state along the reaction coordinate. Two such quartics are needed: one for the uncatalyzed reaction and one for the corresponding specific-acid- (or base) catalyzed reaction. The vertical displacement between the two is determined by the pK_a of the catalyst. Catalysis, by the model described above, can only occur if the pK_a of the catalyst is such that it falls between the two limiting pK_as defined when one curve passed through the transition state of the other. Thus by determining these two limiting pK_a values we can determine the range within which catalysis can be observed. This picture seems to fit the general catalysis data for those reactions for which sufficient information is available. When it is applied to the hydrolysis of ortho esters and acetals, the clear prediction is made that general acid catalysis of both reactions should be observable, but that for acetals much weaker acids must be used if catalysis is to be detectable. The reason that such catalysis has not normally been observed is that the experiments have been done in the wrong pK_a range (and the wrong time scale). Implications for various kinds of catalysis are considered.

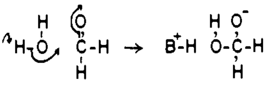
Introduction

Despite recent advances[2,3] in our understanding of general acid and general base catalysis, and particularly catalysis in which proton transfer accompanies the formation or breaking of bonds between heavy atoms (C, N, O, etc.), many features of this phenomenon remain quite mysterious. For instance, the question of which form of general catalysis (concerted,[3] hydrogen bonding,[3] preassociation,[3] trapping,[3] etc.) will be seen in a particular case is not always easy to predict. Furthermore, it has been a continual source of aggravation that some apparently very similar reactions show a striking qualitative difference; for instance, acetals characteristically show only specific acid catalysis, while apparently closely related ortho esters show general acid catalysis of the hydrolysis reaction.[4-6] In addition, there is a longstanding puzzle associated with those reactions, such as aldehyde hydration, which show Brønsted plots which are linear over what appear to be excessively wide ranges of catalyst pK_a.[7]

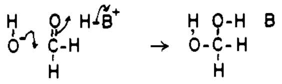
Recently, as an outgrowth of our investigations of the energetics of metastable intermediates in carbonyl and acyl reactions,[8-12] we discovered a simple picture which rationalizes this behavior, permits approximate predictions to be made of the rate constants for general catalysis, by any catalyst, and specifies the range of catalyst pK_as for which it will be possible to detect catalysis.

Results and Discussion

The picture which we use to start with is that depicted for the particular case of general-base-catalyzed hydration of formaldehyde in Figure 1.[13] The limiting cases are uncatalyzed hydration, where the nucleophile is H_2O with attack leading initially to the zwitterion,[12] and specific-base-catalyzed hydration, where the nucleophile is OH^-. General-base-catalyzed hydration is presumed to be a simple general-base-catalyzed reaction, process 1; the alternative, specific-base–general-acid-catalyzed reaction, process 2, involves impossibly large rate constants for some catalysts.



(1)



(2)

We will assume that there is no perturbation when a catalyst is hydrogen bonded to the potential leaving group. (This cannot be correct, but should not introduce a large error.) Our picture of the general-base-catalyzed reaction is then that the proton transfer occurs along the preformed hydrogen bond; the reaction encounter complex of formaldehyde and a water molecule hydrogen bonded to the catalyst starts up the reaction path corresponding to the uncatalyzed reaction and follows it until the pK_a of the developing oxonium ion matches that of the catalyst, at which point (approximately) the proton is transferred, and the reaction proceeds along the path corresponding to the specific-base-catalyzed reaction. The catalysis results from avoiding the maxima of both curves. This picture is simply an elaboration of the "libido rule" of Jencks.[14] The advantage of this elaboration is that it permits an immediate statement of the limits upon the range of catalysts which can accelerate the reaction.

In this picture we have ignored the free-energy barrier to the motion of the proton along the hydrogen bond, because this energy barrier is probably very small;[15] furthermore, we have ignored

---

[1] Alfred P. Sloan Fellow, 1975–1979.
[2] Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705.
[3] Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.
[4] Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.
[5] Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581.
[6] Eliason, R.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 7037.
[7] Albery, W. J. *Prog. React. Kinet.* **1967**, *4*, 355.
[8] Guthrie, J. P. *Can. J. Chem.* **1976**, *54*, 202.
[9] Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898.
[10] Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999.
[11] Guthrie, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 3608.
[12] Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892.

[13] It is simpler to present the argument in terms of the hydration reaction. The experimental data[34] correspond to dehydration which occurs by the microscopic reverse path, i.e., specific base–general acid catalysis. In Figure 2, this reaction is presented in the dehydration sense.
[14] Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.

0002-7863/80/1502-5286$01.00/0

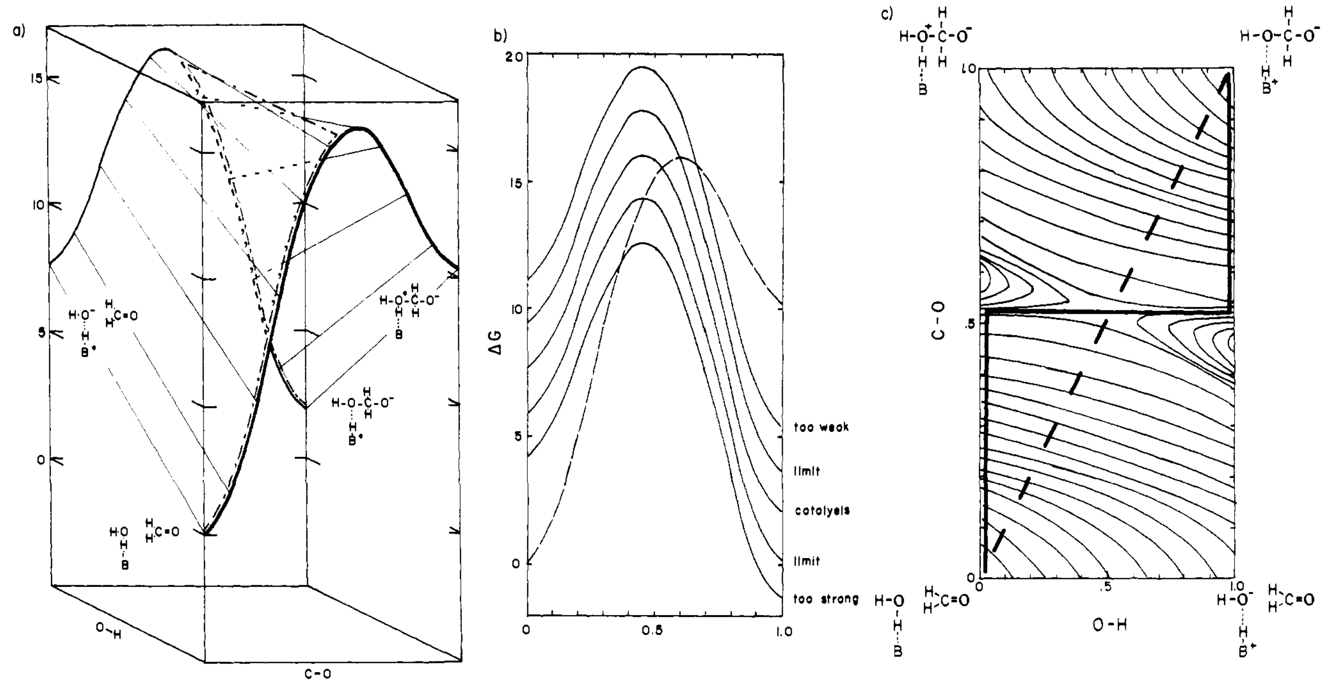


Figure 1. (a) Three-dimensional reaction coordinate diagram for hydration of formaldehyde: (—) limiting reaction paths, uncatalyzed addition of water and hydroxide addition; (—) lines representing proton transfer along a hydrogen bond; (- - -) reaction path for the model proposed in this paper. (b) Superposition of the limiting lines for various strengths of the catalyzing base; vertical displacement corresponds to the free-energy change for proton transfer to the catalyst. General catalysis requires avoiding both maxima; the limits are reached when the catalyst base strength is such that one curve passes through the maximum in the other. For bases stronger or weaker than these limits, the lowest energy path crosses one of the limiting maxima: (- -) uncatalyzed reaction; (—) base-catalyzed reaction. (c) Contour diagram for the general catalysis case. In this diagram, and all diagrams in the paper, there is assumed to be no barrier to proton transfer along a hydrogen bond (see the text): (—) "orthogonal" path, as described in the text; (- - -) possible alternative in which motion occurs simultaneously along both coordinates.

the stabilizing effect of hydrogen-bond formation to the catalyst upon the energy of the two reaction paths, since this effect is also likely to be small. Because the first effect would lead to an increase in free-energy level, and the second to a decrease in free-energy level, and both effects should be modest, it seems not unreasonable to hope that they will approximately cancel.

The above picture is presented as if the reaction coordinate involved first motion along the C–O bond forming coordinate (for the uncatalyzed process), then along the O–H–O proton transfer coordinate, and finally along the C–O bond forming coordinate (for the catalyzed process) (solid line in Figure 1c). Although it is possible that this is indeed the way the reaction proceeds, this is not a necessary part of the argument. The energy surface could well be such that the true reaction path is not one involving "orthogonal" motions, but one where both coordinates are changing together at all points along the reaction path (dashed line in Figure 1c). Our knowledge of the detailed energy surface is far too inadequate to permit a definitive choice. Since our concern is only to make approximate statements about the energy level at the highest point which must be crossed, i.e., the transition state, and not concerning the actual path over the energy surface, we choose a convenient way to calculate this energy, without insisting that it is necessarily the best overall description of the reaction path. However, a number of quantum-mechanical calculations of reaction surfaces[17] (admittedly for simpler reactions, in the gas phase) have led to "reaction coordinates" involving this sort of "orthogonal" motion. This suggests very strongly that "orthogonal" processes must be considered and cannot be dismissed out of hand.

Only those catalysts with pK_a values appropriate to cause crossover of the reaction paths between the two maxima can produce rate enhancements and any catalyst which is stronger or weaker will be ineffective, because the lowest free energy of activation will still involve passing over one of the maxima. Unfortunately, only the free-energy levels of the extrema of a reaction path can be determined experimentally, and there is no way to get information about the nature of the energy surface between extrema. It has been suggested recently[18] that the free energy along the reaction path should be approximately a quartic function of distance along the reaction coordinate, of the form

$$G = ax^2 + bx^3 + cx^4 \qquad (3)$$

where x is the distance along the reaction coordinate and is defined to be 0.0 at the starting material and 1.0 at the product. This equation cannot be exact, but should give a fair approximation to the free energy at points between the known levels. The "reaction coordinate" is of course exceedingly ill-defined in terms of structural parameters. By fitting such equations to the uncatalyzed and specific-acid- or -base-catalyzed reactions, we can then ask how far the curves need to be moved in the vertical (free energy) coordinate to give the two limiting overlap situations, where crossover occurs at one of the maxima.[19] These vertical distances correspond to the pK_a differences for proton-transfer reactions involving catalyst and reactant.

In order to allow for the inevitable imprecision of the curves we use the following procedure: the reaction distance at the maximum is considered to be uncertain by 0.1 out of a total distance of 1.0, and the free energy specified by the quartic is

---

(15) Eigen has shown that for proton transfers involving two electronegative atoms there is only a very small kinetic barrier to the proton transfer.[16] Over most of the range of pK_a difference the reaction is diffusion controlled in the favorable direction. In the present case this means that the barrier to transfer along the hydrogen bond will be only a few kilocalories per mole at most.

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

(17) (a) Baskin, C. P.; Bender, C. F.; Bauschlicher, C. W., Jr.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1974**, *96*, 2709. (b) Bauschlicher, C. W., Jr.; Schaefer, H. F., III; Bender C. F. *Ibid.* **1976**, *98*, 1653.

(18) (a) Dunn, B. M. *Int. J. Chem. Kinet.* **1974**, *6*, 143. (b) Noble, W. J. L.; Miller, A. R.; Hamann, S. D. *J. Org. Chem.* **1977**, *42*, 338.

(19) As an illustration of the sort of curves which we obtain, for Figure 2a, the quartics corresponding to the values in Table II derived using $\rho^* = -1.3$ follow: uncatalyzed, $G = 194.49x^2 - 366.62x^3 + 177.72x^4$ (G in kcal/mol) and $x^* = 0.547$; catalyzed, $G = 108.63x^2 - 264.42x^3 + 144.00x^4$ and $x^* = 0.377$. (This reaction, although apparently general base catalyzed, is actually specific base–general acid catalyzed; thus the uncatalyzed reaction is of the anion, and the catalyzed reaction is of the zwitterion.)

considered to be correct at the extrema, but to have an uncertainty of 3 kcal midway between each pair of extrema. The justification for these limits is frankly empirical: with these limits imposed, for all cases tested to date, the method predicts allowed ranges for the pK_as and rate constants for general acid or base catalysis which include the experimental points.

In order to assess the sensitivity of the limiting pK_a values to errors in the various quantities used in the calculations, we calculated partial derivatives, $\partial \mathrm{p}K_a/\partial a_i$, for each quantity a_i used in the computation. A simple computer program varied each a_i by adding 0.1 to the input value of a_i (in kcal/mol except for x^*), and calculated the corresponding derivatives from the changes in limiting pK_a values. These derivatives clearly show that by far the greatest sensitivity is to the values of x^* ($\partial \mathrm{p}K_a/\partial x^*$ ranges from 8 to 50); this is unfortunate because these values are not experimentally determinable. However, various ways of evaluating x^* normally agree within ±0.1, which leads to errors in pK_a of 2–3 log units in most cases, although the errors are sometimes 5 log units. The sensitivity to errors in the free energy of the reaction surface is also important (derivative values from 0.4 to 0.5), particularly since these errors are large, and, as one might expect, pK_a values are sensitive to the rate constants (derivative values from 0.6 to 0.9); these are usually accurate.

Figure 2 shows that the limits imposed by this analysis define a polygon for each reaction within which the observable rate constants for general catalysis must fall. The lower limit on the rate constant is that for the uncatalyzed reaction, but the upper limit depends on the rate of the specific-acid- or -base-catalyzed reaction, adjusted where necessary by the equilibrium constant for forming the conjugate acid or base of the substrate by reaction with the catalyst.

For each set of input parameters, we have a directly calculated pair of limiting log k, pK_a points, joined by a dotted line in Figure 2, 4, or 5. There are also two pairs of limiting points, calculated using the error limits discussed above. Corresponding pairs of these points are joined by solid lines. Finally, the three points for the lower limit on the observed rate (k_{un}) and the three points for the upper limit of catalyst strength are joined by solid lines to define a polygon (which is often near to being a triangle). For Figure 2, the polygons for various assumed values of the pK_{BH^+} of the intermediate were plotted together, to show the effect of uncertainties in this pK.

The reactions included in this figure include dehydration of aldehyde hydrates, breakdown of hemiacetals, and addition of water to esters. In all cases we have estimated pK_as for tetrahedral intermediates as we have previously described,[12] with some modifications described in the Appendix, and have assumed that uncatalyzed hydration of a carbonyl compound (or its microscopic reverse) is actually rate-determining formation of the zwitterionic form of the carbonyl hydrate.[12] This point is not devoid of controversy, since it is not yet clear what the best way to estimate pK_as and zwitterion contents of tetrahedral intermediates should be,[20] and for some plausible estimates (but not all) the intermediates appear to be too unstable to be on the reaction path.[21] The question of whether the zwitterionic species are on the reaction path clearly needs to be clarified, but, for the moment, it seems permissible to explore the consequences of our mechanistic assignments,[12] and this leads to internally consistent and useful results.

The pK_a values which we have employed are shown in Table I, along with ranges for the pK_as of oxonium ions. For alcohol pK_as, all data seem to be in good accord with the equations proposed by Cohen[22] and Hine,[23] etc., except for the hemithioacetals,[24] for which the only direct experimental values are from as yet unpublished work.[25] For oxonium ions there is a shocking

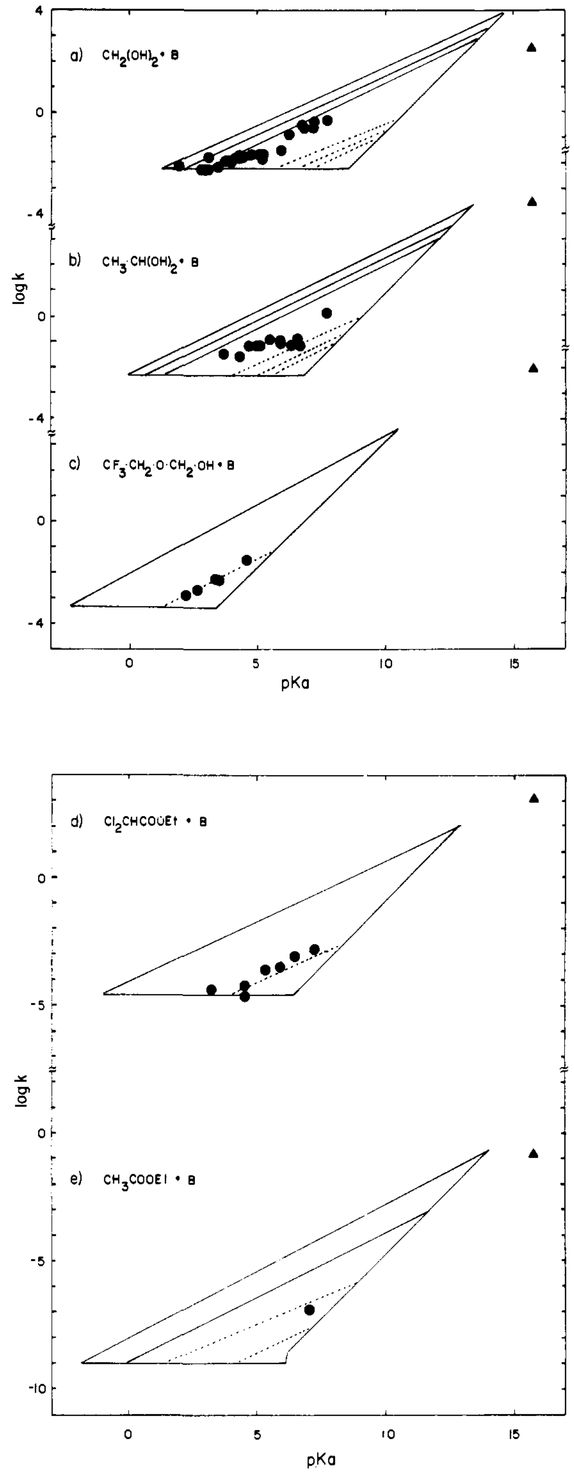


Figure 2. Limits on general catalysis for reactions where it has been studied, and enough information is available to apply our new method. (a) Dehydration of formaldehyde hydrate (ref 47). (b) Dehydration of acetaldehyde hydrate (ref 49). [Shown as dehydration for ease of comparison with (a)]. (c) Breakdown of the hemiacetal of formaldehyde and trifluoroethanol (ref 21). (Several other hemiacetals of formaldehyde were reported in ref 21, and all show patterns consistent with our model.) (d) Hydrolysis of ethyl dichloroacetate (ref 57). (e) Hydrolysis of ethyl acetate (ref 58). Lines are shown for each of the pK_a estimates, except where they led to impossible rate constants. (●) Experimental points for general catalysis. (▲) Observed rate constants for OH^- catalysis (presumed to be specific base catalysis). For each reaction solid lines join the limiting pK_a–rate constant pairs for extreme values allowed by the error limits assumed, and also close the polygons; dotted lines join the best pK_a–rate constant pairs calculated directly from the two quartics. In all cases points and lines corresponding to physically meaningless rate constants have been omitted.

---

(20) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

(21) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444.

(22) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205.

(23) Hine, J.; Koser, G. F. *J. Org. Chem.* **1971**, *36*, 1348.

(24) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931.

Table I. pK_a Values Used in This Paper[a]

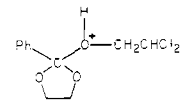
A. Tetrahedral Intermediates, Cationic

compd	pK_a^{+z} [b]	pK_a^{+0} [c,d] $\rho^* = -0.89$	pK_a^{+0} [c,d] $\rho^* = -1.3$	pK_a^{+0} [c,d] $\rho^* = -1.8$	pK_z [d,e] $\rho^* = -0.89$	pK_z [d,e] $\rho^* = -1.3$	pK_z [d,e] $\rho^* = -1.8$
$CH_2(OH)(OH_2^+)$	9.02	−1.89	−2.97	−4.05	10.91	11.99	13.09
$CH_3CH(OH)(OH_2^+)$	9.68	−1.89	−2.97	−4.05	11.57	12.65	13.73
$CF_3CH_2(OH^+)CH_2OH$	8.49	−6.11	−7.91	−9.71	14.60	16.40	18.20
$CHCl_2C(OCH_3)(OH)(OH_2^+)$	5.36	−5.24	−8.09	−10.82	10.60	13.39	16.18
$CH_3C(OCH_3)(OH)(OH_2^+)$	7.93	−3.50	−5.41	−7.31	11.43	13.34	15.24

B. Tetrahedral Intermediates, Neutral

compd	pK_a	compd	pK_a
$CH_2(OH)_2$	13.27[f]	$CH_3C(OCH_3)(OH)_2$	11.80
$CH_3CH(OH)_2$	13.57[f]	$CF_3CH_2OCH_2OH$	12.86
$CHCl_2C(OCH_3)(OH)_2$	9.23		

C. Ortho Esters and Acetals

compd	pK_a [d] $\rho^* = -0.89$	pK_a [d] $\rho^* = -1.3$	pK_a [d] $\rho^* = -1.8$	compd	pK_a [d] $\rho^* = -0.89$	pK_a [d] $\rho^* = -1.3$	pK_a [d] $\rho^* = -1.8$
$PhC(OCH_3)_2(O(H)CH_3^+)$	−5.87	−7.59	−9.71		−6.70	−9.53	−12.36
$PhC(CH_3)(OCH_3)(O(H)CH_3^+)$	−4.44	−5.54	−6.64				

D. Others

compd	pK_a	compd	pK_a
$CH_2{=}OH^+$	−8.2[g]	CH_3OH	15.49[i]
CF_3CH_2OH	11.43[h]	Cl_2CHCH_2OH	12.89[i]

[a] References are given for experimentally determined values; others are estimated as described in the text. [b] Ionization of cationic intermediates to give a zwitterion. [c] Ionization of cationic intermediate to give a neutral species. [d] Estimates are given for the extreme values of ρ^* which have been proposed (−0.89, ref 12, and −1.8, ref 11 (for ammonium ions, assuming that ρ^* for ammonium ions and oxonium ions will be the same; ref 27)), as well as for an average value (−1.3). [e] Negative logarithm of zwitterion formation constant: K_z = (zwitterion)/(neutral). [f] Reference 45. [g] Estimated in ref 12. [h] Reference 40. [i] Reference 22.

dearth of direct experimental information. From an indirect measure of basicity of alcohols reported by Levitt and Levitt,[26] we have deduced a ρ^* value of −0.89 for RCH_2OH.[12] It has been suggested that ρ^* should be the same as for ammonium ions,[21,27] $RCH_2NH_3^+$, or $RCH_2N(Me)_2H^+$, for which we[11] have proposed ρ^* values of ca. −1.8. Various intermediate values of ρ^* have also been proposed.[20] For the present we calculate pK_as calculated for both extreme values of ρ^*, as well as for an average value of ρ^*. We make the reasonable assumption that the true ρ^* value for oxonium ions is highly unlikely to fall outside these limits. Table I also gives values for the zwitterion contents based on the various ρ^* values. It should be noted that for some of the reactions some, but not all, of the pK_a estimates lead to impossibly fast rate constants for one step in the reaction.

The equilibrium constants, and rate constants for the limiting reaction, are given in Table II. For the esters the equilibrium constants are for the methyl esters, while the general base catalysis studies were for the ethyl esters; we expect that any difference in rate constants between the two esters will be trivial compared to the approximations inherent in our treatment.

In drawing the figures we have used linear interpolation between pairs of limiting pK_a, log k points. This assumption is equivalent to approximating the appropriate parts of the two reaction coordinate diagrams (for the catalyzed and uncatalyzed reactions) by straight lines. The slope of the log k vs. pK_a line is then simply related to the slopes of the two lines giving free energy as a function of x for the two processes. Clearly this is a gross oversimplification, since the reaction coordinate diagrams are not linear; by using the quartics, one could calculate a curve relating log k and pK_a. The problem is that the quartic is only a crude approximation to the (unknown) true curve, and is associated with large errors at all points except those which are specified by experimental facts. It seems ill-advised to present such elaborate curves given the magnitude of the uncertainties involved. Examination of curves (not shown) derived from this sort of quartic approximation suggests that the log k vs. pK_a curves will be approximately linear, that curvature at the extrema is quite likely, and that the curves of the quartic curves may compensate so that one sees approximate linearity even when the quartics are markedly curved.

Our picture appears to weaken very considerably the conventional view that the Brønsted slope is a measure, in some approximate sense, of the degree of proton transfer at the transition state.[28] It should, however, be noted that this change in interpretation applies only to reactions in which there is heavy atom bond making/breaking accompanying proton transfer; for reactions in which only proton transfer is important, such as enol ether hydrolysis catalyzed by general acids,[56] the traditional picture still holds. In terms of our model the proton is jumping along a hydrogen bond at the transition state, and thus the degree of proton transfer is the same, to the extent that it is defined at all, for any reaction of this class; the degree of heavy atom bond making/breaking is different for each catalyst, so this is not given by the slope either. The slope of the Brønsted plot is determined by the effective slopes of the reaction energy diagrams for the two limiting processes (i.e., the slopes of the graphs of free energy against reaction coordinate). A long linear Brønsted plot simply requires that the catalyzed and uncatalyzed limiting reactions have very different x^* values so that the limiting pK_a values are very different, and that the curves either be adequately close to linear or else be curved in ways which compensate.

An explanation is now available for the hitherto puzzling behavior of simple ortho esters and acetals; the reason that general acid catalysis has been observed for the ortho esters is simply that it is possible for a more conveniently studied range of catalyst pK_as. From the work of McClelland[29] and Jencks[30] it is possible to calculate the equilibrium constants for oxocarbonium ion formation

---

(25) Referred to as a personal communication in ref 21.

(26) Levitt, L. S.; Levitt, B. W. *Tetrahedron* **1971**, *27*, 3777.

(27) Bunton, C. A.; de Wolfe, R. H. *J. Org. Chem.* **1965**, *30*, 1371.

(28) (a) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; p 241. (b) This reference gives suitable cautions concerning the application of this assumption.

(29) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031.

(30) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.

Table II. Rate and Equilibrium Constants Used in This Paper[a]

A. Elimination from Hydrates and Hemiacetals

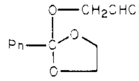
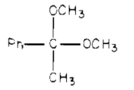
compd	$\log K^{\circ}$ [b]	$\log K^{zp}$ [c]	$\log k_w$ [d]	$\log k^{z}$ [e]	$\log K^-$ [f]	$\log k_{OH^-}$ [g]	$\log k^-$ [h]
$CH_2(OH)_2$	-3.36^{i}	$+9.69^{j}$ $+8.63^{k}$ $+7.55^{l}$	-2.26^{m}	10.79^{j} 9.73^{k} 8.65^{l}	-4.09	3.20^{m}	2.47
$CH_3CH(OH)_2$	-0.03^{n}	13.70^{j} 12.62^{k} 11.54^{l}	-2.35^{o}	11.38^{j} 10.30^{k} 9.22^{l}	-0.46	4.87^{o}	4.44
$CH_2(OH)(OCH_2CF_3)$	-2.30^{p}	15.90^{j} 14.10^{u} 12.30^{l}	-2.37^{p}	14.83^{j*} 13.03^{k*} 11.23^{l}	-1.87	7.04^{p}	5.90

	$\log K^+$ [q]	$\log K_{H^+}$ [r]	$\log k^+$ [s]
$CH_2(OH)_2$	-7.51^{j} -8.59^{k} -9.67^{l}	0.43^{m}	4.48^{j} 3.40^{k} 2.32^{l}

B. Carbonyl Addition Reaction

compd	$\log K^{\circ}{}_{H_2O}$ [t]	$\log K^{z}{}_{H_2O}$ [u]	$\log k_w$ [v]	$\log K^-$ [w]	$\log k_{OH^-}$ [x]
$CHCl_2COOCH_3$	-4.34^{y}	-20.52^{j} -17.73^{k} -14.94^{l}	-4.66^{z*}	0.42	3.09^{aa}
CH_2COOCH_3	-8.2^{bb}	-23.4^{j} -21.5^{h} -19.6^{l}	-9.0^{cc}	-6.0	-0.82^{dd}

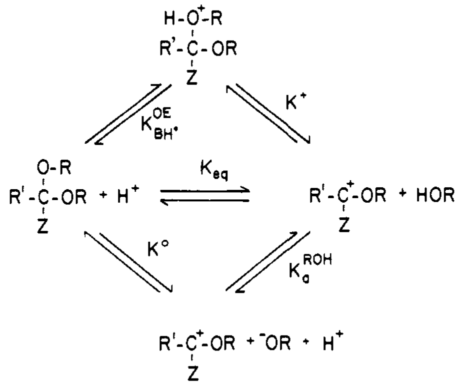
C. Ortho Ester and Acetal Hydrolysis

compd	$\log K^{\circ}$ [ee]	$\log k_w$ [ff]	$\log K_{eq}$ [gg]	$\log K^+$ [hh]	$\log k_H$ [ii]	$\log k^+$ [jj]
$PhC(COH_3)_3$	-17.0	-9.1 ± 2^{kk}	-3.18^{ll}	$+6.5^{j}$ 4.4^{k} 2.3^{l}	1.87^{mm} 7.4^{l}	11.6^{j} 9.5^{k}
	-11.62	-3.22^{nn}	1.27^{kk}	13.6^{j} 10.8^{k} 8.0^{l}	3.09^{nn}	15.5^{j*} 12.6^{k*} 9.8^{l}
	-18.5	-10.2 ± 2^{kk}	-4.77^{oo}	2.1^{j} 0.9^{u} -0.3^{l}	3.2^{oo}	10.1^{j} 8.9^{k} 7.7^{l}

[a] All in aqueous solution at 25 °C; an asterisk indicates that the pK_a estimates led to a physically impossible rate constant. [b] $K^{\circ} = [>C=O][H_2O]/[>(OH)_2]$. [c] $K^{zp} = [>C=O][H_2O]/[>C(O^-)(OH_2^+)]$; calculated from $\log K^{\circ}$ and pK_z (Table I). [d] Observed rate constant for uncatalyzed breakdown of hydrate or hemiacetal. [e] Rate constant for breakdown of the zwitterion; calculated from $\log k_w$ and pK_z (Table I). [f] $K^- = [>C=O][OH^-]/[>C(O^-)(OH)]$; calculated from $\log K^{\circ}$ and pK_a (Table I). [g] Observed rate constant for hydroxide-catalyzed breakdown of hydrate or hemiacetal; $v = k_{OH}[OH^-][SH]$. [h] Rate constant for breakdown of the anion of the hydrate or hemiacetal: $v = k^-[S^-]$. Calculated from k_{OH} and pK_a (Table I). [i] Reference 46. [j] Assuming $\rho^* = -1.8$. [k] Assuming $\rho^* = -1.3$. [l] Assuming $\rho^* = -0.89$. [m] Reference 47. [n] Reference 48. [o] Reference 49. [p] Reference 21. [q] $K^+ = [>C=OH^+][H_2O]/[>C(OH)(OH_2^+)]$; calculated from $\log K^{\circ}$ and pK_a values in Table I. [r] Observed rate constant for hydronium ion catalyzed breakdown of the hydrate. [s] Rate constant for breakdown of the protonated hydrate; calculated from $\log k_{H^+}$ and pK_a (Table I). [t] $K^{\circ}{}_{H_2O} = [>C(OH)_2]/[>C=O][H_2O]$. [u] $K^{z}{}_{H_2O} = [>C(O^-)(OH_2^+)]/[>C=O][H_2O]$; calculated from $\log K^{\circ}{}_{H_2O}$ and pK_z (Table I). [v] Observed rate constant for uncatalyzed addition of water to the carbonyl compound. [w] $K^- = [>C(O^-)(OH)]/[>C=O][OH^-]$; calculated from $\log K^{\circ}{}_{H_2O}$ and pK_a (Table I). [x] Observed rate constant for hydroxide addition to the carbonyl compound. [y] Reference 50. [z] Reference 51. [aa] Reference 52. [bb] Reference 12. [cc] Estimated (ref 50) from the rate constant for the ethyl ester; ref 53. [dd] Reference 54. [ee] $K^{\circ} = [>C=O^+CH_3][^-OCH_3]/[>C(OCH_3)_2]$; calculated as described in the text. [ff] Rate constant for uncatalyzed cleavage of ortho ester or acetal. [gg] $K_{eq} = [>C=O^+CH_3][HOCH_3]/[>C(OCH_3)_2][H^+]$. [hh] $K^+ = [>C=O^+CH_3][HOCH_3]/[>C(O(H)CH_3^+)(OCH_3)]$; calculated from $\log K_{eq}$ and pK_a (Table I). [ii] Observed rate constant for hydronium ion catalyzed hydrolysis of ortho ester or acetal. [jj] Rate constant for breakdown of the protonated ortho ester or acetal; calculated from $\log k_H$ and pK_a (Table I). [kk] Estimated as described in the text. [ll] Reference 29. [mm] Reference 32. [nn] Reference 36. [oo] Reference 30.

from protonated trimethyl orthobenzoate and acetophenone dimethyl acetal (acid-catalyzed reaction) and neutral ortho ester or acetal (uncatalyzed reaction) as indicated in Scheme I. For these calculations it was necessary to have pK_a values for protonated acetals and ortho esters; we have used values from the literature.[31] These values are not experimentally determined, but are derived from various correlations. Since the values which we used are near the midpoint of the two estimates which one might plausibly make, using either a ρ^* value of -0.89 (which we have suggested for oxonium ions) or -1.80 (which applies to ammonium ions), these values seem likely to be approximately correct. It does not seem likely that ρ^* will be outside the limits suggested. The rates of the acid-catalyzed reactions are known,[30,32] but the rates for the uncatalyzed reactions are not. These rates were estimated from the equilibrium constants for the uncatalyzed formation of oxocarbonium ion, and a Marcus curve[59,60] for this reaction based upon the known rate and equilibrium constant for

Scheme I



---

(31) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581.

(32) Bull, H. G.; Koehler, K.; Pletcher, T. C.; Ortz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1971**, *93*, 3002.

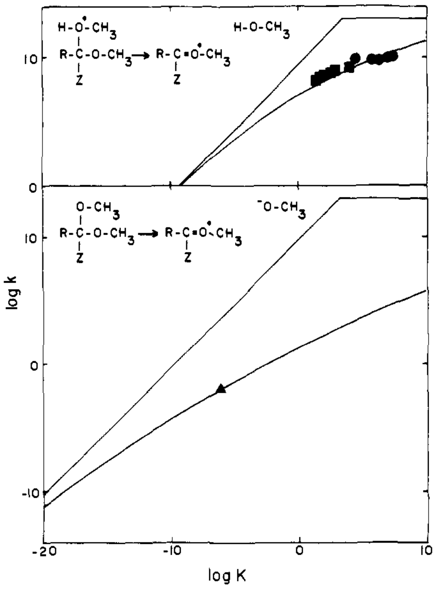


Figure 3. Marcus curves for ortho ester or acetal breakdown: (■) breakdown of protonated ortho esters (data from ref 29 and 32 with pK_a values estimated using a ρ^* value of −1.3); (●) breakdown of protonated acetals (data from ref 30 with pK_a values estimated using a ρ^* value of −1.3); (▲) breakdown of unprotonated tropone diethyl acetal (data from ref 33). Lines calculated from $k_{obsd} = k_1k_2/(k_{-1} + k_2)$ with k_1, the rate constant for the bond-breaking step, given by $\log k_1 = 12.79 - b(1 - (\log K)/4b)^2$ [59,60] k_2, the rate constant for diffusion apart of the products, taken as 10^{11} for the acid-catalyzed reaction and 1.4×10^{10} for the uncatalyzed reaction, and k_{-1} calculated from the equilibrium constant for the bond-breaking process.

the uncatalyzed cleavage of tropone diethyl acetal[33] (the equilibrium constant being calculated on the assumption that water and ethanol have the same second-order rate constant for reaction with the oxocarbonium ion). The available data for the acid-catalyzed reaction[29,30,32] suggest that the Marcus equation[59,60] will give an approximate correlation; see Figure 3. The rate and equilibrium constants so calculated are found in Table II. By applying our treatment it is possible to calculate the lowest catalyst pK_a for which general acid catalysis will be observable; see Figure 4. The lower limit on catalyst pK_a for the ortho ester is 6.7 (−0.1 ↔ 9.0); that for the acetal is 10.8 (5.0 ↔ 12.5). This leads to the clear prediction that general acid catalysis should be observable for acetophenone dimethyl acetal, provided that one is willing to study the reaction with very weak catalysts at high pH, and accept very slow reactions, and that general acid catalysis for the ortho ester should be detectable for catalysts of significantly lower pK_a. This is in fact the sort of behavior which is observed; unfortunately, the equilibrium constants are available for aromatic ortho esters and acetals, and the kinetics data are available for aliphatic ortho esters and acetals. Cordes has studied the hydrolysis of trimethyl orthobenzoate in aqueous solution,[32] and found no catalysis for acetic acid or more acidic carboxylic acids. Brønsted and Wynne-Jones studied the hydrolysis of triethyl orthoacetate,[34] and found no catalysis by acetic acid, but did find catalysis by p-nitrophenol and phenol. Since the rates of acid-catalyzed hydrolysis of orthoacetate and orthobenzoate esters are rather similar,[31] the energetics of the reactions are probably rather similar as well, so this is in accord with our picture.[62]

The estimates of pK_a may be in error as may the estimates of the rate constants for the uncatalyzed reactions, but such errors are likely to be correlated; i.e., it is very unlikely that the acetal pK_a will correspond to a ρ^* near −0.89 while that of the ortho ester corresponds to a ρ^* near −1.8, or that one reaction involves a much smaller rate constant for uncatalyzed reaction than our estimate, while the other has a much larger rate constant. For any plausible pair of rate and equilibrium constants the qualitative prediction holds, although the quantitative details are of course different.

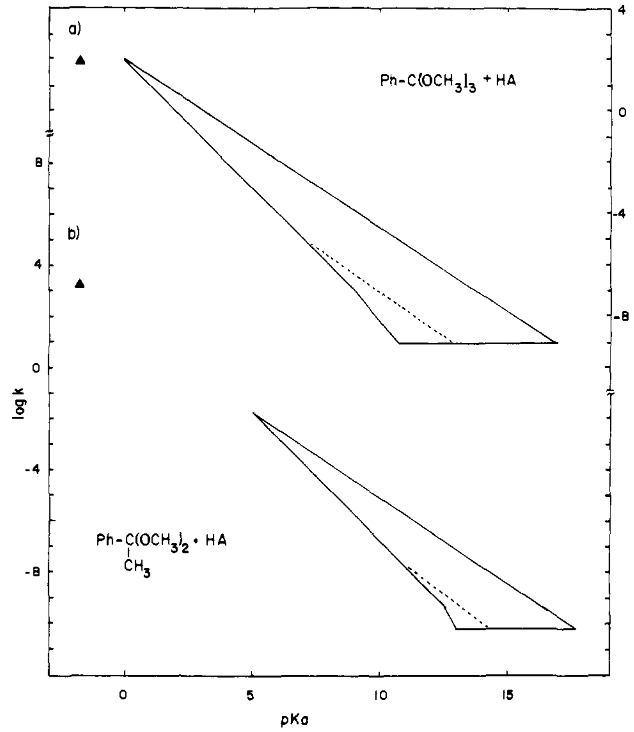


Figure 4. Limits on general acid catalysis for trimethyl orthobenzoate and acetophenone dimethyl acetal: (▲) observed rate constant for catalysis by H^+ (data from Table II, using values based on pK_{BH^+} calculated using a ρ^* value of −1.3 and uncatalyzed rate constants estimated from Figure 3).

Catalysis by hydronium or hydroxide ions could in principle be true specific acid catalysis (preequilibrium proton transfer) or general catalysis, with proton transfer concerted with other bond-making or -breaking steps. Our approach allows a distinction to be made since, in those cases where the possible range of general acid or base catalyst pK_as does not include catalysts as strong as the solvent ions, then the observed reaction catalyzed by one of these ions is true specific catalysis. If the possible range of the appropriate limiting catalyst pK_a is entirely stronger than the pK_a of the solvent ion, then the observed catalysis by the solvent ion must be general, and the assumption involved in our method, that the apparent rate constant for solvent ion catalysis represents specific acid/base catalysis, must be wrong. If the possible range of the appropriate limiting pK_a includes the pK_a of the solvent ion, then the observed catalysis may be general or specific, and other evidence must be used for a final decision.

The question of the nature of the catalysis by H_3O^+ of the hydrolysis of ortho esters has been vexatious, and is still a subject for research. Part of the difficulty in assigning a mechanism is the gross uncertainty concerning the basicity of ortho esters, so that it is not possible to make confident statements concerning the rates of proton-transfer reactions involving protonated ortho esters. In 1974, Kresge et al. reviewed the situation for ortho esters,[35] and concluded that the data in hand allowed three mechanisms: concerted reaction, with proton transfer far advanced, and C–O cleavage just begun; stepwise, with the C–O cleavage and the loss of proton to give back starting material occurring at similar rates; and spectator catalysis with proton transfer complete at the transition state but breakdown of the protonated ortho ester to give products, being faster than the diffusion away of the conjugate base of the catalyst.

More recently Kresge et al. have concluded that, for the special case of 2-alkoxy-2-phenyl-1,3-dioxolanes, the concerted mechanism

---

(33) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027.

(34) Brønsted, J. N.; Wynne-Jones, W. F. K. *Trans. Faraday Soc.* **1929**, *25*, 59.

(35) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494.

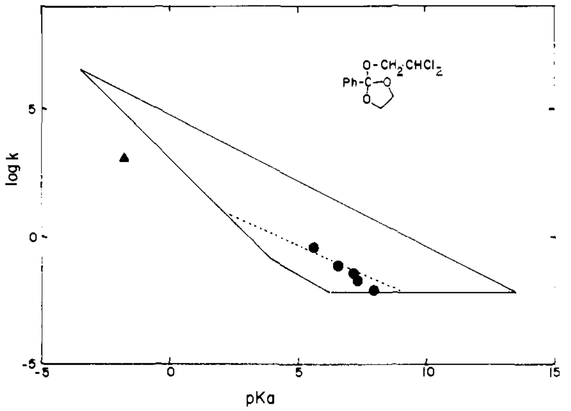


Figure 5. Limits on general catalysis for 2-phenyl-2-[(2,2-dichloroethyl)oxy]-1,3-dioxolane, calculated assuming that the rate constant for H^+ catalysis represents specific acid catalysis: (●) observed rate constants for general catalysis by buffer species; (▲) observed rate constants for H^+ catalysis. Data from ref 36 and Table II.

obtains.[36] Our treatment leads to results in full accord with this conclusion for the dioxolanes. The equilibrium constant for oxocarbonium ion formation from the methoxydioxolane can be calculated from the measured equilibrium constant for formation of this ion from the hydrogen ortho ester,[31] using a value for the equilibrium constant for replacement of methoxyl by hydroxyl calculated as we have previously described.[9] The equilibrium constant for other alkoxy groups can then be estimated by assuming that the equilibrium constant for replacement of methoxy by alkoxy in the dioxolane is the same as for the same alkoxy group in the formaldehyde hemiacetals.[38] The rate constants for the H_3O^+ and uncatalyzed reactions are known.[36] If one tries to treat this set of reactions as described above, the results shown in Figure 5 result. The treatment is clearly not internally consistent, showing that the assumption that the H_3O^+ rate is specific acid catalysis is probably wrong, and that this rate actually represents general acid catalysis by hydronium ion. For trimethyl orthobenzoate the treatment is fully consistent with the assumption that the rate constant for H_3O^+ represents specific acid catalysis.

We believe that the ortho esters are delicately poised so that either stepwise or concerted mechanisms are possible, depending upon the exact structure.

Concerted catalysis, of the sort with which we have been concerned in this paper, can only lead to observable rate enhancements if two conditions are simultaneously satisfied. (1) The difference in pK_a between catalyst and reactants for the proton which is to be transferred must change from unfavorable to favorable as the reaction occurs. (This is the "libido rule"[14].) (2) Crossover from the uncatalyzed limiting reaction energy curve to the catalyzed curve must be possible in a way that avoids both maxima, for pK_a values in the accessible range.

Hydrogen-bonding catalysis, of the sort proposed by Jencks,[3] would occur instead of concerted catalysis only if the "libido rule" were not satisfied, or if crossover from uncatalyzed to catalyzed reaction energy curve occurred after the transition state for the uncatalyzed process had been reached. In this case there would be a small stabilization of the "uncatalyzed" transition state but no large catalysis. If the "libido rule" were satisfied after the transition state but before reaching the product structure, proton transfer along the hydrogen bond would be expected to occur, but no net rate enhancement would be seen.

Catalysis by trapping of an unstable intermediate,[3] with or without preassociation, requires that there be no competitive path for concerted catalysis which avoids the intermediate entirely. The reactions where one sees catalysis by trapping seem to be those where the starting point for the limiting catalyzed reaction is of very high energy relative to the starting point for the uncatalyzed limiting reaction, so that for accessible catalyst pK_a values either concerted catalysis is impossible or else the transition state for concerted catalysis is still very close to that for the uncatalyzed reaction and little rate enhancement is possible. Typical examples would be the general-acid-catalyzed addition of a thiolate to acetaldehyde,[24] where the limiting specific-acid-catalyzed reaction requires thiolate to add to protonated acetaldehyde,[12] and general-base-catalyzed addition of an amine to methyl formate,[38] where the limiting specific-base-catalyzed reaction requires amide ion to add to the ester.

Although our new method is not of universal applicability, because of the requirement that rate and equilibrium constants for both limiting reactions have been measured or estimated, it appears to offer useful insights into the question of when one will and when one will not see concerted catalysis, for reactions where both heavy atom–heavy atom and heavy atom–proton bonds are being made or broken in the rate-determining step. It should be noted that we are led to a prediction that the possibility of concerted general catalysis is dependent upon the nature of the reaction coordinate diagrams for the uncatalyzed and specific-acid- or base-catalyzed reactions, and not upon the lifetime of the intermediate in the uncatalyzed reaction.[3,61]

Acknowledgments. I thank the Natural Sciences and Engineering Council of Canada, the Alfred P. Sloan Foundation, and the Academic Development Fund of the University of Western Ontario for financial support of this research.

Appendix

There has been considerable discussion of the question of whether substituent effects, as measured by σ^*, should be the same for all simple alkyl groups and hydrogen, especially when, as in the cases of interest here, it is a question of various substituted methyl groups bound to the reaction center.[39] It is likely that in addition to electronic effects there are steric effects and steric effects upon solvation involved. We now feel that the best procedure is to use σ^* values suited to the charge type of the process being considered. For dissociation of primary ammonium ions, methyl, ethyl, isopropyl, and *tert*-butyl all have effectively the same pK_a,[40] indicating that σ^* for H and CH_3 should be the same for this process. On the other hand, the ionization of alcohols shows quite different pK_a values: methyl, 15.54;[40] ethyl, 15.90;[22] isopropyl, 17.1;[41] *tert*-butyl, 19.2.[41] This strongly suggests that σ^* values should be different for H and CH_3. This argument is weakened by the fact that the pK_as for the isopropyl and *tert*-butyl alcohols have not been measured, but are estimated from a Brønsted correlation. We have used $\sigma^* = 0.0$ for H and CH_3 for oxonium ions and $\sigma_H^* = 0.49$, $\sigma^*_{CH_3} = 0.0$ for neutral acids. The situation of a cationic species which ionizes to give a zwitterion remains awkward, but we will treat this as a type of neutral acid.

As before we estimate the pK_a of a simple monoprotic alcohol, RR′R″COH, using $pK_a = 17.03 - 1.32\sum\sigma^*$.[12]

For the cationic acids we start with the pK_a values for protonated ethanol, −1.94,[42] and protonated methyl ethyl ether, −2.60.[43] For tetrahedral intermediates of the form $R(Z)C(OH)(OH_2^+)$, making appropriate symmetry corrections, the pK_a is given by $pK_a = -4.05 - 1.8(\sigma^*_R + \sigma^*_Z)$ if $\rho^* = -1.8$, and by $pK_a = -1.89 - 0.89(\sigma^*_R + \sigma^*_Z)$ if $\rho^* = -0.89$. For protonated ortho esters, $RC(OCH_3)_2(O(H)CH_3^+)$, we use $pK_a = -8.63 - 1.8\sigma^*_R$ if $\rho^* = -1.8$ and $pK_a = -5.34 - 0.89\sigma^*_R$ if $\rho^* = -0.89$. For protonated acetals, $R(Z)C(OCH_3)(O(H)CH_3^+)$, we use $pK_a = -5.56 - 1.8(\sigma^*_R + \sigma^*_Z)$ if $\rho^* = -1.8$ and $pK_a = -3.90 - 0.89(\sigma^*_R$

---

(36) Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1979**, *44*, 1639.

(37) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979**, *101*, 2669.

(38) Equilibrium constants for hemiacetal formation were estimated by interpolation from equilibrium constants reported in ref 21, assuming that the equilibrium constant follows σ^*.

(39) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.

(40) Jencks, W. P.; Regenstein, J. In "Handbook of Biochemistry", 1st ed.; Chemical Rubber Publishing Co.: Cleveland, 1968.

(41) Murto, J. *Acta Chem. Scand.* **1964**, *18*, 1043.

(42) Lee, D. G.; Cameron, R. *J. Am. Chem. Soc.* **1971**, *93*, 4724.

(43) Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960.

$+ \sigma^*_Z$) if $\rho^* = -0.89$. For protonated hemiacetals, RCH_2OH^+-CH_2OH, we use $pK_a = -5.01 - 1.8\sigma^*_R$ or $pK_a = -3.79 - 0.89\sigma^*_R$.

For cationic tetrahedral intermediates ionizing to give zwitterions, $R(Z)C(OH_3^+)(OH)$, we use $pK_a = 10.32 - 1.32(\sigma^*_R + \sigma^*_Z)$.[12] For ionization of the CH_2OH group in hemiacetals, or protonated hemiacetals, we estimate ρ^* using a fall-off factor of 0.36.[44] This leads to $pK_a = 8.93 - 0.17\sigma^*_R$ for RCH_2OH^+-CH_2OH and to $pK_a = 13.31 - 0.17\sigma^*_R$ for RCH_2OCH_2OH. For neutral tetrahedral intermediates we use the Hine equation.[23]

Supplementary Material Available: Table III, limiting pK_a values for the reactions considered (3 pages). Ordering information is given on any current masthead page.

---

(44) Barlin, G. B.; Perrin, D. D. *Q. Rev., Chem. Soc.* **1966**, *20*, 75.

(45) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1.

(46) Le Henaff, P. *Bull. Soc. Chim. Fr.* **1968**, 4687.

(47) Bell, R. P.; Evans, P. G. *Proc. R. Soc. London, Ser. A* **1966**, *291*, 297.

(48) Kurz, J. L. *J. Am. Chem. Soc.* **1967**, *89*, 3524.

(49) Bell, R. B.; Rand, M. H.; Wynne-Jones, K. M. A. *Trans. Faraday Soc.* **1956**, *52*, 1093.

(50) Guthrie, J. P.; Cullimore, P. A., *Can. J. Chem.*, in press.

(51) Salmi, E. J.; Suonpaa, J. *Chem. Ber.* **1940**, *73*, 1126.

(52) Barthel, J.; Bader, G.; Schmeer, G. *Z. Phys. Chem. (Frankfurt am Main)* **1968**, *62*, 63.

(53) Skrabal, A.; Zahorka, A. *Monatsh. Chem.* **1929**, *53-54*, 562.

(54) Fairclough, R. A.; Hinshelwood, G. N. *J. Chem. Soc.* **1937**, 538.

(55) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638.

(56) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228.

(57) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743.

(58) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

(59) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249. Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155, and references cited therein.

(60) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.

(61) Necessarily, an "intermediate" with a lifetime of less than one molecular vibration cannot be said to exist as a discrete species, and there cannot be a stepwise path via such an intermediate. Our treatment leads to the conclusion that even intermediates with finite lifetimes can be avoided by concerted paths if the reaction coordinate diagrams permit.

(62) Recently[63] it has been shown that the hydrolysis of substituted benzaldehyde acetals is subject to general acid catalysis. Unfortunately, the equilibrium constant for oxocarbonium ion is not known for any of the benzaldehydes, so we cannot apply our method.

(63) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergei, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672.

Nanosecond Time-Resolved Fluorescence of Phototautomeric Lumichrome[1]

Jung Do Choi, Robert D. Fugate, and Pill-Soon Song*[2]

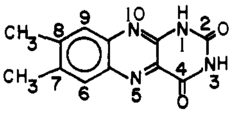
Contribution from the Department of Chemistry, Texas Tech University, Lubbock, Texas 79409.

Received January 18, 1980

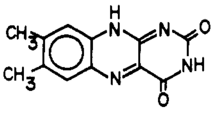
Abstract: Lumichrome (7,8-dimethylalloxazine) emits two fluorescence bands with maxima at 440 and 540 nm in pyridine–dioxane and acetic acid–ethanol mixtures. The nanosecond time-resolved fluorescence of lumichrome shows a fast growth of the latter upon excitation of lumichrome with a 2-ns pulse, as the result of proton transfer from N_1 to N_{10} during the lifetime of the lumichrome singlet. The rate depends on the concentration of general base (pyridine) and bifunctional catalysts (acetic acid). From pH-dependence study of the nanosecond time-resolved fluorescence spectra of lumichrome in aqueous solution, the photodissociation of the N_1 proton appears to be slower than the phototautomerism in pyridine–dioxane or acetic acid–ethanol mixtures. The temperature dependence of the phototautomerism of lumichrome showed an efficient proton transfer from N_1 to N_{10} at temperatures higher than 100 K.

Introduction

Lumichrome (7,8-dimethylalloxazine, **1**), a flavin tautomer, exhibits two fluorescence emission maxima, 440 and 540 nm, in pyridine–dioxane mixture.[3] These fluorescence spectra are attributed to emission from the excited states of lumichrome (**1**) and its tautomer flavin (**2**). The latter is formed during the excited-state lifetime of the former, catalyzed by pyridine which facilitates transfer of a proton from the N_1 to the N_{10} position.[3,4]



1



2

Similar phototautomerism of **1** occurs in an acetic acid–ethanol mixture, in which the acid functions as a bifunctional catalyst for the excited-state proton transfer.[3] Various substituted alloxazines display phototautomerism.[5] In aqueous alloxazine solutions, multiple excited-state equilibria occur as the result of tautomeric and ionization equilibria.[5,6]

In the previous work mentioned above,[3,5] the phototautomerism was indirectly measured in terms of steady-state fluorescence and it was possible neither to extract rate constants nor to discriminate between the phototautomerism and photodissociation of **1**. Although the phase-modulation fluorescence lifetime data were consistent with the steady-state fluorescence studies,[4] it was not possible to elucidate the kinetics and mechanism of phototautomerism of **1** in detail. In the present paper, we report nanosecond time-resolved fluorescence measurements of the phototautomerism of **1** in order to more fully describe the excited-state behavior of **1**.

Experimental Section

Materials. Lumichrome (7,8-dimethylalloxazine, **1**) was obtained and purified as described previously,[3,7] and as a gift from Professor J. Koziol. Spectroquality solvents (*p*-dioxane and ethanol) were obtained from Matheson Coleman and Bell and U.S. Industries, respectively. Acetic acid (Ultrex grade, 99.9%) was purchased from J. T. Baker Chemical Co. Pyridine, spectroquality, was obtained from Matheson Coleman and Bell.

---

(1) Supported by the Robert A. Welch Foundation (D-182) and the National Science Foundation (PCM75-05001).

(2) To whom correspondence should be addressed.

(3) Song, P.-S.; Sun, M.; Koziolowa, A.; Koziol, J. *J. Am. Chem. Soc.* **1974**, *96*, 4319.

(4) Fugate, R. D.; Song, P.-S. *Photochem. Photobiol.* **1976**, *24*, 479.

(5) Koziolowa, A. *Photochem. Photobiol.* **1979**, *29*, 459.

(6) Müller, F.; Dudley, K. H. *Helv. Chim. Acta* **1971**, *54*, 1487.

(7) Sun, M.; Moore, T. A.; Song, P.-S. *J. Am. Chem. Soc.* **1972**, *94*, 1730.

0002-7863/80/1502-5293$01.00/0