Concerted General Base and Bifunctional General Acid Catalysis of the Aminolysis of Phenyl Acetate by Pyrazole[1]

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Abstract: The reaction of phenyl acetate with pyrazole is catalyzed by general bases and by bifunctional general acids. The Brønsted plot for general base catalysis shows downward curvature. It is consistent with either a Hammond effect on proton transfer, as described by a positive coefficient $p_x = \partial\beta/-\partial pK_{AH}$, or separate lines with $\beta = 0.65$ for cacodylate and substituted acetate monoanions and $\beta = 0.38$ for phosphate, phosphonate, and methylarsonate dianions. Base catalysis shows a solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 1.8 \pm 0.2$ with no isotope effect maximum. These results are not consistent with trapping or stepwise preassociation mechanisms. It is concluded that the reaction involves concerted general base catalysis of proton abstraction from pyrazole as it attacks the ester. An estimated rate constant of $k_{-a} > 6 \times 10^{12}$ s^{-1} for collapse of the zwitterionic addition species, $T^{\pm}$, to reactants suggests that the concerted mechanism is enforced by the absence of a significant lifetime for $T^{\pm}$. Catalysis is observed with buffer acids when the acid is bifunctional. The rate constants are larger than expected for catalysis by the basic site on the catalyst but decrease with increasing acidity of the catalyst; the Brønsted slope is $\alpha = -0.2$ or $\beta = 0.2$. This catalysis is consistent with a fully concerted mechanism in which bifunctional acid-base catalysis occurs simultaneously with nucleophilic attack.

We would like to understand mechanisms of general acid-base catalysis and the reasons that a particular mechanism is followed for a reaction. Some mechanisms are determined by the lifetimes of reaction intermediates. For example, addition reactions to aldehydes occur by a predictable series of mechanisms with (1) no buffer catalysis, (2) general acid catalysis by diffusion-controlled trapping of an unstable anionic intermediate, (3) a preassociation mechanism that is required by a decrease in the lifetime of this intermediate, with stabilization of the transition state by hydrogen bonding, and (4) a fully concerted mechanism when the initially formed addition intermediate becomes too unstable to have a significant lifetime.[2,3]

More limited studies of general acid and base catalysis of the aminolysis of phenyl esters suggest that the mechanisms of these reactions can also be determined by the lifetime of tetrahedral intermediates along the reaction path. Brønsted plots for the acid-catalyzed partitioning of 4-methylphenyl *N*-methylacetimidate toward ester formation follow typical "Eigen curves" that are expected for an addition intermediate that undergoes diffusion-controlled proton transfer; the same addition intermediate is formed in the aminolysis of 4-methylphenyl acetate by methylamine and can be trapped by diffusion-controlled proton transfer. The lifetime of the initial addition intermediate in the aminolysis reaction, $T^{\pm}$, was estimated to be approximately 10^{-9} s.[4] The aminolysis of phenyl acetate by methoxyamine, which gives a less stable intermediate, follows Brønsted plots for both general acid and general base catalysis with values of α and $\beta = 0.1$-0.2 for strong acid and base catalysts and 1.0 for weaker catalysts, for which the proton-transfer step is thermodynamically unfavorable. Furthermore, there is a maximum in the solvent isotope effect near the break in the Brønsted plot, where the proton-transfer step becomes partially rate-limiting,[5] and a large β-deuterium isotope effect.[6] This is the behavior that is expected for catalysis by a preassociation mechanism, in which the transition state for the addition step is stabilized by hydrogen bonding to relatively strong acids or bases and diffusion-controlled separation from the unstable intermediate after proton transfer becomes rate-limiting with weakly acidic or basic catalysts. The preassociation mechanism is enforced by the short lifetime of the addition intermediate formed from this weakly basic amine, with an estimated lifetime of approximately 2×10^{-10} s for $T^{\pm}$. A preassociation mechanism provides the lowest energy pathway for reaction when the complex containing the catalyst and the addition intermediate collapses to reactants faster than the catalyst diffuses away.[7]

We report here a study of general acid-base catalysis of the aminolysis of phenyl acetate by pyrazole, a still less basic amine that is expected to form an even less stable addition species. We conclude that general base catalysis of this reaction occurs by a concerted reaction mechanism and that this mechanism is required because the species $T^{\pm}$ does not have a sufficient lifetime to exist as an intermediate.

Experimental Section

Materials. Unless otherwise stated, chemicals were reagent grade. Catalysts were purified by redistillation or by recrystallization as the potassium salt with the following exceptions: glacial acetic acid was used without further purification, methylarsonate was recrystallized as the sodium salt, 4-bromoimidazole (Vega) was recrystallized from chloroform/carbon tetrachloride, and phenyl acetates were purified as described elsewhere.[8] Water was glass distilled and deuterium oxide was 99.77% pure from Bio-rad.

Methods. Kinetic measurements were made on a Zeiss PM6 spectrophotometer with a thermostated cell carriage. All experiments were carried out at 25 °C, ionic strength 1 M maintained with KCl, except that in experiments with methylarsonate NaCl was used. In experiments with phenyl acetate and methylarsonate, 70% or 50% dianion, 0.4 M in NaCl and ionic strength maintained with KCl, the observed catalysis was found to be 15% and 50% smaller, respectively, compared with experiments in which ionic strength was maintained with NaCl. With substituted phenyl acetates reaction mixtures contained 5% acetonitrile (v:v). Control experiments with phenyl acetate showed that the presence of 5% acetonitrile altered the rate constant for catalysis by phosphate dianion by <10%. Reactions were followed at 275 nm for phenyl acetate, 370 nm for *m*-nitrophenyl acetate, and 370 or 400 nm for *p*-nitrophenyl acetate.

Most of the rate constants were determined from initial rate measurements, in which <10% of the total reaction was followed. The first-order rate constant, k_{obsd}, was obtained by dividing the initial rate of absorbance change by the end point absorbance, A_∞. The value of A_∞ was obtained for each experiment by alkaline hydrolysis of a known amount of ester, neutralization to the pH of the experiment, and dilution to a concentration appropriate for spectrophotometric determination. The absorbance at zero time was <3% of A_∞. Pseudo-first-order conditions were used for the reaction of *p*-nitrophenyl acetate and pyrazole with ethylphosphonate or methylarsonate catalysts. For these reactions k_{obsd} was taken as $0.693/t_{1/2}$, where $t_{1/2}$ was obtained from plots of log $(A_\infty - A_t)$ against time for at least 3 half-times. Generally, values of k_{obsd}

(1) Supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 81-17816).
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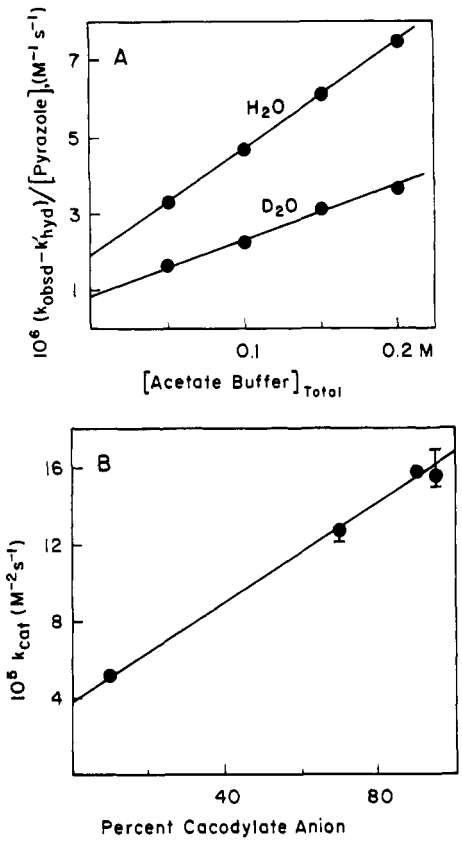


Figure 1. (A) Catalysis by acetate buffer, 90% anion, of the reaction of pyrazole with phenyl acetate in H_2O and D_2O at 25 °C, ionic strength 1 M (KCl); $k'_{hyd} = k_0 + k_{hyd}$[buffer] (eq 1). (B) Dependence of k_{cat} for the reaction of pyrazole with phenyl acetate on the fraction of cacodylate anion. The values of k_A and k_B are taken as the left and right intercepts, respectively.

were determined at four buffer concentrations for each of at least three buffer ratios per catalyst. The total hydrolysis rate constant, k'_{hyd}, was determined in parallel experiments in which the nucleophile was not present. Thus, at a given buffer ratio linear plots of $(k_{obsd} - k'_{hyd})/$[pyrazole] against [buffer]$_{total}$ were obtained. The intercept at [buffer]$_{total}$ = 0 gives the rate constant for "water-catalyzed" aminolysis and the slope of the second-order plot, k_{cat}, gives a third-order rate constant for catalysis based on total buffer concentration. For experiments at pH >7 with ethylphosphonate, methylarsonate, and bicarbonate buffers a contribution due to reaction of pyrazole anion was observed as an increase in the intercept values of the second-order plots with increasing pH.

Solvent isotope effects were determined by measuring rate constants simultaneously in H_2O and D_2O for four buffer concentrations at a single buffer ratio. Under the conditions of these experiments the fraction of the total catalyzed reaction which was due to base catalysis was >96% in all cases, except for a single experiment to determine the isotope effect on acid catalysis in which >80% of the observed catalysis was due to acid catalysis. The deuterium oxide reaction mixtures contained ≤3% HOD.

Results

The reactions of ring-substituted phenyl acetates with pyrazole were found to follow the rate law of eq 1, in which A^- and HA represent the basic and acidic buffer components, k_0 and k_{hyd} are

$$k_{obsd} = k_0 + k_{hyd}[\text{buffer}]_{total} + k_1[\text{pyr}] + k_B[A^-][\text{pyr}] + k_A[HA][\text{pyr}] + k_p[\text{pyr}^-] \quad (1)$$

rate constants for the uncatalyzed and buffer-catalyzed hydrolysis of the ester, and pyr and pyr^- represent pyrazole and its anion. The rate constants k_1, k_B, and k_A are for the "water-catalyzed", base-catalyzed, and acid-catalyzed aminolysis, respectively. Typical data for the determination of k_{cat}, for catalysis based on total buffer concentration in H_2O and D_2O, are presented in Figure 1A for acetate buffer, 90% anion. The rate constants k_A and k_B were determined from the intercept values of plots of k_{cat} against the percent base in the buffers, as shown in Figure 1B for cacodylate buffers. Except for the reactions of *p*-nitrophenyl acetate

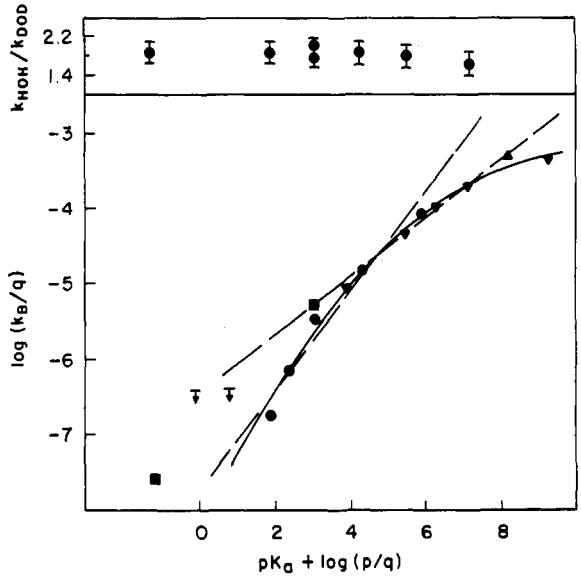
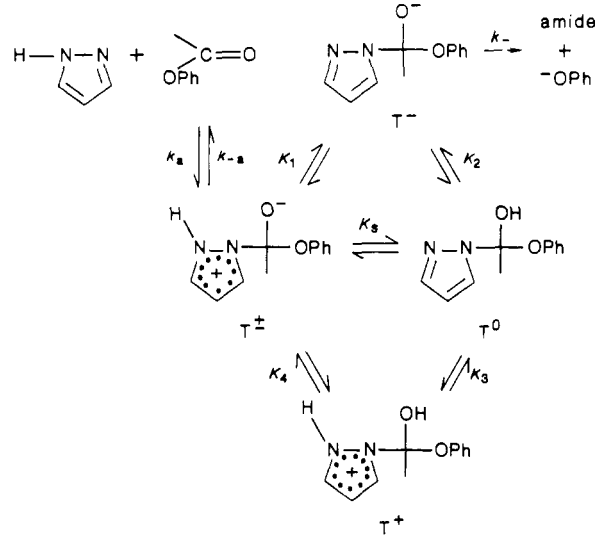


Figure 2. Statistically corrected Brønsted plot for k_B and solvent deuterium isotope effects on k_{cat} for the base-catalyzed aminolysis of phenyl acetate by pyrazole in water at 25 °C and ionic strength 1 M (KCl): (▼) phosphate, substituted phosphonate, and carbonate dianions; (●) substituted acetate and cacodylate monoanions; (■) H_2O and pyrazole; and (▲) methylarsonate dianion (ionic strength maintained with NaCl). The dashed lines have slopes of β = 0.38 and 0.65. The solid line was calculated from $p_x = \partial\beta/-\partial pK_{AH} = 0.1$, as described in the text.

Scheme I



and pyrazole with ethylphosphonate and methylarsonate buffers, for which pseudo-first-order conditions were used, all rate constants were derived from initial rate measurements as described in the Experimental Section. The experimental conditions and rate constants for the base- and acid-catalyzed aminolysis of phenyl acetates by pyrazole and 4-bromoimidazole are presented in Table I. Table II summarizes the data for solvent isotope effect measurements. The mean value of k_{HOH}/k_{DOD} for general base catalysis is 1.8 ± 0.2. A series of rate and equilibrium constants for reactions of possible intermediates in the reaction, as defined in Scheme I, was calculated as described in the Appendix; the results are summarized in Table III.

Discussion

The Brønsted plot for general base catalysis of the reaction of phenyl acetate with pyrazole is shown in the lower part of Figure 2. The rate constants for catalysts in the range of pK_a 2.2–9.8 are consistent with either a single line that has downward curvature or the two dashed lines, with least-squares slopes of β = 0.65 for cacodylate and substituted acetate monoanions and β = 0.38 for

Table I. Rate Constants and Experimental Conditions for the Aminolysis of Phenyl Acetates by Pyrazole and 4-Bromoimidazole[a]

catalyst (basic form)	pK_a	% base	buffer concn, M	10^5k_{cat},[b] M^{-2} s^{-1}	10^5k_B,[c] M^{-2} s^{-1}	10^5k_A,[c] M^{-2} s^{-1}
			Pyrazole and Phenyl Acetate			
trifluoroacetate	0.23	100	0.4–0.8	<0.083	<0.083	
dichloroacetate	1.03	99	0.20–0.8	<0.083	<0.083	
cyanoacetate	2.23	95	0.19–0.84	0.035	0.035[d,e]	
chloroacetate	2.65	80	0.20–0.8	0.13	0.14[l]	
		90	0.20–0.8	0.14		
		85	0.20–0.8	0.15		
methoxyacetate	3.33	50	0.10–0.4	0.25	0.68	<0.2
		70	0.10–0.4	0.43		
		90	0.10–0.4	0.70		
		95	0.10–0.4	0.60		
(trichloromethyl)phosphonate dianion	4.28	20	0.07–0.27	0.57	2.8	0.23
		50	0.07–0.27	1.50		
		80	0.05–0.2	2.32		
acetate	4.60	20	0.10–0.4	1.13	3.0	0.67
		80	0.10–0.4	2.52		
(chloromethyl)phosphonate dianion	5.95	10	0.05–0.2	4.6	13.6	3.3
	(0.95)[f]	70	0.05–0.2	10.2		
		76[g]	0.05–0.2	11.0		
		90	0.05–0.2	12.5		
cacodylate	6.16	10	0.025–0.15	5.2	16.8	3.8
	(1.77)[f]	70	0.025–0.15	12.7		
		90	0.025–0.15	15.9		
		95	0.05–0.20	15.6		
phosphate dianion	6.46	10	0.05–0.20	10.6	34	7.1
	(1.72)	70	0.05–0.20	25		
		90	0.05–0.20	34		
ethylphosphonate dianion	7.60	10	0.05–0.20	11.8	56	4.6[h]
	(2.23)	47	0.05–0.20	25		
		90	0.05–0.20	48		
		95	0.05–0.20	57		
methylarsonate dianion[i]	8.50	10	0.03–0.11	14.4	144	<6.7
	(3.98)	70	0.04–0.12	96		
		90	0.04–0.12	133		
carbonate dianion	9.78	2	0.05–0.20	17.7	130[j]	11.3
	(3.8)	5	0.05–0.20	19.2		
		10	0.05–0.20	26.7		
pyrazole[k]	2.74	50	0.10–0.5	0.22	0.48	<0.1
		80	0.10–0.5	0.38		
H_2O[l]	−1.74			0.0028	0.0028	
HO^-	15.74		$(0.03–7) \times 10^{-6}$		8×10^5	
			Pyrazole and *m*-Nitrophenyl Acetate[m]			
acetate	4.60	50	0.07–0.28	22.3	21.2	22.8[j]
		70	0.05–0.21	21.7		
phosphate dianion	6.46	20	0.05–0.21	78	210	43
	(1.72)	70	0.04–0.16	163		
H_2O[l]	−1.74			0.10	0.10	
			Pyrazole and *p*-Nitrophenyl Acetate[m]			
acetate	4.60	20	0.17–0.50	38	58	33
		50	0.13–0.52	45		
		70	0.12–0.48	52		
phosphate dianion	6.46	20	0.11–0.44	112	400	38[e]
	(1.72)	50	0.09–0.36	222		
ethylphosphonate dianion	7.60	10	0.11–0.44	85	312[e]	60
	(2.23)	20	0.12–0.48	112		
		30	0.12–0.48	87		
		40	0.07–0.28	162		
		70	0.09–0.36	330[j]		
		80	0.03–0.12	262		
		90	0.08–0.32	243		
methylarsonate dianion[n]	8.50	20	0.04–0.16	20	67	6.7[h]
	(3.95)	50	0.05–0.20	37		
H_2O[l]	−1.74			0.28	0.28	
			4-Bromoimidazole and Phenyl Acetate			
acetate	4.60	70	0.06–0.24	1.97	2.43[j]	<1.5
		90	0.05–0.22	2.22		
(chloromethyl)phosphonate dianion	5.95	50	0.03–0.13	6.0	11.0	<3
	(0.95)	90	0.03–0.12	10.0		
ethylphosphonate dianion	7.60	30	0.08–0.32	11.7	50[e]	<8.3
	(2.23)	50	0.03–0.14	28		
		70	0.04–0.16	38		
H_2O[l]	−1.74			0.0083	0.0083	

[a] At 25 °C, 1 M ionic strength (KCl); pK_a values from ref 5 unless otherwise indicated, numbers in parentheses are pK_a values for the first ionization. [b] Slope of the second-order plot (see Experimental Section). [c] ±10% unless otherwise stated. [d] Based on eight buffer concentrations with a rate increase over background of 25%. The rate increase due to 0.80 M trifluoroacetate anion is less than 3%. [e] ±20%. [f] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 1228. [g] At 0.91 M ionic strength (KCl). [h] ±50%. [i] At 1 M ionic strength (NaCl). [j] ±15%. [k] As reported in ref 5. [l] The rate constant was obtained by dividing the intercept of plots of $(k_0 - k_{hyd})$/[nucleophile] against [buffer] by 55.5 M, for experiments at pH <7. The error is ±20%. [m] Solutions contained 5% (v:v) acetonitrile. [n] 0.4 in NaCl, ionic strength 1 M with KCl.

Table II. Solvent Deuterium Isotope Effects for Catalysis of the Reaction of Pyrazole with Phenyl Acetate[a]

catalyst (basic form)	pK_a	% base	buffer concn, M	$10^5 k_{cat}(H_2O)$, M^{-2} s^{-1}	$10^5 k_{cat}(D_2O)$, M^{-2} s^{-1}	$k_{cat}(H_2O)/k_{cat}(D_2O)$[b]
cyanoacetate[c]	2.23	95	0.25–0.98	0.039	0.020	1.9
methoxyacetate	3.33	90	0.05–0.28	0.56	0.27	2.0
		70	0.12–0.48	0.46	0.25	1.8
acetate	4.60	90	0.05–0.28	2.68	1.4	1.9
(chloromethyl)phosphonate dianion	5.95	90	0.045–0.18	10	5.7	1.8
		5	0.01–0.39	3.0	1.7	1.7[d]
ethylphosphonate dianion	7.60	90	0.047–0.19	43	26	1.6
L_2O[e]	−1.74					1.9

[a] At 25 °C, ionic strength 1 M (KCl); the values of pK_a are from ref 5 and references therein. [b] Under these conditions 95% of k_{cat} represents the base-catalyzed reaction. The values of isotope effects are ±10%. [c] Based on a 20% increase in k_{obsd} above background at the highest buffer concentration. [d] Under these conditions >80% of k_{cat} is due to the acid-catalyzed reaction. [e] From the ratio of intercepts for the reactions in H_2O and D_2O at zero buffer concentration, from plots of $(k_{obsd} - k'_{hyd})/[pyrazole]$ against buffer concentration. The value of the isotope effect is an average taken from the experiments with methoxyacetate, acetate, and ethylphosphonate buffered reactions.

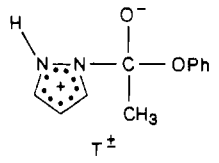
Table III. Summary of Rate and Equilibrium Constants for Scheme I, Calculated As Described in the Appendix[a]

rate constant	log k	equilib const	log K[b]
k_1'	8[c]	K_1	−2.1
k_{-1}'	2.3[c]	K_2	−11.2
k_2'	4.6[c]	K_3	2.7
k_{-2}'	8[c]	K_4	−6.4
k_3'	8[c]	K_s	9.1[d]
k_{-3}'	−2.6[c]		
k_4'	8[c]		
k_{-4}'	6.5[c]		
k_a	>−0.12[e]		
k_{-a}	>12.7[f]		
k_s	8[g]		
k_{-s}	−1.1[h]		
k_-	>10[f]		

[a] The constants are defined in Scheme I. [b] Units of M, unless otherwise noted, see Appendix. [c] Pseudo-first-order rate constants based on calculated pK_a values (Appendix), a rate constant of 10^9 M^{-1} s^{-1} for thermodynamically favorable proton transfer, and the presence of 0.1 M each of the monoanion and dianion of ethylphosphonate. [d] Dimensionless. Calculated from $K_s = K_3/K_4$. [e] M^{-1} s^{-1}. [f] s^{-1}, see Appendix. [g] s^{-1} ref 44; see text. [h] s^{-1}, calculated from $k_{-s} = k_s/K_s$.

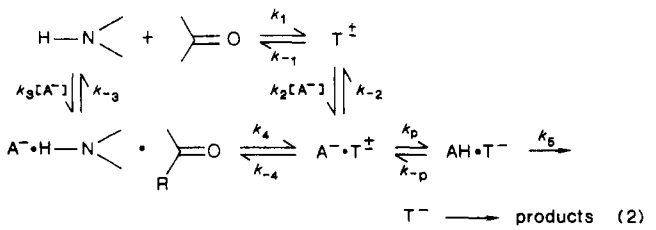
phosphate, phosphonate, and methylarsonate dianions; there is a negative deviation of 0.4 log units from this line for carbonate. The slope of a single least-squares line for all of the catalysts except water is $\beta = 0.42$; however, the large negative deviations from this line of 0.75 and 0.4 log units for cyanoacetate and chloroacetate ions, respectively, are not consistent with a single straight line.

Stepwise Mechanisms. The Brønsted correlation is clearly inconsistent with the "Eigen curve" that is expected for a simple stepwise mechanism in which the initially formed addition intermediate $T^{\pm}$ is trapped by proton transfer to a catalyzing base,



$T^{\pm}$

followed by rapid breakdown of the anionic intermediate T^- to products.[4,5,8] This mechanism proceeds through the upper k_1, k_2, k_p, k_5 pathway of eq 2. For bases of pK_a greater than the estimated pK_a of 2.1 for $T^{\pm}$ (Table III), the Brønsted slope would be $\beta = 0$ for this mechanism because the rate-limiting step is the diffusion-controlled encounter of the base with $T^{\pm}$, k_2, which is independent of the pK_a of the catalyst. A mechanism involving rate-limiting proton transfer at the OH group of an uncharged addition intermediate, T^0, is also inconsistent with the Brønsted plot of Figure 2 because the estimated pK_a of 11.2 for this group (Table III) would give a slope of $\beta = 1.0$ for all catalysts examined. Rate-limiting protonation of the phenolic oxygen atom of T^- would not show buffer catalysis because the pK_a of <−3.6 for this group means that protonation would be brought about only by the solvated proton.[9]



$T^- \longrightarrow$ products (2)

The Brønsted correlation is not inconsistent with a stepwise preassociation mechanism that proceeds through the lower k_3, k_4, k_p, k_5 pathway in eq 2. In this mechanism hydrogen bonding of the stronger bases to the attacking amine can stabilize the transition state for the addition step, k_4. With less basic catalysts near the pK_a of 2.1 for $T^{\pm}$ the proton-transfer step becomes partially rate-limiting, and with still less basic catalysts diffusion-controlled separation of the catalyst or breakdown of T^- may become rate limiting. With a preassociation mechanism the break in the nonlinear Brønsted plot for general base catalysis occurs 1–2 pK units above the pK_a of $T^{\pm}$.[5] A fair fit to the data can be obtained with a Brønsted line calculated from the parameters $\beta = 0.1$, $pK_a = 2.4$ for $T^{\pm}$, $k_{-4} = 10^{12}$ s^{-1}, $k_{-2} = k_5 = 10^{11}$ s^{-1}, k_p and $k_{-p} = 10^{(10\pm0.5\Delta pK_a)}$ s^{-1}, and $k_B^{DC} = 1.5 \times 10^{-7}$ M^{-2} s^{-1} (not shown: see Appendix).

However, three observations are inconsistent with a stepwise preassociation mechanism.

(1) A stepwise preassociation mechanism will show little or no solvent deuterium isotope effect in the region of the Brønsted plot in which nucleophilic attack or diffusional steps are rate-limiting, but it is expected to give an isotope effect maximum when the proton-transfer step becomes partly rate-limiting. This was observed for catalysis of the methoxyaminolysis of phenyl acetate through a stepwise preassociation mechanism, with a maximum observed isotope effect of $k_{HOH}/k_{DOD} = 4$.[5] There is no such maximum for catalysis of the reaction of pyrazole with phenyl acetate; the observed solvent deuterium isotope effects are $k_{HOH}/k_{DOD} = 1.8 \pm 0.2$ and do not change significantly with changing pK_a of the catalyst (Table II, Figure 2: upper section). The parameters above that were used to calculate a Brønsted line for this mechanism predict that the maximum isotope effect of $k_{HOH}/k_{DOD} = 5$ would be observed for catalysts of $pK_a \sim 4.5$, assuming a constant isotope effect of 5 for the proton-transfer step, k_p.[5]

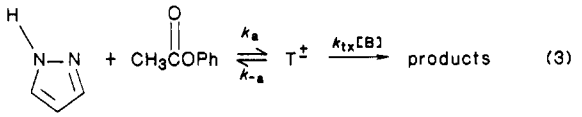
(2) If the base catalysis occurs by a stepwise preassociation mechanism, there must also be general acid catalysis by a preassociation mechanism with similar limiting rate constants, but no such catalysis is observed. The stepwise preassociation mechanism involves rate-limiting attack of the nucleophile in the presence of relatively strong base or acid catalysts, followed by

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

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

rapid proton transfer that prevents the addition intermediate $T^{\pm}$ from reverting to reactants. If there is base catalysis by this mechanism that traps $T^{\pm}$ by removing a proton, there must also be acid catalysis that traps $T^{\pm}$ by protonating the anionic oxygen atom.[10] The limiting rate constants for the two mechanisms will be the same, except for the extent to which assistance by hydrogen bonding increases the rate. Both mechanisms, with similar rate constants for relatively strong acid and base catalysts, were observed for the methoxyaminolysis of phenyl acetate.[5] However, only very weak general acid catalysis is observed for the reaction with pyrazole, and this catalysis has the peculiar property that the catalysis decreases with increasing acidity of the catalyst; no catalysis could be detected with methoxyacetic acid or protonated pyrazole (Table I; this catalysis will be discussed below).[11]

(3) If the reaction proceeded through a preassociation mechanism, it would require a rate constant of $>10^{13}$ s^{-1} for breakdown of the tetrahedral species $T^{\pm}$. This rate constant is at the limit for a vibration frequency, so that a species which reacted with this rate constant would not have a significant lifetime and would not be an intermediate; if there is no intermediate the reaction is not stepwise. No catalysis by pyrazole through a simple trapping mechanism is observed, so that the rate constant k_T for catalysis by trapping must be less than the observed rate constant of $k_B = 0.48 \times 10^{-5}$ M^{-2} s^{-1} for catalysis by pyrazole (Table I). The rate constant for base catalysis by the trapping mechanism (eq 3) is given by eq 4. The limit of $k_T < 0.48 \times 10^{-5}$ M^{-2} s^{-1} and

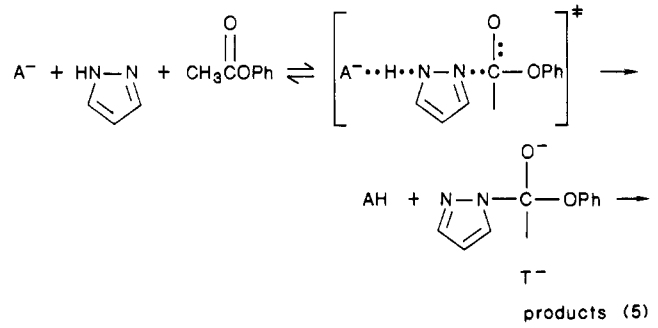


(3)

$$k_T = k_{tx}k_a/k_{-a} = k_{tx}K_a \quad (4)$$

a value of $k_{tx} = 1 \times 10^8$ M^{-1} s^{-1} for the nearly thermoneutral proton transfer between $T^{\pm}$ and the pyrazole catalyst ($\Delta pK_a = 0.6$)[12] gives $K_a = <5 \times 10^{-14}$ M^{-1}. The value of $k_a = 0.8$ M^{-1} s^{-1} (Table III) gives $k_{-a} = k_a/K_a = >1.6 \times 10^{13}$ s^{-1}. This limit is not exact, but it is large enough to make it unlikely that the reaction can proceed through an intermediate with a significant lifetime.

Concerted Mechanisms. We conclude that the reaction proceeds through a concerted mechanism in which the unstable species $T^{\pm}$ is bypassed and a proton is removed from pyrazole as it attacks the ester, to give T^- directly. The anionic intermediate T^- then expels phenolate ion rapidly to give acetylpyrazole (eq 5).



(5)

Mechanisms involving catalysis of the breakdown of the intermediate T^0 or T^- can be excluded because breakdown of these intermediates is not rate-limiting; i.e., they collapse to products faster than they revert to reactants. The estimated rate constant of $k_- > 10^{10}$ s^{-1} for the breakdown of T^- to products is 10^7 larger than the rate constant for protonation of the pyrazole group and breakdown to reactants in the presence of 0.1 M ethylphosphonate monoanion and dianion ($k_{-1}' = 200$ s^{-1}, Scheme I, Table III). The rate constant $k_2' = 10^{4.6}$ s^{-1} for the conversion of T^0 to T^-, which gives products rapidly, is $>10^5$ larger than the rate constant for reversion to $T^{\pm}$ and reactants through a proton switch or pyrazole protonation, k_{-s} or k_{-3}' (Table III). The Brønsted plot in Figure 2 is inconsistent with a mechanism involving rate-limiting breakdown of $T^{\pm}$. The rate-limiting step for such a mechanism with catalysts of $pK_a > 3$ would be diffusion-controlled encounter of the base catalyst and $T^{\pm}$, followed by fast proton transfer and breakdown of T^- (the pK_a of $T^{\pm}$ is 2.1, Table III). The Brønsted plot would then have a slope of $\beta = 0$ for catalysts of $pK_a > 3$, which is not observed.

The solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 1.8 \pm 0.2$ is small, but it is larger than expected for a reaction that does not involve proton transfer in the rate-limiting step. A similar isotope effect of $k_{HOH}/k_{DOD} = 1.9 \pm 0.2$ was observed for general base catalysis of the hydrolysis of a cationic imine, which also occurs through a concerted mechanism.[13] Coupling of the proton transfer to motion of heavy atoms in the transition state is one of several explanations that can account for small deuterium isotope effects. The observed isotope effect of $k_{HOH}/k_{DOD} = 3.7$ for the mutarotation of tetramethylglucose catalyzed by 2-pyridone, with two protons "in flight", is close to a calculated value of 3.8 that includes coupling to heavy atom motion but is much smaller than a value of 38 calculated without such motion.[14]

There is evidence that the effect of polar substitutents in the nucleophile on the rate of the base-catalyzed reaction is small. This is also consistent with concerted proton removal and nucleophilic attack because removal of the proton will decrease the development of positive charge on the nucleophile as it attacks the ester. Insufficient data are available for an accurate analysis, but a crude estimate of β_{nuc} for the catalyzed reaction can be made from a Brønsted-type plot of log k against the pK_a of the nucleophile for the reactions of pyrazole and 4-bromoimidazole with phenyl acetate, catalyzed by diethylphosphonate (Table I), and of imidazole with *p*-methylphenyl acetate, catalyzed by imidazole (not shown).[8,15,16] The slope of this correlation is $\beta_{nuc} = 0.2$, which is much smaller than the slope of $\beta_{nuc} = 0.7$ for the corresponding uncatalyzed (or water-catalyzed) reactions. If $\beta = 0.4$ corresponds to about 40% proton removal from pyrazole and there is 0.6–0.7 C–N bond formation and positive charge development on pyrazole in the transition state, the difference corresponds to $\beta_{nuc} = 0.2$–0.3 for the base-catalyzed reaction, in agreement with this estimate.

Finally, the rate constant for the collapse of $T^{\pm}$ to reactants was estimated to be $k_{-a} > 6 \times 10^{12}$ s^{-1}. This rate constant was calculated from a limit for the leaving ability of pyrazole and the value of k_{-a} for dimethylamine expulsion from the $T^{\pm}$ intermediate that is formed in the hydrolysis of *p*-methylphenyl *N*-dimethylacetimidate and undergoes diffusion-controlled reaction with catalysts (Table III).[4] Because this lower limit is close to the frequency of a stretching vibration of $\sim 10^{13}$ s^{-1}, an "intermediate" with this lifetime would not have a significant existence as a chemical species. (It should be noted that this calculation is different from the limit of $k_{-a} > 10^{13}$ s^{-1} described above, which shows that the observed rate constants require that $T^{\pm}$ cannot exist

(10) Acid catalysis by a stepwise preassociation mechanism would not be observed if there were a different mechanism of general acid catalysis that is faster than the preassociation mechanism; however, no acid catalysis with a rate equal to or faster than that expected for the preassociation mechanism is observed. The fact that acid catalysis by a preassociation mechanism is observed for the reaction with methoxyamine[5] indicates that it should also be observed for the pyrazole reaction if the base-catalyzed reaction occurs by the preassociation mechanism.

(11) The product of protonation, T^+, has an estimated pK_a of -2.7 and will lose a proton to solvent very rapidly to form T^0. As described later, T^0 gives products faster than it is reprotonated (see the rate constants in Table III).

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

(13) Fischer, H.; Decandis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 1340.

(14) Engdahl, K.-A.; Bivehed, H.; Ahlberg, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 4767.

(15) The pK_a values of imidazole and ethyl phosphonate are 7.21 and 7.60, respectively, at ionic strength 1 (Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622);[5] for phenol and *p*-methylphenol they are 9.95 and 10.2, respectively. The value of k_B for the bromoimidazole reaction is adjusted by adding 0.32 log units. There is a deviation of -0.32 log units for bromoimidazole from the β_{nuc} plot for the uncatalyzed reaction of phenyl acetate with imidazoles, pyrazole, and triazoles, presumably due to a steric effect. (Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622 and Table I.)

(16) Unpublished experiments.

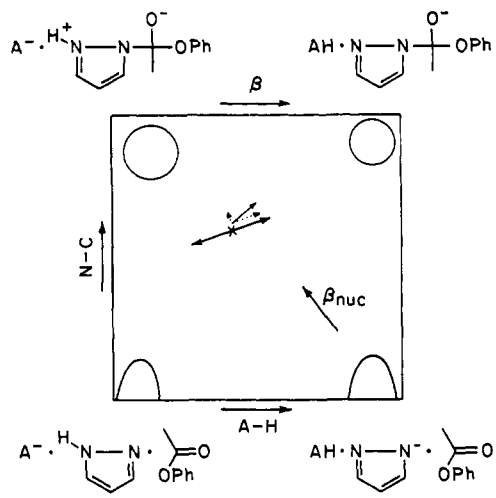


Figure 3. Reaction coordinate diagram for the base-catalyzed aminolysis of phenyl acetate by pyrazole. The transition state is at X, the double headed arrow represents the reaction coordinate, and the dashed vectors represent parallel and perpendicular effects on the reaction coordinate upon decreasing catalyst basicity; the solid arrow is the resultant of the vectors.

as an intermediate on the observed reaction path; this calculation suggests that $T^{\pm}$ cannot exist because of its inherent instability.)

Structure–Reactivity Correlations and the Structure of the Transition State. The downward curvature in the Brønsted plot of Figure 2 can be accounted for by either or both of two explanations. It could represent a change in transition-state structure with increasing pK_a of the base catalyst, i.e., a "Hammond effect" on the proton-transfer component of the reaction, or a combination of two linear Brønsted correlations with slopes of $\beta = 0.65$ for catalysis by monoanions and 0.38 for catalysis by dianions. A requirement for an initial desolvation step for reaction of basic, strongly solvated oxygen anions can decrease the observed Brønsted slope for these anions and lead to a curved Brønsted correlation. Downward curvature in Brønsted plots for proton removal from carbon and for nucleophilic attack on esters has been attributed to a requirement for such a desolvation step and the small value of $\beta_{nuc} = 0.3$ for reaction of substituted phosphonate dianions, compared to $\beta_{nuc} = 0.7$ for substituted phenolate anions, has also been ascribed to strong solvation.[17-20]

A Hammond effect on proton transfer corresponds to an increase in β with decreasing basicity of the catalyst that can be described by a positive value of the coefficient $p_x = \partial\beta/-\partial pK_{AH}$.[21] The solid line in Figure 2 is drawn for a value of $p_x = 0.1$ and provides a satisfactory fit to the data.[22]

There is precedent for a Hammond effect in base catalysis of other reactions that involve proton transfer. The closest analogy to the present work is the base-catalyzed cyclization of a bicyclic hydroxyamide, which shows an increase in β from 0.5 to 0.7 as the pK_a of the leaving amine is increased from 5.8 to 10.8. In the reverse direction, the attack of amine on the lactone, this represents a larger amount of proton removal from the less acidic attacking amine. This unusual behavior corresponds to a reaction coordinate in which there is a major component of proton transfer, rather than a hydrogen-bonded proton in a potential well, in the transition state.[23] It suggests that there is also a significant change in transition-state structure in the reaction described here, although the possibility of a solvation effect on the Brønsted slopes is not excluded.

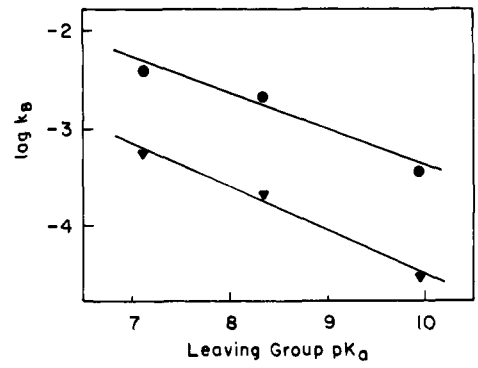


Figure 4. The dependence on leaving group pK_a of the rate constants for catalysis of the reaction of pyrazole with substituted phenyl acetates by phosphate dianion and acetate anion. The values of β_{lg} are −0.38 and −0.46 for reactions catalyzed by phosphate dianion (●) and acetate anion (▼), respectively.

Downward curvature in Brønsted plots has been reported for general acid or base catalysis of a number of simple proton-transfer reactions to or from carbon, but this has not been observed in others.[24-26] The different α values for general acid catalysis of vinyl ether hydrolysis by substituted acetic acids and phosphonate monoanions[24] could represent a change in transition-state structure or a solvation effect, or both. The large change in α for acid catalysis of diphenyldiazomethane cleavage by substituted acetic acids and phenols in 80% Me_2SO is more likely to represent a change in transition-state structure[25] because there appears to be little effect of desolvation on structure–reactivity parameters for reaction rates that involve phenols or phenolate ions, at least in aqueous solution.[18]

The structure–reactivity behavior for the reaction of pyrazole with phenyl acetate can be described by the reaction coordinate–energy diagram of Figure 3.[21,27] The x and y coordinates of this diagram are defined by structure–reactivity parameters for proton transfer and N–C bond formation, respectively, and the energy in the third dimension may be indicated by contour lines (not shown). The dependence of log k on the pK_a of an attacking amine, β_{nuc}, is defined by a diagonal axis between the lower right corner, with a full negative charge on the nucleophile and $\beta_{nuc} = -1$, and the upper left corner, with a positive charge on the nucleophile and $\beta_{nuc} = 1$. The position of the transition state on the reaction coordinate for general base catalysis of the formation of T^{-} is shown, with values of $\beta = 0.4$ for proton transfer and $\beta_{nuc} = 0.2$ for the diagonal axis.

Figure 4 shows the dependence of log k on the pK_a of the leaving group for the base-catalyzed reactions of pyrazole with three substituted phenyl acetates. The slopes of the lines are $\beta_{lg} = -0.46$ and −0.38 for catalysis by acetate anion and phosphate dianion, respectively; rate constants for the "water" reaction give $\beta_{lg} = -0.74$ (Table I, plot not shown). A value for β_{lg} of approximately −(0.6–0.7) is expected for complete formation of an addition intermediate,[28] so that the average observed value of $\beta_{lg} = -0.42$ corresponds to approximately two-thirds progress of the reaction toward the tetrahedral intermediate in the transition state. This is in reasonable agreement with the position of the transition state

(17) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1962**, *84*, 2910. Hupe, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(18) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045.
(19) Hupe, D. J.; Pohl, E. R. *J. Am. Chem. Soc.* **1984**, *106*, 5634.
(20) Shames, S. L.; Byers, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 6170.
(21) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948. Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.
(22) The solid line in Figure 2 was calculated[21] from

$$-\log k = \tfrac{1}{2}p_x(pK)^2 - \beta_0(pK) + F$$

with $p_x = 0.10$, $\beta_0 = 1$, and $F = 8.25$.

(23) Morris, J. J.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1980**, 685.
(24) Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805.
(25) Hassid, A. I.; Kreevoy, M. M.; Liang, T.-M. *Faraday Symp. Chem. Soc.* **1975**, *No. 10*, 69.
(26) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737 and references therein.
(27) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274.
(28) A value of $\beta_{lg} = -0.6$ is expected for the fully formed tetrahedral intermediate based on $\beta_{eq} = 1.6$ for acetyl transfer between phenolates and $\beta = 1$ for the annihilation of a charge on an attacking phenolate ion (Gerstein, J.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 4655).

in Figure 3 that was estimated from β and β_{nuc} and indicates that there is no significant imbalance between these structure–reactivity parameters.

The direction of the reaction coordinate and the curvatures of the surface parallel and perpendicular to the reaction coordinate at the transition state in Figure 3 define the changes in structure–reactivity parameters that are observed with changing reactant structure.[21] The reaction coordinate in Figure 3 is drawn with a large horizontal component for proton transfer in order to take account of the downward curvature of the Brønsted plot for general base catalysis. This corresponds to a normal Hammond effect for the proton-transfer component of the reaction, i.e., a shift of the position of the transition state along, or parallel to, the reaction coordinate with changing basicity of the catalyst. Decreasing the pK_a of the catalyst increases the energy of the right edge relative to the left in Figure 3. This will tend to shift the position of the transition state along the reaction coordinate toward the position of higher energy on the right side if the reaction coordinate is largely horizontal, with a major component of proton transfer in the transition state. This corresponds to the observed increase in β with decreasing pK_a of the catalyst (Figure 2). Analogous behavior for a reaction in the reverse direction was observed by Morris and Page with changing pK_a of the leaving amine in lactonization.[23] If the proton were hydrogen bonded and resting in a potential well, the reaction coordinate would be largely vertical and would represent primarily formation of the N–C bond. Raising the right edge of the diagram would then tend to shift the reaction coordinate downhill and to the left toward the position of lower energy, perpendicular to the reaction coordinate. This is an "anti-Hammond" effect and is not observed.

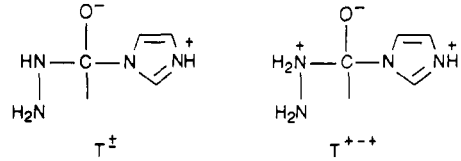
The dotted arrows parallel and perpendicular to the reaction coordinate in Figure 3 show the expected movements of the transition state in more detail. Decreasing the pK_a of the base and raising the right edge of the diagram will create an energy gradient along the x coordinate and cause a relatively large shift of the transition state toward the position of higher energy, in the direction parallel to the largely horizontal reaction coordinate. The change in the energy perpendicular to this reaction coordinate will be relatively small, so that there will be little movement in this direction. The observed change, shown by the diagonal arrow, is the resultant of these two changes. It corresponds to a relatively large change in the amount of proton transfer, as measured by β, and a small increase in the amount of N–C bond formation. This is consistent with the more negative value of $\beta_{lg} = -0.46$ for catalysis by acetate ion compared with $\beta_{lg} = -0.38$ for phosphate dianion, but the difference is too small to allow a definite conclusion.

Related Reactions. The concerted mechanism for the reaction of pyrazole with phenyl acetate represents the third class of mechanism to be observed in the aminolysis of phenyl esters; it completes the series of mechanisms described in the introduction. The calculated lifetime for collapse of the species $T^{\pm}$ is consistent with the notion that the changes in mechanism can be enforced by changes in the lifetimes of intermediates. The lifetime of $T^{\pm}$ progressively decreases and k_{-a} increases, as the basicity of the nucleophile is decreased from methylamine[4] to methoxyamine[5] to pyrazole, and this change in lifetime requires the mechanism of catalysis to change from diffusion-controlled trapping to preassociation stepwise to preassociation concerted.

Several reports of concerted catalysis in aminolysis or related reactions have appeared. An understanding of the mechanisms and properties of these reactions is central to understanding what determines the mechanism of general acid–base catalysis that is followed in a particular reaction; a concerted mechanism can be followed in some general acid–base catalyzed reactions even when it is not required by the nonexistence of intermediates with a significant lifetime.[29]

General base catalysis of the hydrazinolysis of acetylimidazole occurs by a stepwise mechanism and follows a nonlinear Brønsted plot with a break below the estimated pK_a of $T^{\pm}$. This can be accounted for by expulsion of imidazole anion from T^- at a faster rate than the diffusional separation of the protonated catalyst from this species, so that the breakdown step occurs by a preassociation mechanism in reverse and the rate constant for collapse of T^- is $>10^{10}$ s^{-1}.[30] It is probable, therefore, that the analogous reaction of acetyltriazole with methoxyamine follows an enforced concerted mechanism because the triazole anion is some 4 pK units less basic than imidazole anion, so that T^- in this reaction is not likely to have a significant lifetime.[31] The nonlinear Brønsted plot for general base catalysis of this reaction is consistent with a slope of $\beta = 0$ for strong bases, which represents diffusion-controlled encounter of the base with $T^{\pm}$ followed by fast proton removal and collapse of T^-, and $\beta = 0.7$ for weak bases, which represents concerted catalysis of proton transfer and decomposition of T^- to products. The very similar behavior of *N*-acetylbenzotriazole is consistent with the same reaction mechanism.[32]

General acid catalysis of the hydrazinolysis of acetylimidazole has been attributed to the kinetically equivalent concerted general base catalysis of the reaction with protonated acetylimidazole, $AcImH^+$, based on the known reaction path for other reactions of acetylimidazole and an observed value of $\alpha = 0.72$, which corresponds to $\beta = 0.28$ for the reaction with $AImH^+$.[30] The concerted mechanism is almost certainly enforced with respect to the nonexistence of $T^{\pm}$ because imidazole (pK 7.2) is a much better leaving group than imidazole anion (pK 14) and the breakdown of T^- to expel imidazole anion occurs with a rate



constant of $>10^{10}$ s^{-1}, as indicated above. However, it is likely that the initially formed intermediate, T^{+-+}, has a significant lifetime in the absence of catalysts because it was concluded from the general base catalyzed reaction that $T^{\pm}$ (protonated on hydrazine) has a sufficient lifetime to diffuse through solution[30] and the additional proton on T^{+-+} should decrease the driving force for hydrazine expulsion. It might therefore be expected that T^{+-+} would cleave upon diffusion-controlled encounter with a strong base, which would give fast proton transfer to form $T^{\pm}$ and a value of $\beta = 0$ ($\alpha = 1.0$). Catalysis is difficult to detect with acids of $pK_a > 8$, and it is possible that the catalysis that is observed with these acids involves formation of T^{+-+} by a preassociation mechanism with the base present, followed by fast proton transfer and concerted expulsion of imidazole. The alternative is that the mechanism is fully concerted but is not enforced by the nonexistence of intermediates.

The lactonization of norbornyl hydroxyamides represents ester aminolysis in the reverse direction, as noted above, and the positive value of β_{lg} and the values of $\beta = 0.5$ and 0.7 for trifluoroethylamine and propylamine leaving groups provide strong support for a concerted mechanism in which there is proton transfer to or from the amine in the rate-limiting step.[23] It is possible that the concerted mechanism is enforced by the nonexistence of $T^{\pm}$ as an intermediate. The rate constant for methylamine expulsion from the $T^{\pm}$ intermediate in the reaction with 4-methylphenyl acetate[4] is about 10^9 s^{-1}, and bond cleavage in the norbornyl system may be accelerated enough to require a concerted mechanism because of increased electron donation from the more basic alcohol and favorable geometric and steric factors; the weakly basic trifluoroethylamine leaving group will provide an additional rate increase.[23] General base catalysis of the cyclization of norbornenylanilic acids occurs by a similar concerted mechanism, with $\beta = 0.62$ and 0.66 for *p*-nitroaniline and *m*-nitroaniline leaving groups, respectively, and a positive value of $\beta_{lg} = 0.2$.[33]

(29) Palmer, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6466.

(30) Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8828.

(31) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436 and references therein.

(32) Reboud-Ravaux, M. *J. Am. Chem. Soc.* **1980**, *102*, 1039.

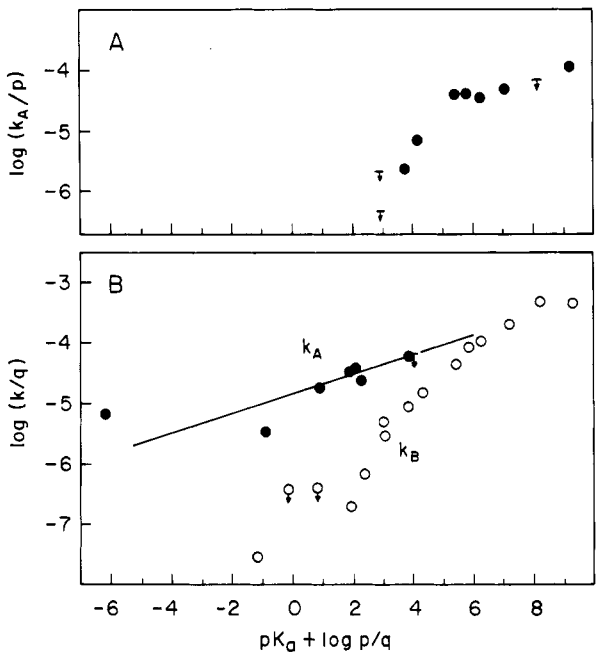


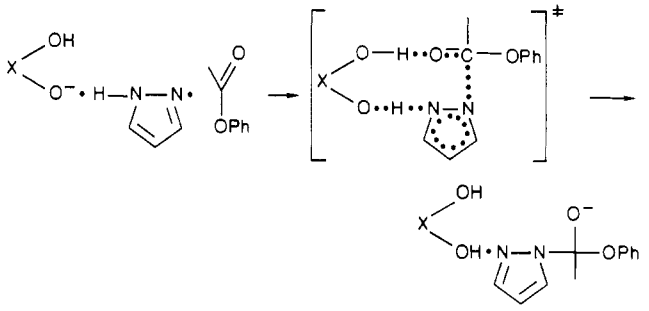
Figure 5. (A) Statistically corrected Brønsted plot for catalysis by buffer acids of the reaction of pyrazole with phenyl acetate. The upper limits are for catalysis by pyrazole cation, methoxyacetic acid, and methylarsonate monoanion. (B) Statistically corrected Brønsted plot for general base catalysis of the reaction of pyrazole with phenyl acetate. The open circles (○) are for monofunctional bases as in Figure 2. The solid circles (●) are log k_A (Table I) plotted against pK_a for the conjugate acids of the catalysts. The line of slope $\beta = 0.17$ is based on a least-squares fit to the rate contents for catalysts of $pK_a > 0$.

General base catalysis of the intramolecular aminolysis of the methyl and trifluoroethyl esters of 2-aminophenylacetic acid, with $\beta = 0.5$ and 0.2, respectively, has been attributed to concerted base catalysis of the breakdown of T^0; it is not known whether this represents enforced concerted catalysis.[34] It has been suggested[35] that catalysis by hydroxide ion of the reaction of ethylamine with hippurate esters represents concerted formation of T^- and this could represent nonenforced concerted catalysis if $T^\pm$ has a significant lifetime. However, the structure–reactivity behavior for the analogous catalysis by hydroxide ion of amine addition to carbon dioxide suggests an asymmetric transition state with assistance by hydrogen bonding of hydroxide ion to the attacking amine as it develops positive charge in the transition state;[36] a similar mechanism may facilitate ester aminolysis.

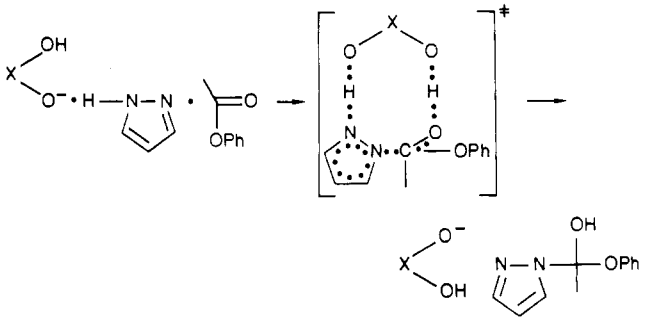
In conclusion, we are not aware of definitive evidence for a concerted mechanism of acid–base catalysis of any acyl transfer reaction involving proton transfer from or to nitrogen in which the intermediate has been shown to have a significant lifetime. The limited amount of available evidence appears to be consistent with the notion that concerted catalysis of this class of reaction occurs only when it is required to occur because the "intermediate" species that would be formed in a stepwise reaction has too short a lifetime to exist.

Concerted general acid–base catalysis has been observed for reactions involving proton transfer to or from oxygen even when the addition intermediate has a significant lifetime.[29] It is possible that this nonenforced catalysis is made possible by the small barrier for proton transfer to and from oxygen, which is smaller than that for nitrogen.[37] Concerted catalysis is expected to occur most readily when the barrier for proton transfer is small.

Scheme II



Scheme III



Catalysis by General Acids. The acid components of the buffers examined are less effective than the bases by factors of up to ~10-fold. The Brønsted plot for this catalysis, shown in Figure 5A, is remarkable in that the catalytic constants *decrease* with increasing acidity of the catalysts; the slope of the line is 0.2 ± 0.1 and the Brønsted coefficient, α, is −0.2 ± 0.1. This means that proton donation cannot be the only function of these catalysts.

All of the active catalysts shown in Figure 5A are bifunctional and can act as proton acceptors as well as proton donors. Pyrazole cation, which can act only as an acid, shows no detectable catalysis. The upper line in Figure 5B shows a Brønsted plot of the observed catalytic constants based on the pK_a of the *basic* site of the bifunctional catalysts (solid circles). The observed catalytic constants are now larger than the rate constants for ordinary base catalysts (open circles) by factors of up to ~100-fold. The line is drawn with a slope of 0.17; the point for (trichloromethyl)phosphonate falls below this line.

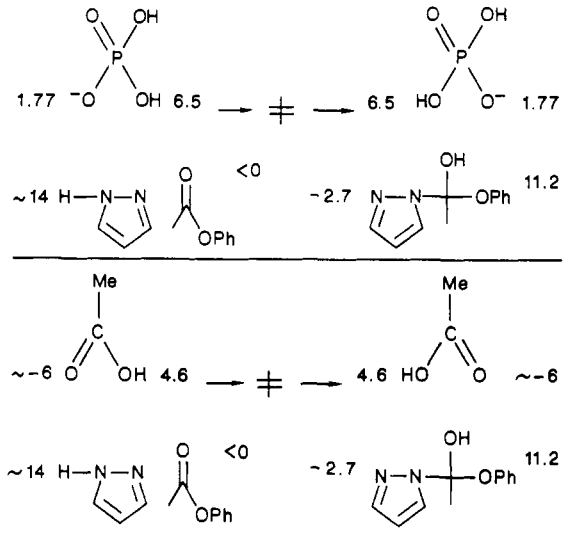
The enhanced activity of these catalysts compared with other bases cannot be accounted for by an electrostatic effect or by assistance through hydrogen bonding to the carbonyl oxygen atom (Scheme II). Several of the catalysts are monoanions, so an electrostatic effect does not explain why they are more reactive than substituted acetate anions. Catalysis cannot occur by concerted transfer of one proton assisted by hydrogen bonding to the carbonyl oxygen atom (Scheme II) because several of the active catalysts are such weak bases that proton transfer is thermodynamically unfavorable even from fully formed $T^\pm$ ($pK_a = 2.1$); the pK_a values of the conjugate acids of (chloromethyl)phosphonate and (trichloromethyl)phosphonate monoanions and of acetic acid are 0.95, ca. −0.9 and ca. −6, respectively.[38,39] Concerted catalysis requires that the proton transfer must become thermodynamically favorable in the course of the reaction in order to provide a driving

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(37) Fischer, H.; DeCandis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 1340. Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 972.

(38) The pK_a for acetic acid cation is ≃−6.1 (Goldfarb, A. R.; Mele, A.; Gutstein, N. *J. Am. Chem. Soc.* **1955**, *77*, 6194) and for trichloromethylphosphonic acid the pK_a was estimated as $pK_1 = pK_2 - 5.17$, which is derived from the known values for other phosphonates (for thermodynamic values, $pK_2 - pK_1 = 5.05$: Freedman, L. D.; Doak, G. O. *Chem. Rev.* **1957**, *57*, 479). For the pK_a values of other catalysts see Table I.

(39) The difference in pK_a between the products in Scheme II can be reduced by hydrogen bonding but the change in pK_a expected is not enough to make the proton transfer thermodynamically favorable. Using $\alpha = 0.2$ for hydrogen bonding and considering that when there is complete proton transfer between acetic acid cation and T^- to give $T^\pm$ the change in the pK_a of acetic acid is ~10 units, the partial proton transfer due to hydrogen bonding will raise the pK_a of acetic acid cation by about 2 units, to −4.1. Thus, the proton transfer to give products in Scheme II is still highly unfavorable.

Scheme IV



force for catalysis, as described by a rule for concerted catalysis; otherwise the reaction will proceed by a lower energy, stepwise pathway.[40]

We conclude that this bifunctional catalysis involves the transfer of two protons as well as N–C bond formation in a fully concerted mechanism that gives T^0 and the isomer of the catalyst in a single step, as shown in Scheme III. Bifunctional catalysis of the methoxyaminolysis of phenyl acetate provides a precedent for the concerted transfer of two protons in catalysis of an aminolysis reaction. The concerted proton transfer in the methoxyaminolysis reaction avoids the decrease in the rate constant and the solvent isotope effect maximum that are observed with monofunctional catalysts because the proton-transfer step never becomes rate limiting; however, the attack of methoxyamine on the ester occurs in a previous step.[5] In the pyrazole reaction N–C bond formation is concerted with transfer of a single proton for monofunctional catalysts; with bifunctional catalysts it is concerted with the transfer of two protons, presumably because the species $T^{\pm}$ does not exist as an intermediate. A single determination with 95% (chloromethyl)phosphonate monoanion buffer, in which 80% of the catalysis is due to the monoanion, gave a small but significant solvent isotope effect of $k_{HOH}/k_{DOD} = 1.7 \pm 0.2$. The small isotope effect may reflect a major role of heavy atom motion in the transition state or other factors that decrease solvent isotope effects.

The driving force for concerted catalysis comes from the changes in pK_a that occur during the course of the reaction, as shown for catalysis by phosphate monoanion and acetic acid in Scheme IV. The pK_a values in Scheme IV refer to the indicated acidic sites and to the conjugate acids of basic sites. All of the proton transfers are thermodynamically unfavorable in the ground state but become strongly favorable as the reaction proceeds. In particular, proton transfer to the developing negative charge on the carbonyl oxygen atom of the ester increases the basicity of the other site on the catalyst, so that it can facilitate the attack of pyrazole by proton abstraction without violating the rule for concerted catalysis.

Similar positive deviations of the rate constants for catalysis by ethylphosphonate monoanion and a few other bifunctional catalysts were noted for the reaction of acetyltriazole with methoxyamine.[31] Base catalysis of this reaction is believed to be concerted, as indicated above, and it is possible that the bifunctional catalysts also react by the concerted mechanism of Scheme IV.

Concerted acid–base catalysis of this kind, in which the transfer of two protons appears to be coupled to bond formation or cleavage of heavy atoms, provides an attractive model for the catalysis of analogous reactions by enzymes.[14,41]

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Appendix

A number of rate and equilibrium constants for proton transfer and other steps that might be involved in the reaction of pyrazole with phenyl acetate were calculated as described in this section. The constants are defined in Scheme I and the results are summarized in Table III. Rate constants that are not noted explicitly in Scheme I are identified by the respective equilibrium constants, e.g., $K_1 = k_1/k_{-1}$.

(1) Equilibrium Constants for Tetrahedral Intermediates and Rate Constants for Their Interconversion in the Presence of Buffers. The pK_a values of tetrahedral addition intermediates were calculated as outlined by Fox and Jencks using $\rho_I = -8.4$ and an attenuation factor of 2.5 for transmission of a polar substituent effect through a tetrahedral carbon atom.[31] All calculations are based on values of pK_a at ionic strength zero and reported[42] values of σ_I. We have taken σ_I for pyrazole to be 0.18, intermediate between 0.1 for primary amines and 0.25 for amides, and equal to the value used for triazole.[31] The calculations treat pyrazolium ion as a normal secondary ammonium ion. While this introduces little uncertainty into the value of pK_1, because there is normally little or no difference between the pK_a of a secondary ammonium ion and the pK_a of the ammonium ion in the zwitterionic tetrahedral intermediate, pK_3 and pK_4 may be somewhat higher than estimated due to delocalization of positive charge in the pyrazolium cation.

pK_2: The parent compound, CH_3CH_2OH,[43] has $pK_a = 15.9$ and σ_I is 0.18 for pyrazole and 0.38 for phenol.

$$pK_2 = 15.9 - 8.4(0.18 + 0.38) = 11.2$$

pK_3: The pK_a of *N*-methylpyrazolium ion[43] is 2.04. Addition of OH to a methyl group of a secondary amine lowers the pK_a by 1.88 units while the addition of a methyl group to the *N*-methyl carbon atoms raises the pK_a by 0.3 units.[27] Taking $\sigma_I = 0.38$ for phenol gives

$$pK_3 = 2.04 - 1.88 + 0.3 - (8.4 \times 0.38) = -2.7$$

pK_4: The pK_a of the parent compound, $CH_3NH_2CH_2OH^+$, for formation of the zwitterion is 9.98.[31] Replacement of a proton with a methyl group raises the pK_a by 0.3 units,[31] replacing $CH_3NH_2^+$ with pyrazolium ion gives $\Delta\sigma_I = (0.18 - 0.1)$, and substitution of phenol for a proton gives

$$pK_4 = 9.98 + 0.3 - 8.4(0.08 + 0.38) = 6.4$$

pK_1: The pK_1 is given by the following

$$pK_1 = pK_2 - pK_4 + pK_3 = 2.1$$

The rate constants for interconversion of the intermediates, the primed rate constants in Table III, were calculated from these pK_a values in the presence of 0.1 M of both the monoanion and the dianion of ethylphosphonate, $pK_a = 7.85$ (at ionic strength zero[43]), and a rate constant of 1×10^9 M^{-1} s^{-1} for thermodynamically favorable proton transfer.[12] The value of k_s is taken as 10^8 s^{-1}, the rate constant for a thermodynamically favorable proton switch to form a zwitterion from neutral amino acids.[44] The rate constant k_{-s} was calculated from the equilibrium constant.

(2) Other Rate Constants in Scheme I. A lower limit for k_a of 0.8 M^{-1} s^{-1} was estimated from a plot of log k for the uncatalyzed reactions of imidazoles, triazoles, and pyrazole and their anions with phenyl acetate by extrapolating back to the pK_a of pyrazole a line of slope $\beta_{nuc} = 0.25$ for rate-determining attack by nucleophiles of high pK_a.[16]

An approximate lower limit for k_{-a} was estimated as follows. The Brønsted plot for general acid catalysis of the partitioning of products in the hydrolysis of *p*-methylphenyl *N*-dimethyl-

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(44) Grunwald, E.; Chang, K. C.; Skipper, P. L.; Anderson, V. K. *J. Phys. Chem.* **1976**, *80*, 1425.

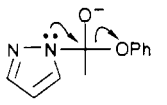
acetimidate is nonlinear because of a change in rate-limiting step with changing catalyst pK_a in a simple diffusion-controlled trapping mechanism. The pK_a of the intermediate obtained from this "Eigen curve" and the observed product partitioning allow the calculation[4] that k_{-a}, for the expulsion of dimethylamine from $T^{\pm}$, is $>4 \times 10^9$ s^{-1}. The value of β for k_{-a} is -0.7, from $\beta_{nuc} = 0.2$ for rate-determining amine attack in ester aminolysis with acidic leaving groups (k_a) and $\beta = 0.9$ for the formation of $T^{\pm}$ at equilibrium.[4] The leaving ability of imidazole is equal to that of a secondary amine of $pK_a = 11$ in the breakdown of amine addition compounds to a phthalimidium cation.[45] Pyrazole, imidazoles, and triazoles form a common family of nucleophiles in the uncatalyzed aminolysis of phenyl acetate so that, by analogy to imidazole, pyrazole should have a leaving ability from the phthalimidium cation adduct equal to that of a secondary amine of $pK_a = 6.5$. The value of $\beta = -0.7$ and the effective pK_a for pyrazole of 6.5 give $k_{-a} = 6 \times 10^{12}$ s^{-1} for the expulsion of pyrazole from $T^{\pm}$. This value is a lower limit because there is evidence that the leaving ability of imidazole and related compounds compared to secondary amines is not as poor for $T^{\pm}$ intermediates as for phthalimidium cation adducts.[46,47]

The value of k_- was estimated in two ways:

(A) The rate constant k_- for the expulsion of phenoxide ion from T^- can be calculated by (1) estimating the rate constant k_-', for expulsion of phenoxide ion from formaldehyde hemiacetal anion, and (2) allowing for the effects on k_-' of substitutions on the hemiacetal anion of pyrazole and methyl groups.

The value of k_-' was calculated from rate constants for the hydroxide ion catalyzed decomposition of formaldehyde hemiacetals. The second-order rate constant for alkaline cleavage of $HOCH_2OPh$ was estimated to be $\geq 10^9$ M^{-1} s^{-1} from $\beta_{lg} = -1.1$.[9] The pK_a of formaldehyde phenyl hemiacetal was estimated to be 12.4 from $pK_a = 13.6$ for $HOCH_2OEt$[9] and, using a falloff factor of 0.2 for two intervening atoms,[48] exchanging PhOH for EtOH ($\Delta pK_a = 0.2(10 - 16) = -1.2$). The value of $k_-' = 2.5 \times 10^7$ s^{-1} was obtained from $pK_a = 13.6$ and k_{OH}[9], where $k_{OH} = k_-'K_a/K_{HOH}$ and $K_{HOH} = 10^{-14}$ M^2.

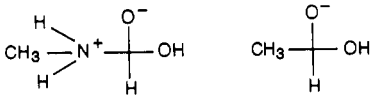
The rate constant k_-, for T^- decomposition, may now be determined by accounting for the effect of replacing the two hydrogen atoms in $^-OCH_2OPh$ by methyl and pyrazole. Replacement of H by CH_3 increases k_- by a factor of 16, from the ratio of the rate constant k_- for cleavage of the anions of acetaldehyde and formaldehyde hydrates. The rate constant k_- is 390 s^{-1} for formaldehyde hydrate[9] and 6400 s^{-1} for acetaldehyde hydrate.[3] Replacement of H by pyrazole is expected to increase k_- by a factor of $>10^{2.6}$ because of electron donation from the pyrazole, as in **1**. This is deduced as follows: (1) Imidazoles, triazoles,



1

and pyrazole show an overall rate advantage of $10^{2.6}$ when compared to primary and secondary amines of the same pK_a on a Brønsted type plot of log k against the pK_a of the nucleophile for the uncatalyzed aminolysis of phenyl acetate.[16] Increases in rate and equilibrium constants of similar magnitude have been observed for nucleophiles of this type, including substituted pyridines, in other systems.[46,49] (2) The overall rate advantage can be ascribed specifically to an increase in the first-order rate constant, $k_{\pm}$, for the breakdown to products of the addition intermediate $T^{\pm}$, which is rate-limiting in the uncatalyzed aminolysis reaction, due to resonance structures analogous to the above. It cannot be ascribed to an increase in the equilibrium constant for formation of the tetrahedral intermediate because the equilibrium constant for the hydroxymethylation of imidazole by formaldehyde hydrate is smaller than that for an aliphatic secondary amine.[46,47] (3) The "push" by the pyrazole ring will be larger than $10^{2.6}$ because in T^- the pyrazole ring is not protonated.

The polar effect of replacing H by pyrazole, a more electron-withdrawing substituent, is probably negligible because leaving group expulsion is not sensitive to small changes in inductive effects. This is suggested by the calculation that the rate constant for the expulsion of hydroxide ion is $k_{\pm} = 2 \times 10^4$ s^{-1} for the zwitterion **2** and $k_- = 6.4 \times 10^3$ s^{-1} for the anion of acetaldehyde hydrate, **3**. The rate constant for hydroxide ion expulsion from **2** was estimated from the rate constant for leaving group expulsion

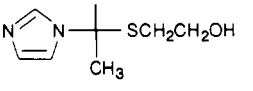


2 **3**

from the zwitterion with phenolate ion as the leaving group, $k_{\pm} = 2 \times 10^7$ s^{-1}, using a value of $\beta_{lg} \simeq -0.4$ for $k_{\pm}$ and $pK_a = 17.4$ for the leaving hydroxide ion.[4,50] From 2×10^7 s$^{-1} \times 10^{-0.4(17.4-10)}$, $k_{\pm}$ is 2×10^4 s^{-1}.

The rate constant for decomposition of the adduct T^- (Scheme I) may now be calculated as the product of k_- for the expulsion of phenolate ion from the hemiacetal anion, the factor of 16 for replacement of H by CH_3, and the factor of $\geq 10^{2.6}$ for the replacement of H by pyrazole to give $k_- \geq 1.6 \times 10^{11}$ s^{-1}.

(B) Second, k_- may be calculated on the basis of $k_- = 1.3 \times 10^7$ s^{-1} for the expulsion of 2-mercaptoethanol anion from **4**.[51] It has been shown that, for leaving groups of the same pK_a,



4

$k_{-RO^-}/k_{-RS^-} = 800$ for leaving group expulsion from hemi(thio)-acetal anions, and in the uncatalyzed hydrolysis of benzaldehyde *O,S*-acetals oxyanions are better leaving groups than thiol anions of the same pK_a by a factor of 10^5.[52] These factors give a range

(45) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 499.

(46) We deduce that imidazole expulsion from $T^{\pm}$ is not as abnormally slow as expulsion from phthalimidium cation adducts, compared to a secondary amine of the same pK_a, from two analyses: (a) The observed equilibrium constant, K', for the hydroxymethylation of imidazole by formaldehyde hydrate is one to two orders of magnitude smaller than that for hydroxymethylation of secondary amines of $pK_a = 8.6$–11.[47] The overall equilibrium constant $K' = K_1K_2$ includes two equilibria involving $T^{\pm}$. The equilibrium constant K_2 for imidazole, K_{2im}, may be slightly larger than that for a secondary amine, K_{2am}, of the same pK_a because of a smaller electrostatic stabilization of $T^{\pm}$ by the delocalized charge of imidazole. Because K'_{im} is less than K'_{am}, K_1 for imidazole is smaller than that for a secondary amine of similar pK_a. In ester aminolysis reactions where k_1 is rate-limiting, imidazole reacts as expected for a secondary amine of the same pK_a so that k_1 is similar for these nucleophiles. The different equilibrium constants require, therefore, that k_{-1} be at least as large, and probably larger for imidazole compared with a secondary amine of the same pK_a. (b) For leaving groups of equal pK_a, amines are expelled 10^5 faster than alkoxide ions from phthalimidium cation adducts,[45] whereas amines are expelled $\sim 10^4$ slower than alkoxides when an oxyanion electron pair is the driving force, based on the estimates that the rate constant for the expulsion of phenoxide ion (leaving group $pK_a = 9.95$) from the formaldehyde hemiacetal anion is 2.5×10^7 s^{-1} (see below) and the rate constant for expulsion of trimethylamine (leaving group $pK_a = 9.85$) from the formaldehyde carbinolamine zwitterion is 3.4×10^3 s^{-1} (Hine, J.; Kokesh, F. C. *J. Am. Chem. Soc.* **1970**, *92*, 4383).[45] A significant factor contributing to this reversal of leaving group ability must lie in the retardation of amine expulsion due to electrostatic stabilization of the zwitterion in the latter system. This stabilization will be less in the case of imidazole because the positive charge is somewhat delocalized. The smaller retarding effect on expulsion of imidazole compared to alkylamines will make imidazole a comparatively better leaving group in departure from $T^{\pm}$ systems than in departure from phthalimidium cation adducts.

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(48) Wells, P. R. *Linear Free Energy Relationships*; Academic: New York, 1968.

(49) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.

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(51) Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 1419.

(52) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476.

for k_- of 10^{10}–1.3×10^{12} s^{-1}, neglecting the pK difference of 0.3 units between phenol and 2-mercaptoethanol. The small sensitivity of k_- to changes in polar effects of substituents suggests that this range is not very different for the pyrazole adduct T^-.

(3) Brønsted Plots. Brønsted plots were calculated by using the equations below; the mechanisms and rate constants are defined in eq 2.

(A) For diffusion-controlled trapping (upper path, eq 2), the third-order rate constants, k_B, were obtained from

$$k_B = \frac{K_1 k_2 k_p k_5}{k_p k_5 + k_{-2} k_5 + k_{-2} k_{-p}}$$

using $k_p = 10^{(10 \pm 0.5 \Delta pK_a)}$, in which ΔpK_a refers to the difference between the pK_a values of the catalyst and intermediate.[12]

(B) For preassociation mechanisms with hydrogen bonding (lower path, eq 2), k_B is calculated from

$$k_B = \frac{k_B^{DC}(k_{-2} + k_{-4}(10^{\beta(1.74+pK_{cat})}))k_p k_5 / k_{-2}}{k_5 k_p + (k_{-2} + k_{-4}(10^{\beta(1.74+pK_{cat})}))(k_5 + k_p)}$$

in which k_B^{DC} is the maximal catalytic rate constant calculated for the diffusion-controlled trapping mechanism, when proton transfer between the catalyst and intermediate is thermodynamically favorable, β is the Brønsted slope for hydrogen bonding by basic catalysts, and pK_{cat} is the pK_a of the catalyst.[2]

Registry No. PhOAc, 122-79-2; D^2, 7782-39-0; $AcOC_6H_4$-m-NO_2, 1523-06-4; $AcOC_6H_4$-p-NO_2, 830-03-5; pyrazole, 288-13-1; 4-bromoimidazole, 2302-25-2.

Photohydration of Styrenes and Phenylacetylenes. General Acid Catalysis and Brønsted Relationships

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Abstract: The acid-catalyzed photohydrations of a series of substituted styrenes and phenylacetylenes have been investigated in aqueous buffer solutions. General acid catalysis was clearly detected in five cases with a range of catalysts, and approximately linear Brønsted plots gave α values in the range 0.14–0.18. The rate enhancements caused by excitation from S_0 to S_1 were estimated from comparisons with thermal hydration data to be in the 10^{11}–10^{15} range. Treatment of the dependence of the rate constants for general acid catalysis (k_{HA}) on the buffer pK_{HA} values with multiple regression analysis suggests that the Brønsted plots are smoothly curved, as predicted by Eigen and by the Marcus equation. However, reliable values of the Brønsted curvature could not be established. The possible catalytic reactivity of analogous triplet states was examined with a series of nitrosubstituted analogues, but no general acid catalysis could be detected. The factors controlling the detection of general acid catalysis in these photoreactions are discussed.

The thermal acid-catalyzed hydrations of styrenes[1] and phenylacetylenes[2] have been studied extensively, and these slow ground-state reactions ($k_{H^+} \sim 10^{-5}$–10^{-7} M^{-1} s^{-1}) have also been shown to be subject to general acid catalysis in a number of cases.[3] Reported values of the Brønsted α exponent are typically in the 0.5–0.85 range. Although the photochemistry of alkenes[4] has been a topic of continuing interest to photochemists, photohydrations in aqueous solution[5] have been much less extensively studied, and this is also the case for the analogous reactions of phenylacetylenes. Previous investigations[5,6] have shown that these reactions are catalyzed by H_3O^+, and where electron-releasing groups are present in the ring, both styrenes and phenylacetylenes react via their lowest singlet excited states, and the reactions are regiospecific in the Markovnikov direction. Values of the rate constant (k_{H^+}) for proton transfer from H_3O^+ to S_1 show these to be very fast reactions, especially for those involving protonation on carbon. Typical values of k_{H^+} are in the 10^6–10^7 M^{-1} s^{-1} range,[5,6] as determined independently from the pH (or Ho) dependence of fluorescence quenching, fluorescence lifetime, and quantum yield for product formation. The mechanism proposed for these photohydrations, namely rate-determining protonation of S_1, followed by rapid attack of H_2O on the intermediate carbocation (whether either step is adiabatic or not),[7] is supported by kinetic solvent isotope effects ($k_H/k_D \sim 1.3$–1.8) and the complementary sigmoidal variations of the quantum yields for fluorescence (Φ_F) and product formation (Φ_p).[5,6]

Since Φ_p values do not approach zero at pH 7, the reactions are evidently subject to water catalysis, and this in turn raised the interesting possibility that they might also be subject to detectable general acid catalysis, as are the ground-state analogues. Buffer catalysis was in fact observed for two substituted styrenes in a preliminary study,[6] and plots of the log k_{HA} vs. pK_{HA} for a

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(6) Wan, P.; Yates, K. *J. Org. Chem.* **1983**, *48*, 869.

(7) Although it is inherently unlikely that the attack of water on the intermediate carbocation takes place on the excited state surface, it has recently been shown that carbocations of the type involved here can be generated adiabatically[8] in aqueous solution, so that the proton-transfer step may be adiabatic.

(8) Wan, P.; Yates, K.; Boyd, M. K. *J. Org. Chem.* **1985**, *50*, 2881.

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