The existence of an isotope effect maximum means that there is a sharper curvature of the Brønsted curve for protium than for deuterium acids near $\Delta pK = 0$. This can be described formally by the approach of Marcus, Kreevoy, Kresge, and others[45,52,53] by assigning a smaller intrinsic barrier for the transfer of protium than of deuterium, and a satisfactory fit to the data of Figure 5 may be obtained by assigning a value of $\Delta G_0^{\ddagger} = 0.6$ kcal mol^{-1}.[2] However, this formalism does not provide an explanation for the isotope effect maximum and may even be misleading.

According to the Marcus treatment there are two different reasons why the isotope effect can decrease with increasing ΔpK. First, at sufficiently large ΔpK the ordinary chemical barrier for reaction will disappear and the reaction will be limited by the work required to bring the reactants in position to react, w^r, and (in the unfavorable direction) by $\Delta G^{0\prime}$ for the reaction. The work term w^r is normally independent of ΔpK, and for proton transfer between electronegative atoms it corresponds to diffusion together of the reactants, steric effects, and possibly a rearrangement of solvent. The latter two terms are small or insignificant for a large favorable ΔpK because the observed rate constants approach or reach the diffusion-controlled limit. This corresponds to a change in rate-limiting step with decreasing pK_a of the acid (k_a, eq 1, and dotted line, Figure 4), and does not account for the isotope effect maximum in this reaction, as described above. Second, an isotope effect maximum could be caused by different intrinsic barriers, $\lambda/4$ or $\Delta G_0^{\ddagger}$, for protium and deuterium that give different curvatures of the Brønsted lines for the two isotopes. Different shapes or curvatures of the energy barriers can give rise to different rates of change of the barriers with changing reactant structure.[44,45] However, it is usually assumed that the potential barriers for hydrogen and deuterium are identical and that isotope effects are caused primarily by differences in zero-point energy and tunneling frequencies. Furthermore, this description does not provide an explanation for the isotope effect maximum, so that it is still necessary to invoke the Melander-Westheimer effect or some other explanation to account for how the difference in the zero-point energies for hydrogen and deuterium in the reactants can be retained in the transition state when ΔpK becomes large and the isotope effect becomes small.

Supplementary Material Available: A table and three figures describing experimental rate constants (9 pages). Ordering information is given on any current masthead page.

(51) Kaldor, S. B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7594-7599.
(52) Kreevoy, M. M.; Oh, S.-w. *J. Am. Chem. Soc.* **1973**, *95*, 4805-4810. Kreevoy, M. M. In "Isotopes in Organic Chemistry"; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1976; Vol. 2, pp 1-31.
(53) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228-7233.

Concerted Bifunctional Proton Transfer and General-Base Catalysis in the Methoxyaminolysis of Phenyl Acetate[1]

Michael M. Cox and William P. Jencks*

Contribution No. 1341 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. *Received July 7, 1980*

Abstract: The bifunctional acid-base catalysts cacodylic acid, bicarbonate, and the monoanions of phosphate, substituted phosphonates, and methylarsonate are up to 10^2-10^3 more effective than monofunctional acids or bases of comparable pK for catalysis of the methoxyaminolysis of phenyl acetate. The absence of the downward break in the Brønsted plot and the solvent isotope effect maximum that are observed with monofunctional acid catalysts when proton transfer becomes partially rate limiting indicates that these bifunctional catalysts avoid this stepwise proton-transfer step. It is concluded that the two proton transfers occur through a mechanism with no detectable barrier or isotope effect, which appears to be concerted and is so fast that proton transfer never becomes kinetically significant; the rate-limiting step is amine attack with hydrogen bonding by the catalyst. Glycine and water show smaller rate increases that probably represent stepwise bifunctional proton transfer through a nine-membered ring or two water molecules in a one-encounter mechanism. Pyrazole and triazole show little or no enhancement of catalytic activity, indicating that bifunctional proton transfer through a seven-membered ring is relatively unfavorable in aqueous solution. Catalysis by monofunctional bases follows a nonlinear Brønsted plot and is attributed to a preassociation mechanism analogous to that for general-acid catalysis.

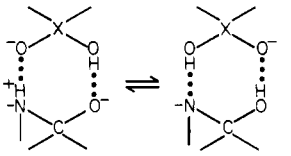
"Concerted acid-base catalysis" means different things to different people including (1) a reaction in which several processes occur in one step with no intermediate, (2) proton transfer that is electronically coupled to some other bond-making or -breaking process, (3) a term in a rate law that contains both an acid and a base molecule, and (4) bifunctional catalysis by a single molecule containing both an acidic and a basic group. We will be concerned here with *bifunctional* acid-base catalysis by a single molecule and the extent to which this catalysis is *concerted* in the sense of two processes occurring with no intermediate step. Bifunctional acid-base catalysis is a venerable and popular hypothesis to help explain the chemical mechanism of enzymic catalysis and has been studied extensively in nonenzymic reactions following the pioneering work of Lowry and Swain and Brown.[2,3] The rate increases from such catalysis in aqueous solution are generally not dramatic because water is itself a good acid-base catalyst, possibly a bifunctional acid-base catalyst. It has been suggested that fully concerted bifunctional catalysis that involves changes in bonding to heavy atoms is rare or nonexistent because of the low probability that all of the requirements for the several processes that must take place at once can be met in a single, low-energy transition state.[4]

(1) Supported by grants from the National Science Foundation (Grant BG-31740) and the National Institutes of Health (Grants GM20888 and GM20168). M.M.C. was supported by a training grant from the National Institutes of Health (Grant 5-T01-GM00212).

(2) Lowry, T. M.; Falkner, I. J. *J. Chem. Soc.* **1925**, *127*, 2883-2887. Lowry, T. M. *Ibid.* **1927**, 2554-2565;
(3) Swain, C. G.; Brown, J. F., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2534-2537, 2538-2543.

0002-7863/81/1503-580$01.00/0

The most clear-cut examples of bifunctional acid–base catalysis in aqueous solution involve the trapping of unstable intermediates in a stepwise reaction mechanism.[5-11] Such trapping can be diffusion controlled when the proton transfer is strongly favored thermodynamically.[12] With monofunctional acids and bases this catalysis drops off sharply with changing pK of the catalyst when the proton transfer becomes unfavorable, but bifunctional catalysts can transfer two protons and maintain a high catalytic activity in this pK region.[7] This is shown in eq 1 for the trapping of a



(1)

dipolar intermediate, $T^{\pm}$, that is formed upon the addition of an amine to a carbonyl group. It has been suggested that the enhanced activity of bifunctional catalysts can be explained by two stepwise proton transfers that occur in a "one-encounter" mechanism before separation of the catalyst and intermediate or by a fully concerted proton transfer after encounter with the intermediate.[5,7,13] It has remained uncertain which of these mechanisms is correct.

We describe here bifunctional acid–base catalysis of the methoxyaminolysis of phenyl acetate by a series of phosphonate monoanions and related compounds that contain both acidic and basic sites. The absence of a break in the Brønsted curves and of a solvent isotope effect for this catalysis provides evidence that the single proton-transfer step that becomes rate limiting with monofunctional catalysts is bypassed with the bifunctional catalysts, so that the observed catalysis appears to proceed through a concerted transfer of the two protons. This proton transfer is so fast that it never becomes kinetically significant; the rate-limiting step in the presence of these catalysts is attack of the amine that is assisted by hydrogen bonding to the catalyst. Thus, the overall reaction is stepwise although the proton transfer is concerted. This work has been reported briefly in preliminary communications.[14] We also describe the Brønsted curve for general base catalysis by monofunctional catalysts through a preassociation mechanism, which is complementary to the general-acid catalysis described in the preceding paper.[15]

Experimental Section

Materials and experimental procedures were generally as described in the preceding paper.[15] Disodium methylarsonate[16] and potassium ethylphosphonate,[17] trichloromethylphosphonate,[17] and chloromethylphosphonate[18] were prepared as described previously. Pseudo-first-order rate constants were determined spectrophotometrically by initial rate measurements below pH 9.2 and by following the entire reaction course above pH 9.2.[15] The rate constants for catalysis by carbonate buffers were corrected for the decrease in the concentrations of methoxyamine and bicarbonate caused by carbamate formation.[16] This resulted in a correction of <10% for catalysis by carbonate dianion but increased the observed catalytic constant for bicarbonate by a factor of 2, so that the latter rate constant is an approximate value. The experimental conditions for determination of the rate constants for buffer catalysis are given in Table SI of the supplementary material.

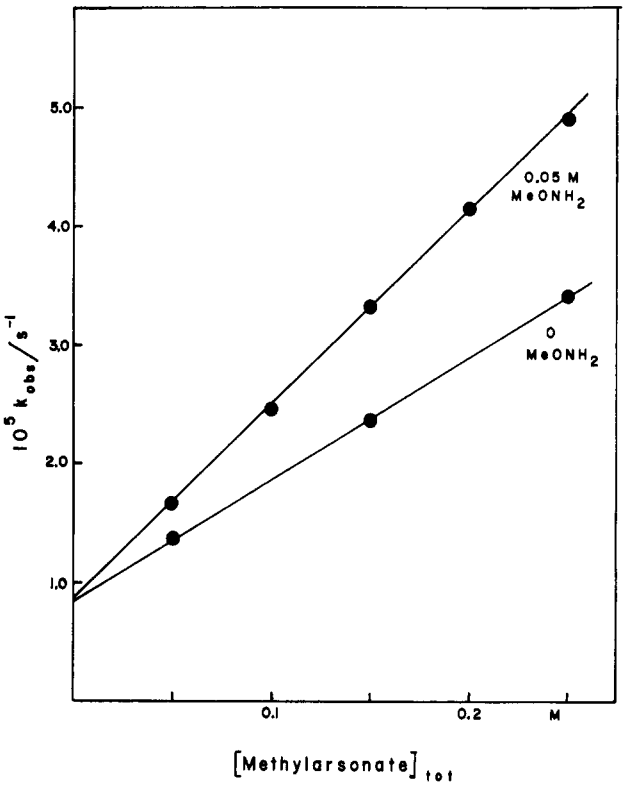


Figure 1. The effect of the concentration of methylarsonate buffers on the pseudo-first-order rate constants for the cleavage of phenyl acetate in the presence and absence of methoxyamine at pH 8.67, 25 °C, ionic strength 1.0 M (KCl).

The theoretical curves for the Brønsted plot were calculated from eq 2 for proton transfer according to the Eigen mechanism[12,15] and from eq 3 for the preassociation mechanism,[19,20] in which $K_1 = k_1/k_{-1}$, k_B^{dc} is the

$$k_B = \frac{K_1 k_a k_p k_b}{k_p k_b + k_{-a} k_b + k_{-a} k_{-p}} \quad (2)$$

$$k_B = \frac{k_B^{dc}[k_{-a} + k_{-1}\,\text{antilog}\,[\beta(1.74 + pK_B)]](k_p k_b/k_{-a})}{k_p k_b + [k_{-a} + k_{-1}\,\text{antilog}\,[\beta(1.74 + pK_B)]](k_b + k_{-p})} \quad (3)$$

limiting rate constant when diffusion-controlled trapping is rate limiting, pK_B is the pK of the conjugate acid of the base catalyst, and the other terms are defined in eq 6. Equation 3 describes the rate constant for the preassociation mechanism in terms of the rate constant for the trapping mechanism plus the rate increase resulting from preassociation and hydrogen bonding,[19,20] as described previously for general acid catalysis.[15]

Results

Rate constants for the reaction of methoxyamine with phenyl acetate (eq 4) at 25 °C and ionic strength 1.0 M, maintained with

$$k_{obsd} = k_0 + k_w[MeONH_2] + k_A[MeONH_2][HA] + k_B[MeONH_2][B] \quad (4)$$

potassium chloride, were determined from a series of rate measurements in buffer solutions, which were corrected for the rate constant of the methoxyamine-independent reaction, k_0, under the same conditions. The data obtained with methylarsonate buffers at pH 8.67 are shown in Figure 1. This example was chosen because it represents one of the most unfavorable cases examined with respect to the fraction of the total reaction that

(4) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718.
(5) Cunningham, B. A.; Schmir, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 551–558; **1967**, *89*, 917–922. Chaturvedi, R. K.; Schmir, G. L. *Ibid.* **1968**, *90*, 4413–4420. Okuyama, T.; Sahn, D. J.; Schmir, G. L. *Ibid.* **1973**, *95*, 2345–2352.
(6) Lee, Y.-N.; Schmir, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 3026–3035.
(7) Barnett, R. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 2358–2369.
(8) Aldersley, M. F.; Kirby, A. J.; Lancaster, P. W.; McDonald, R. S.; Smith, R. S. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1487–1495.
(9) Hogg, J. L.; Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 4772–4778.
(10) See also: (a) Robinson, D. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1967**, *89*, 7088–7198; (b) Sander, E. G.; Jencks, W. P. *Ibid.* **1968**, *90*, 6154–6162; (c) Glutz, B. R.; Zollinger, H. *Helv. Chim. Acta* **1969**, *52*, 1976–1984; (d) Eugster, P.; Zollinger, H. *Ibid.* **1969**, 1985–1996.
(11) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7031–7044.
(12) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.
(13) Eigen, M. *Discuss. Faraday Soc.* **1965**, *39*, 7–15.
(14) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5956–5957; *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 473.
(15) Cox, M. M.; Jencks, W. P., preceding paper in this issue.
(16) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449.
(17) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637–5649.
(18) Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 6708–6714.
(19) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931–7947.
(20) Jencks, W. P.; Gilbert, H. F. *Pure Appl. Chem.* **1977**, *49*, 1021–1027.

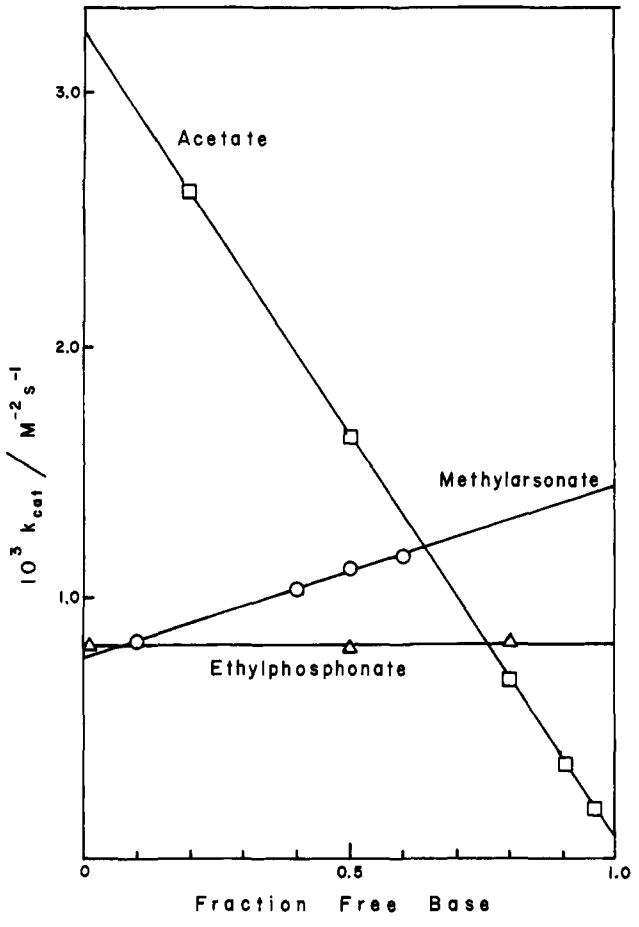


Figure 2. Observed catalytic constants for the methoxyaminolysis of phenyl acetate plotted against the fraction free base of the buffer, to illustrate the separation of the terms representing catalysis by the acid and base components of the buffer.

represents reaction with methoxyamine. The catalytic constants for the different buffers and buffer ratios examined are given in Table SI of the supplementary material. No catalysis by hydroxide ion was detected under the conditions of these experiments.

The rate constants k_A and k_B for catalysis by the acidic and basic species of the buffers, respectively, were obtained from the intercepts of plots of the catalytic constants obtained at different buffer ratios against the fraction free base of the buffer, as illustrated for catalysis by acetate, ethylphosphonate, and methylarsonate buffers in Figure 2. The catalytic constants for buffer bases, k_B, and for the bifunctional catalysts cacodylic acid, bicarbonate, glycine, *O*-methylisourea (upper limit), water, and the monoanions of phosphate, substituted phosphonates, and methylarsonate are given in Table I. Catalysts that could act as either acids or bases such as the phosphonate monoanions and water were classified as acid or base catalysts depending on the Brønsted plot for acid or base catalysis to which they showed a good fit or the smallest positive deviation. This assignment is unambiguous for all catalysts except methylarsonate and ethylphosphonate monoanions, which showed a satisfactory fit or a small positive deviation for the extended Brønsted line of slope $\beta = 0.11$ for general-base catalysis as well as a good fit to the extended Brønsted line of slope $\alpha = 0.16$ for general-acid catalysis; however, both compounds show large positive deviations from the Brønsted curves for catalysis by monofunctional acids and bases.

There is an ambiguity for the reaction with pyrazole and methoxyamine because pyrazole is itself a strong nucleophilic reagent that can react with phenyl acetate with general-base catalysis by methoxyamine (k_{pyr}, eq 5), in addition to serving as a catalyst for

$$v_{gbc} = k_B[MeONH_2][pyr][AcOPh] + k_{pyr}[pyr][MeONH_2][AcOPh] \quad (5)$$

Table I. Rate Constants for General-Base and Bifunctional Catalysis of the Methoxyaminolysis of Phenyl Acetate[a]

catalyst	pK_a	k_A, $M^{-2} s^{-1}$	k_B, $M^{-2} s^{-1}$
trichloromethylphosphonate	4.2[b]	2.47×10^{-3}	
chloromethylphosphonate	5.95[c]	1.6×10^{-3}	2.83×10^{-4}
cacodylate	6.16[b]	1.2×10^{-3}	3.5×10^{-4}
D_2O		7.0×10^{-4}	
phosphate	6.49[b]	1.92×10^{-3}	
	(1.72)[b]		
D_2O		1.18×10^{-3}	
ethylphosphonate	7.6[b]	8.3×10^{-4}	
	(2.23)[b]		8.3×10^{-4}
D_2O		5.2×10^{-4}	
methylarsonate[d]	8.5[b]	7.83×10^{-4}	1.45×10^{-3}
	(3.98)[b]		
D_2O		4.83×10^{-4}	1.15×10^{-3}
bicarbonate	9.78[b]	$(6.7 \pm 3.0) \times 10^{-4}$	$(1.8 \pm 0.5) \times 10^{-3}$
	(3.8)		
O-methylisourea	10.09[e]	$\leq 1.0 \times 10^{-6}$ [f]	
glycine	9.81[e]		1.53×10^{-5}
	(2.5)[e]		
D_2O			7.12×10^{-6}
H_2O[g]	−1.74		$(3.4 \pm 1.5) \times 10^{-8}$
cyanoacetate	2.23[b]		1.6×10^{-6}
chloroacetate	2.65[b]		4.3×10^{-6}
methoxyacetate	3.33[b]		1.24×10^{-5}
glycolate	3.62[h]		2.22×10^{-5}
acetate	4.6[b]		8.0×10^{-5}
1,2,4-triazole	2.58[b]		$<1.7 \times 10^{-5}$ [f]
pyrazole	2.74[e]		1.3×10^{-5}
methoxyamine	4.72[b]		3.3×10^{-5}
triethylenediamine (DABCO)	9.22[i]		1.4×10^{-3}
3-chloroquinuclidine	9.13[d]		7.7×10^{-4}
quinuclidinol	10.13[i]		1.22×10^{-3}

[a] 25 °C, ionic strength maintained at 1.0 M with potassium chloride. [b] Reference 16. [c] Reference 18. [d] The disodium salt was used and the ionic strength was brought to 1.0 M with potassium chloride. The reaction is not sensitive to small changes in the nature or concentration of salt.[15] [e] This work. [f] Upper limit. [g] From $k_w/55.5$ M, based on the average of three experiments. [h] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* 1977, *99*, 1206–1214. [i] Reference 17.

the reaction with methoxyamine as the nucleophile (k_B, eq 5). The contribution of the k_{pyr} term was estimated by determining the rate constants for the reaction of phenyl acetate with pyrazole in the presence of other base catalysts (Table II). The rate constant for catalysis by methoxyamine of the reaction with pyrazole was estimated to be $k_{pyr} = 3.0 \times 10^{-5}$ $M^{-2} s^{-1}$ from a three-point Brønsted plot for other general-base catalysts, as shown in Figure 3. The observed rate constant of 4.3×10^{-5} $M^{-2} s^{-1}$ then gives an approximate rate constant for catalysis of the reaction with methoxyamine by pyrazole of $k_B \leq 1.3 \times 10^{-5}$ $M^{-2} s^{-1}$; in view of the uncertainty of the correction it is possible that k_{pyr} accounts for all of k_{obsd} and k_B is insignificant.

Discussion

Bifunctional Acid–Base Catalysis. The rate constants for catalysis of the methoxyaminolysis of phenyl acetate by cacodylic acid and by the monoanions of phosphate, methylarsonate, bicarbonate, and a series of substituted phosphonates are shown as the open circles in the Brønsted plot of Figure 4A. These catalysts all contain acidic and basic functions and have the potential for bifunctional catalysis, as shown in eq 1. The rate constants fall on an extension of the Brønsted line of slope $\alpha = 0.16$ that represents catalysis of the attack of methoxyamine through hydrogen bonding to the carbonyl group of phenyl acetate by carboxylic acids, acidic protonated amines, and the proton, according to the preassociation mechanism that has been proposed for this reaction.[15] The observed rate constants for the bifunctional catalysts

Table II. Rate Constants for Catalysis of the Reaction of Pyrazole with Phenyl Acetate[a]

buffer	pH	concn range, M	k_{cat}, M^{-2} s^{-1}	k_B,[b] M^{-2} s^{-1}	k_A,[c] M^{-2} s^{-1}
H_2O[d]				2.16×10^{-8}	
pyrazole	2.74	0.1-0.5	2.17×10^{-6}	4.8×10^{-6}	
	3.36	0.1-0.5	3.8×10^{-6}		
acetic acid	5.28	0.1-0.4	2.52×10^{-5}	2.97×10^{-5}	6.7×10^{-6}
	4.02	0.1-0.4	1.14×10^{-5}		
chloromethylphosphonate	6.36	0.05-0.2	8.71×10^{-5}	1.01×10^{-4}	5.6×10^{-5}
	5.37	0.05-0.2	6.5×10^{-5}		

[a] At 25 °C, ionic strength maintained at 1.0 M with potassium chloride. Each rate constant is based on pseudo-first-order rate constants obtained at four buffer concentrations. [b] Obtained from the intercept of a plot of k_{cat} against the fraction of buffer in the basic form at 100% base, unless noted. [c] Obtained from the same plot as k_B, from the intercept at 100% buffer acid. [d] Obtained from the second-order rate constant for the reaction of pyrazole with phenyl acetate divided by 55.5 M water.

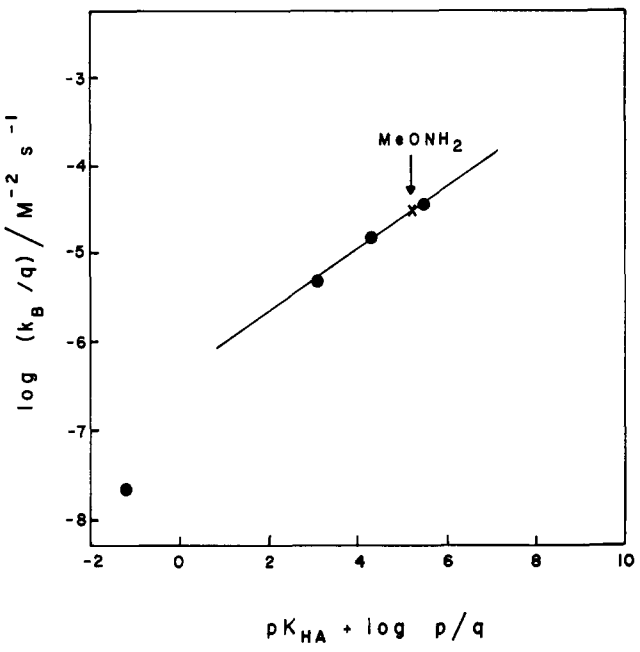


Figure 3. Three-point Brønsted plot for general-base catalysis of the reaction of phenyl acetate with pyrazole at 25 °C, ionic strength 1.0 M (KCl). The circles are observed rate constants for catalysis by water, pyrazole, acetate, and chloromethylphosphonate, and the cross represents the estimated rate constant for catalysis by methoxyamine.

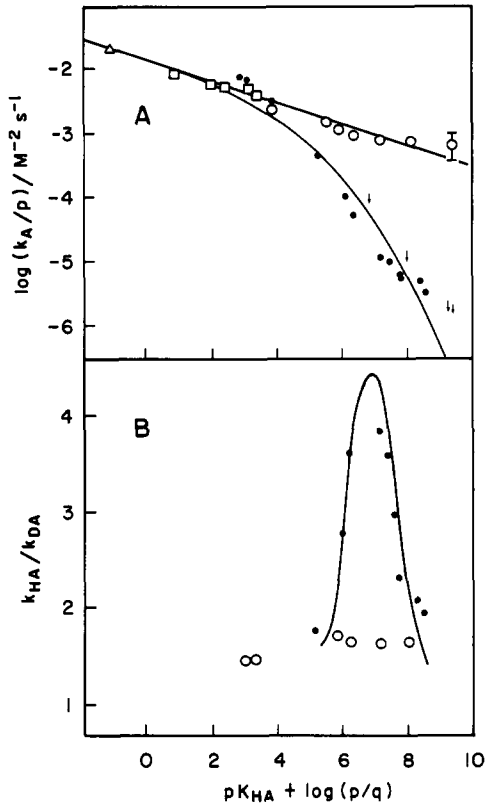


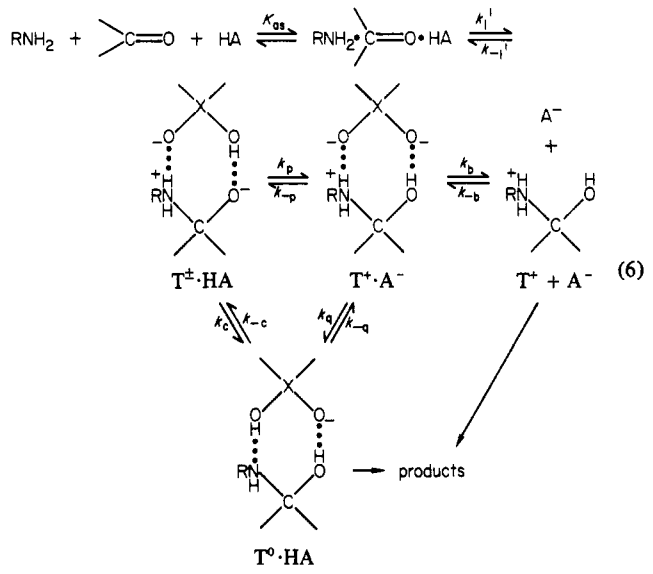
Figure 4. (A) Brønsted plot for catalysis of the methoxyaminolysis of phenyl acetate by bifunctional acids (open symbols) and monofunctional acids (closed symbols):[15] carboxylic acids, □; cacodylic acid, phosphate, substituted phosphonate, methylarsonate and bicarbonate monoanions, ○; protonated amines, ●; upper limits for catalysis by fluoroacetone hydrates, hexafluoro-2-propanol and 2-chloroethylammonium ion, ↓. (B) Solvent deuterium isotopes effects for catalysis by monofunctional[15] (●) and bifunctional (○) acids.

are larger than those for monofunctional protonated amines by up to 2 orders of magnitude, and the rate constant for bicarbonate is larger than the calculated rate constant for a monofunctional catalyst of the same pK by 3 orders of magnitude. These rate increases do not represent an inherently larger catalytic activity of oxygen than of nitrogen acids because both classes of acids have similar catalytic activity in the range of pK = 2–4. Furthermore, fluoroacetone hydrates and hexafluoro-2-propanol, which are not bifunctional catalysts, show little or no increase in catalytic activity compared with cationic nitrogen acids of comparable pK (Figure 4A). We conclude that the methoxyaminolysis of phenyl acetate is subject to bifunctional catalysis and that this mechanism causes an enhanced activity for bifunctional acid–base catalysts of pK > 4, in the region in which the activity of monofunctional catalysts falls off (Figure 4A).

This conclusion is in agreement with an earlier conclusion reached by Cordes and co-workers for catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate.[21] However, the relatively acidic bifunctional catalysts that were examined by these workers do not show an advantage over monofunctional catalysts of comparable pK; bifunctional catalysis becomes significant only with acids of pK > 4, as the Brønsted plot for monofunctional catalysts curves downward.

Possible mechanisms for bifunctional catalysis are shown in eq 6. The two proton transfers that convert $T^{\pm}$ to T^0 could occur either in a stepwise, one-encounter mechanism, with the rate constants k_p and k_q, or in a single concerted step, with the rate constant k_c. The one-encounter mechanism can provide an advantage for bifunctional over monofunctional catalysts because it bypasses the separation of A^- from T^+ (k_b, eq 6), which becomes rate limiting for thermodynamically unfavorable proton transfers.[12] The concerted mechanism allows the k_p step to be bypassed, as well as k_p, thus potentially providing a greater advantage than the one-encounter mechanism. Both mechanisms have been proposed previously for bifunctional proton transfer[5,7,13,22-24] but no clear-cut experimental distinction between the two mechanisms has been reported.

(21) Do Amaral, L.; Koehler, K.; Bartenbach, D.; Pletcher, T.; Cordes, E. H. *J. Am. Chem. Soc.* **1967**, *89*, 3537-3545.
(22) Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766-5771.
(23) Grunwald, E.; Eustace, D. "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; Chapter 4.
(24) Albery, W. J. *Prog. React. Kinet.* **1967**, *4*, 355-398.



The fact that the rate constant for the bifunctional catalysts fall on the Brønsted line of slope $\alpha = 0.16$ indicates that the rate-limiting step for these catalysts is attack of the amine with hydrogen bonding, k_1', so that the subsequent proton transfer must be fast. The Brønsted plot for catalysis by monofunctional acids of pK = 4–7 curves downward because the proton-transfer step, k_p, becomes rate limiting when the proton transfer is no longer strongly favorable.[15] The absence of this downward curvature in the Brønsted plot for bifunctional catalysts means that the proton transfer with these acids does not proceed through this k_p step; it must then proceed by the faster, concerted mechanism that bypasses this step (k_c, eq 6). The stepwise, one-encounter mechanism for bifunctional catalysts proceeds through the same proton-transfer step, with the rate constant k_p, as does the mechanism for catalysis by monofunctional acids (eq 6). Since the observed rate constants with bifunctional catalysts of pK > 4 are faster than the observed rate constants for catalysis with k_p rate determining, the bifunctional catalysts cannot react through the stepwise mechanism of proton transfer. An initial proton transfer to the basic site of the bifunctional catalyst is less favorable thermodynamically than proton transfer from the acidic site, so that this does not provide an alternative pathway that would be faster than k_p.

A solvent deuterium isotope effect with a sharp maximum at pK_{HA} = 6.8 for catalysis by monofunctional acids provides evidence for a kinetically significant proton-transfer step, k_p, with these catalysts,[15] but no such maximum is observed for bifunctional catalysts (closed and open circles, respectively, in Figure 4B). The absence of a deuterium isotope effect is further evidence consistent with the concerted mechanism of proton transfer (k_c) that bypasses the proton transfer step (k_p) for bifunctional catalysts. Isotope effect maxima have also been reported for catalysis of carbonyl addition and transimination reactions and provide evidence for a kinetically significant step involving transfer of a single proton (k_p) in catalysis of these reactions by a trapping mechanism; both monofunctional nitrogen and bifunctional oxygen catalysts were included in these studies.[25] However, the absence of an isotope effect maximum does not by itself provide rigorous proof of a concerted proton-transfer mechanism because such a maximum has not yet been demonstrated for a system in which oxygen atoms act as both proton donor and acceptor. There is evidence that the isotope effect is larger when nitrogen replaces oxygen as the proton donor or acceptor.[25,26]

The driving force for concerted proton transfer arises from the changes in pK that occur upon transfer of a proton in a cyclic

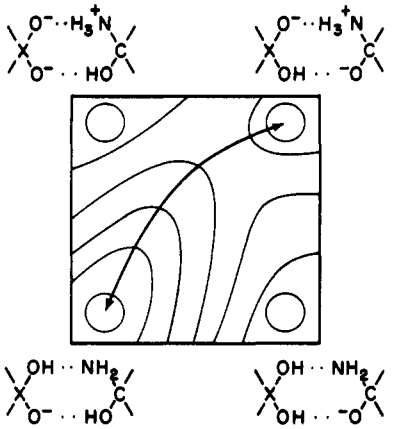
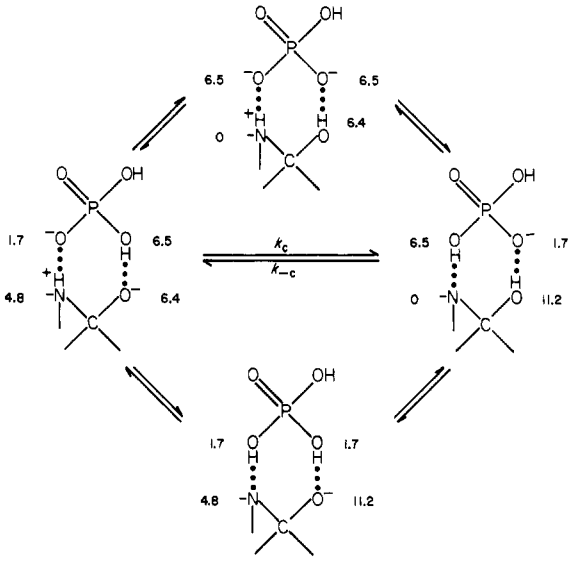


Figure 5. Reaction coordinate–energy diagram for bifunctional proton transfer. The curved line is the reaction coordinate for a concerted proton transfer in which the intermediate in the upper left corner is more stable than that in the lower right corner.

Scheme I



system. This is illustrated for the reaction of T± and phosphate monoanion in Scheme I, in which the numbers represent the pK values of the reacting groups or their conjugate acids. Initially, the proton transfer from the catalyst to the carbonyl oxygen atom is approximately thermoneutral, and the proton transfer from the protonated amine to the catalyst is thermodynamically unfavorable. Proton transfer to the carbonyl oxygen atom increases the basicity of the catalyst and the acidity of the intermediate so that the second proton transfer becomes strongly favorable thermodynamically; complete transfer gives pK values of 6.5 and 0, respectively, so that the proton transfer can occur with a small or no barrier. The final pK values show that the overall proton-transfer process is strongly favored thermodynamically. The advantage from bifunctional catalysis involving concerted transfer of two protons thus arises only indirectly from the fact that two protons are transferred; it comes primarily from the rapid rate of proton transfer that is made possible by the concerted mechanism.

It is likely that a concerted process of this kind will take place through a transition state that resembles the most stable intermediate, as shown in Figure 5 for a system in which proton transfer from the catalyst to oxygen is more favorable that from T± to the catalyst. An increase in the basicity of the catalyst would be expected to stabilize the intermediate in the lower right-hand corner of Figure 5 and cause a shift in the position of the transition state toward this intermediate, perpendicular to the reaction coordinate. Calculations have suggested that the two proton transfers in such cyclic systems could occur by a concerted mechanism,

(25) Bergman, N.-A.; Chiang, Y.; Kresge, A. J. *J. Am. Chem. Soc.* **1978**, *100*, 5954–5956. Fischer, H.; DeCandis, F. X., Ogden, S. D.; Jencks, W. P. *Ibid.* **1980**, *102*, 1340–1347.

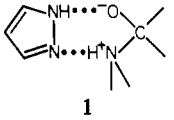
(26) Kresge, A. J.; Tang, Y. C.; Onwood, D. P., personal communication.

which may involve tunneling,[27,28] and ultrafast proton transfers are believed to occur in hydrogen-bonded systems with a favorable ΔpK.[29]

Additional stabilization of the complex $T^{\pm}$·HA by hydrogen bonding to bifunctional catalysts does not account for the increased activity and the absence of an isotope effect with these catalysts, because there is no difference in the activity of monofunctional and bifunctional catalysts of $pK < 4$ and hydrogen bonding does not remove the requirement for a kinetically significant proton-transfer step in the one-encounter mechanism. Hydrogen bonding of the basic site of a bifunctional catalyst to the acidic site of $T^{\pm}$ might be thought to increase the acidity of the acidic site of the catalyst, so that the break in the Brønsted curve would come at a higher pK for such catalysts. However, if complete proton transfer changes the pK of a bifunctional catalyst (such as phosphate) by ~5 units and hydrogen bonding occurs with the same value of $\alpha = 0.16$ as for the addition step, the partial proton transfer from hydrogen bonding would be expected to change the pK by <1 unit, which could not account for the absence of a break in the Brønsted plot for catalysts of pK up to 9. Values of α which reflect the expected strength of hydrogen bonds between compounds with the pK values of $T^{\pm}$ and the catalysts examined here can be calculated by using the equation proposed by Hine with $\tau = 0.024$[22] and in all cases are <0.16.

Requirements for Bifunctional Acid–Base Catalysis. The highly effective bifunctional catalysts that follow the Brønsted line of slope $\alpha = 0.16$ (Figure 4A) all have their acidic and basic groups in a 1,3 relationship. This structure permits cyclic proton transfer to occur along linear hydrogen bonds in an eight-membered ring (eq 1)[30] and is found in virtually all reported examples of effective bifunctional catalysis in aqueous solution.[5-10] Rapid proton transfer through an eight-membered ring also occurs in the bimolecular tautomerization of 2-hydroxypyridines to 2-pyridones in aprotic solvents, which has been reported to occur in a viscosity-sensitive, encounter-controlled reaction with a deuterium isotope effect of 1.0–1.2.[31] A broadening of the infrared absorption bands has been attributed to rapid proton transfer within the dimer.[31,32] However, this bimolecular tautomerization reaction is inhibited by the presence of water, which interferes with dimerization by hydrogen bonding to the hydroxypyridine and serves as a bridge for a first-order tautomerization with a rate constant of 10^3–10^4 s^{-1} and a deuterium isotope effect of 4.0–4.5.[33] Proton transfer between the nitrogen atoms of dimeric 7-azaindole takes place rapidly after excitation but appears to occur with a significant activation barrier.[34]

Bifunctional catalysis by pyrazole and triazole involves proton transfer through a seven-membered ring, as shown for pyrazole in **1**. These compounds should be ideal bifunctional catalysts



1

from an electronic point of view because of the large change in pK of the acidic or basic sites when proton transfer occurs at the adjacent atom. The pK values of pyrazole and its conjugate acid

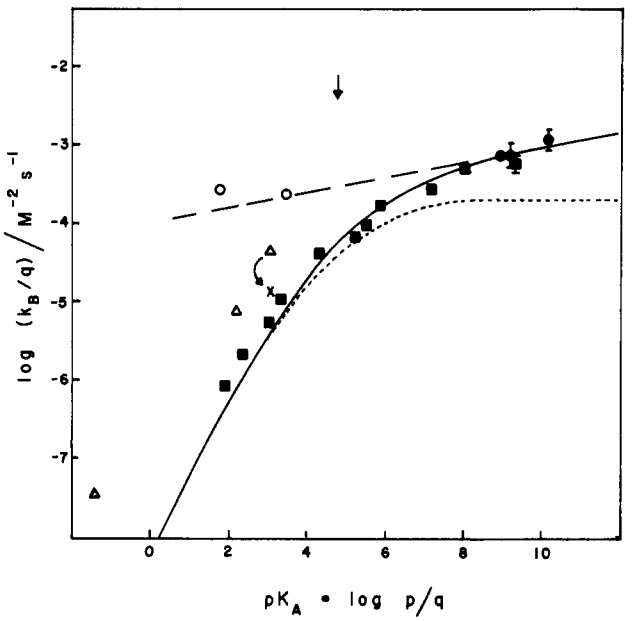


Figure 6. Brønsted plot for catalysis of the methoxyaminolysis of phenyl acetate by monofuntional bases (closed symbols) and bifunctional bases (open symbols): oxygen bases, ■; tertiary amines, ●; pyrazole, glycine, and water, Δ (the × is a corrected rate constant for pyrazole; see text); methylarsonate and ethylphosphonate monoanions, O. The solid and dotted lines are calculated for preassociation and trapping mechanisms by using eq 3 and 2, respectively, and the rate and equilibrium constants in the text. The dashed line is drawn with slope $\beta = 0.11$, and the arrow indicates the calculated pK of $T^{\pm}$.

are ~14 and 2.7, for example.[35] However, these compounds show little or no bifunctional catalysis in water. The observed rate constant for pyrazole is only tenfold above the rate constant expected for a monofunctional base of the same pK and after correction for the contribution of the kinetically equivalent nucleophilic attack of pyrazole catalyzed by methoxyamine the advantage is reduced to threefold; the corrected and uncorrected values are shown by a cross and a triangle, respectively, in Figure 6. No catalysis by triazole could be detected and an upper limit for the rate constant for catalysis by this compound is only fivefold larger than expected for a monofunctional catalyst of the same pK. Pyrazole and triazole have been reported to be weak bifunctional catalysts in benzene solution.[10d] We conclude that the constraints of a seven-membered ring are unfavorable for bifunctional acid–base catalysis, especially concerted bifunctional catalysis.

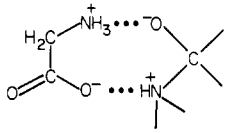
Pyrazole undergoes an intermolecular proton exchange in nonpolar solvents that is fast on the NMR time scale at room temperature and has a rate constant of 10^2–10^3 s^{-1} at temperatures near −100 °C.[36] However, the rate is inhibited by polar solvents that presumably bind to pyrazole and inhibit the intermolecular tautomerization.[37] There is also a slow proton exchange through a six-membered ring between acetic acid and methanol in tetrahydrofuran (k = 350 M^{-1} s^{-1} at 258 K); the relatively small negative $\Delta S^{\ddagger}$ suggests that this reaction does not proceed through an intermediate ion pair.[38]

Bifunctional catalysis through a seven-membered ring has been suggested as a possible explanation for the high activity of acetone oxime in catalyzing ester formation during imidate hydrolysis.[6] However, this high activity may reflect some other special property of oximes. Oximes have been reported to be unusually effective catalysts for the dehydration of acetaldehyde hydrate in aqueous

(27) Löwdin, P.-O. *Adv. Quantum Chem.* **1965**, *2*, 213–360.
(28) Dogonadze, R. R.; Kharkats, Y. I.; Ulstrup, J. *J. Chem. Soc., Faraday Trans. 2* **1974**, *70*, 64–77.
(29) Grunwald, E. *Prog. Phys. Org. Chem.* **1965**, *3*, 317–358. Robinson, B. H. "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; p 128.
(30) Gandour, R. D. *Tetrahedron Lett.* **1974**, 295–298.
(31) Bensaude, O.; Chevrier, M.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7055–7060.
(32) Bellamy, L. J.; Rogasch, P. E. *Proc. R. Soc. London, Ser. A* **1960**, *257*, 98–108.
(33) Bensaude, O.; Chevrier, M.; Dubois, J.-E. *J. Am. Chem. Soc.* **1979**, *101*, 2423–2429.
(34) Ingham, K. C.; El-Bayoumi, M. A. *J. Am. Chem. Soc.* **1974**, *96*, 1674–1682. See also: Bulska, H.; Chodkowska, A. *Ibid.* **1980**, *102*, 3259–3261.
(35) Albert, A.; Serjeant, E. P. "The Determination of Ionization Constants", 2nd ed.; Chapman and Hall: London, 1971.
(36) Nesmeyanov, A. N.; Zavelovich, E. B.; Babin, V. N.; Kochetkova, N. S.; Fedin, E. I. *Tetrahedron* **1975**, *31*, 1461–1462.
(37) Chenon, M. T.; Coupry, C.; Grant, D. M.; Pugmire, R. J. *J. Org. Chem.* **1977**, *42*, 659–661.
(38) Limbach, H.-H.; Seiffert, W. *J. Am. Chem. Soc.* **1980**, *102*, 538–542.

acetone, and their high acitvity has been attributed to charge localization in the immediate product of proton transfer.

Glycine shows a tenfold advantage over carboxylate bases of similar pK (open triangle at pK = 2.2, Figure 6) that is consistent with stepwise bifunctional catalysis through a nine-membered ring (**2**). Stepwise bifunctional catalysis avoids the diffusional sep-

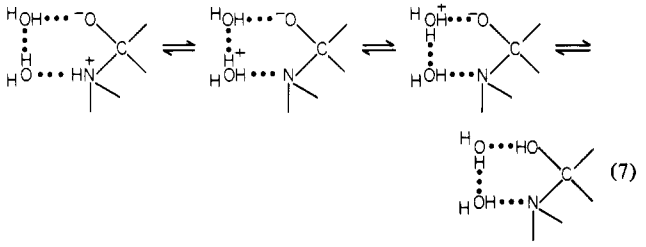


2

aration step that is rate limiting for thermodynamically unfavorable proton transfers with monofunctional catalysts, as noted above, and is significant whenever the second proton transfer is faster than this separation ($k_q > k_b$, eq 6). The absence of a faster, concerted bifunctional proton transfer with glycine can be attributed to the unfavorable geometry of the nine-membered ring and to the relatively small change in the pK of one site when proton transfer occurs at a site that is three atoms away. For example, the pK of the protonated amino group of glycine ethyl ester is only 1.9 units below that of glycine.

A similar stepwise bifunctional proton transfer is consistent with the proton-exchange reaction between two glycine molecules. The reaction occurs by direct transfer between the two molecules through a ten-membered ring and by transfer through water at similar rates. The exchange can be accounted for by proton transfer within a complex of zwitterionic and uncharged glycine molecules, with an estimated rate constant of (2–6) × 10^8 s^{-1}.[40]

The catalytic constant for water is 100-fold larger than predicted by the Brønsted plot for general-base catalysis (Figure 6; general-base catalysis is the preferred mechanism because there is an even larger positive deviation from the Brønsted plot for general-acid catalysis). This suggests that water acts as a bifunctional catalyst for proton transfer through an eight-membered ring in a stepwise mechanism with one or two intermediates (eq 7).[41] The mechanism is written with the most thermodynamically

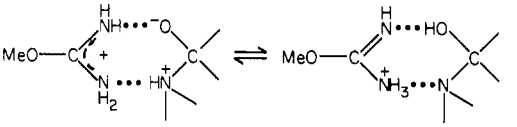


(7)

favorable proton transfer in the first step. The absence of a rapid, fully concerted proton transfer presumably reflects the requirement for transfer of three protons and the relatively unfavorable ΔpK values of the reacting groups. The mechanism is the same as that suggested by Grunwald for cyclic proton transfer between the two oxygen atoms of carboxylic acids in water or methanol with rate constants of 7 × 10^4 to 10^8 s^{-1}.[23,42] Catalysis by buffer acids and bases would, of course, be insignificant if rapid, concerted proton transfer could take place through water molecules.

An eight-membered ring is also optimal for intramolecular catalysis of proton abstraction from ketones by diamines through an intermediate imine.[43] Transfer of a proton between atoms other than carbon occurs through rings that vary in size from five to ten members, which may include one to two water molecules, with rate constants that are generally in the range 10^6–10^8 s^{-1}.[40,44] Most of these reactions have little or no driving force from a thermodynamically favorable proton transfer. However, it is of interest that the thermodynamically favorable formation of the zwitterion of an α-amino acid from the uncharged amino acid has a rate constant of only ~10^7 s^{-1}. This suggests that the proton transfer through a five-membered ring and through 1–2 intermediate water molecules is relatively slow.[40]

No catalysis could be detected with the conjugate acid of *O*-methylisourea, although bicyclic proton transfer could occur through an eight-membered ring with this compound (**3**) and the



3 **4**

pK of 10.1 for this compound is only slightly higher than that of bicarbonate. The absence of catalysis is presumably due to the instability of the product,[45] which is the unstable tautomer of a protonated amidine (**4**). The amidine that is formed from proton transfer to oxygen would have to undergo protonation on the weakly basic amino group, with loss of resonance stabilization, to give the product.

Beyond the requirement for proton transfer within an eight-membered ring, the molecular configuration of the catalyst makes little difference. Lee and Schmir have shown that compounds with tetrahedral, planar, or pyramidal configurations are equally efficient as bifunctional catalysts.[6] Furthermore, there is no evidence that resonance or changes in π bonding are important for bifunctional cyclic proton transfer in systems of this kind. Lee and Schmir's finding that monoanions of fluoroacetone hydrates are effective bifunctional catalysts shows that the changes in pK that arise simply from the loss or gain of protons on nearby atoms are sufficient to provide the driving force for the bifunctional proton transfer.[6]

The advantage for bifunctional catalysts depends in part on translational diffusion being faster than rotational diffusion for the separation of the catalyst and intermediate in this type of reaction. If the intermediate T^+ could rotate within the solvent cage after protonation of $T^{\pm}$ by AH, for example, A^- would be able to abstract a proton from the nitrogen atom to give T^0 before it diffused away. A monofunctional acid would then have the same activity as a stepwise bifunctional catalyst and would not show the large decrease in activity with decreasing acid strength that is found on the descending limb of an Eigen curve.

The requirements of efficient bifunctional catalysis of this type of reaction may be summarized as follows.

(1) The reaction must proceed through an unstable intermediate which has pK values that permit its conversion into a stable intermediate or product by two proton transfers after encounter with the catalyst.

(2) The proton transfer must be slow and is usually thermodynamically unfavorable with monofunctional catalysts, in order for bifunctional catalysts of the same pK to show enhanced activity.

(3) The proton transfer should occur through an eight-membered ring containing a single catalyst molecule to be concerted; slower, stepwise catalysis through a one-encounter mechanism is possible with other ring sizes or if the ring includes water.

(4) The product from the transfer of one proton must have a favorable ΔpK for transfer of the second proton. The most favorable situation usually arises with symmetrical systems such as monoanions of phosphonates or gem diols.

(39) Bell, R. P.; Higginson, W. C. E. *Proc. R. Soc. London, Ser. A* **1949**, *197*, 141–159.

(40) Chang, K. C.; Grunwald, E. *J. Phys. Chem.* **1976**, *80*, 1422–1425. Grunwald, E.; Chang, K. C.; Skipper, P. L.; Anderson, V. K. *Ibid.* **1976**, *80*, 1425–1431.

(41) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018–7031. Rosenberg, S.; Silver, S. M.; Sayer, J. M.; Jencks, W. P. *Ibid.* **1974**, *96*, 7986–7998.

(42) Grunwald, E.; Jumper, C. F.; Meiboom, S. *J. Am. Chem. Soc.* **1963**, *85*, 522–528.

(43) Hine, J.; Li, W.-S. *J. Am. Chem. Soc.* **1976**, *98*, 3287–3294. Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1–7.

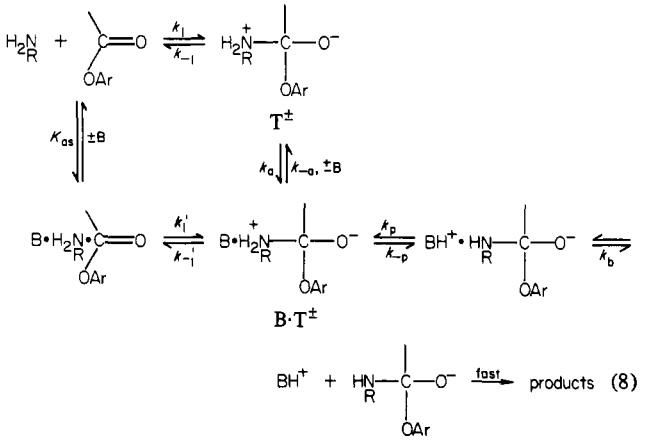
(44) Bensaude, O.; Dreyfus, M.; Dodin, G.; Dubois, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 4438–4446.

(45) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1973; p 155. Rony, P. R.; Neff, R. O. *J. Am. Chem. Soc.* **1973**, *95*, 2896–2905.

(5) Catalysis is most effective when the ΔpK values of the individual proton transfer steps are most favorable.

It was suggested previously that fully concerted bifunctional catalysis of this class of reaction, involving the formation or breaking of bonds to heavy atoms as well as the simultaneous transfer of two protons, is rare.[4] Such catalysis is most likely to be found when the requirements for concerted catalysis of the proton transfer are met and when the "intermediate" formed in the absence of proton transfer is so unstable as to have an insignificant or no lifetime.

General-Base Catalysis. If general-acid catalysis of the methoxyaminolysis of phenyl acetate proceeds through a preassociation mechanism that is enforced by the short lifetime of $T^{\pm}$, general-base catalysis might also be expected to proceed through an enforced preassociation mechanism. General-acid catalysis serves to prevent the return of the intermediate to reactants, by protonating the carbonyl oxygen atom of $T^{\pm}$, and stabilizes the transition state for attack of the amine by hydrogen bonding;[15] general-base catalysis can serve the same function by removing a proton from the cationic nitrogen atom of $T^{\pm}$ and might stabilize the transition state by hydrogen bonding to this proton (eq 8,



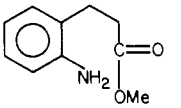
pathway through K_{as} and k_1'). This expectation is supported by the nonlinear Brønsted plot shown in Figure 6 for general-base catalysis by monofunctional catalysts. Although the data are less extensive than those for general-acid catalysis, the plot is curved and is qualitatively and quantitatively consistent with a three-step preassociation mechanism in which general-base catalysis of amine attack is rate determining with strong bases (k_1'), proton transfer causes negative curvature near $\Delta pK = 0$ (k_p), and separation of the protonated base from T^- becomes rate limiting with weak bases (k_b).

The solid line in Figure 6 was calculated for the preassociation mechanism of eq 8 by using eq 3 and agrees satisfactorily with the observed rate constants. The same constants were used as in the calculated Brønsted curve for general acid catalysis,[15] except for $pK_{T\pm} = 4.3$, $\beta = 0.11$, $\log k_p = 10.3 + 0.5\,\Delta pK$, and $\log k_{-p} = 10.3 - 0.5\Delta pK$ ($\Delta pK = pK_{BH} - pK_{T\pm}$). In particular, the value of $k_B^{dc} = 2 \times 10^{-4}$ M^{-2} s^{-1} is the same as the corresponding value of k_{HA}^{dc} and the value of $k_{-1} = 2 \times 10^{10}$ s^{-1} is the same as for the acid-catalyzed reaction, as expected if both mechanisms involve the same intermediate. The value of $pK_{T\pm} = 4.3$ is within the estimated uncertainty of the value of $pK_{T\pm} = 4.8$ for the acidic proton of $T^{\pm}$ that was calculated from structure-reactivity correlations.[15] The dotted line in Figure 6 shows the calculated Brønsted curve for a trapping mechanism, on the basis of the Eigen mechanism for proton transfer and eq 2.

The rate constants for catalysis by the bifunctional catalysts methylarsonate and ethylphosphonate monoanions, which fit the Brønsted line of slope $\alpha = 0.16$ for acid catalysts by hydrogen bonding, also fall close to the extended Brønsted line of slope $\beta = 0.11$ for general-base catalysis by hydrogen bonding when plotted against the appropriate pK values (open circles, Figure 6). This suggests that there is some contribution of catalysis by hydrogen bonding to the attacking amine as well as to the carbonyl oxygen atom with these catalysts; the subsequent proton-transfer step is fast and occurs by the same mechanism in both cases.

The absolute values of the rate constants are also consistent with a preassociation mechanism with hydrogen bonding and provide further evidence against a diffusion-controlled trapping mechanism. If buffer catalysis of this reaction proceeded through a simple trapping mechanism, general-acid catalysis by strong acids and general-base catalysis by strong bases should both be diffusion controlled and should be characterized by the same observed rate constants. This is not the case. For an acid of $pK = 1.0$, which has a favorable ΔpK for proton transfer to $T^{\pm}$ of 5.4 units, the value of k_A is 0.01 M^{-2} s^{-1}, whereas for a base of $pK = 10.2$, which has the same favorable ΔpK for proton removal from the nitrogen atom of $T^{\pm}$, the value of k_B is 0.001 M^{-2} s^{-1}, 1 order of magnitude less. The difference is expected for the preassociation mechanism because of the greater importance of hydrogen bonding of an acid to the developing negative charge on the carbonyl oxygen atom than of a base to the developing positive charge on the nitrogen atom in this mechanism. This difference appears in the larger value of $\alpha = 0.16$ for general acid catalysis compared with $\beta = 0.11$ for general base catalysis. It also arises from the larger difference of 14.7 units between the pK values of water and an acid of $pK = 1.0$ compared with the difference of 11.9 units between the pK values of the conjugate acids of water and a base of $pK = 10.2$. The advantage from hydrogen bonding depends on the difference in the acidity or basicity of the catalyst compared with water as well as the difference between the pK values of $T^{\pm}$ and the catalyst,[22] as is apparent in the terms for hydrogen bonding in eq 3 and eq 3 of the previous paper.[15]

A similar advantage for general-acid over general-base catalysis is found for the reaction of *p*-chlorobenzaldehyde with 2-methylthiosemicarbazide, which has also been proposed to proceed through a preassociation mechanism.[17,46] Hydrogen bonding in a preassociation mechanism might also provide an explanation for the larger rate constants for general-acid catalysis than for general-base catalysis in the intramolecular aminolysis of **5**, which



5

occurs with $\alpha = 0.4$, $b \approx 0$ for strong bases, a nonlinear Brønsted plot for general-base catalysis, a rate constant for the proton that fits on the line of slope $\alpha = 0.4$, and positive deviations from the Brønsted lines for several bifunctional catalysts.[47]

Supplementary Material Available: A table and three figures describing experimental rate constants (9 pages) follow the preceding paper in the microfilm edition. Ordering information is given on any current masthead page.

(46) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432.
(47) Kirby, A. J.; Mujahid, T. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1610–1616.