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Concurrent General Acid and General Base Catalysis in the Hydrolysis of an Imidate Ester. 2. Bifunctional Catalysis[1a]

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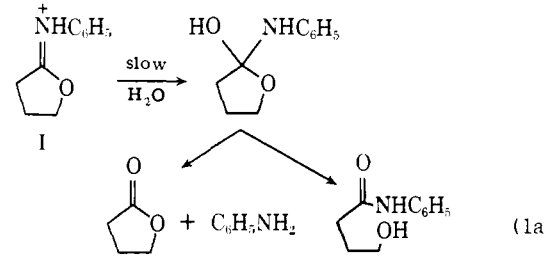
Abstract: Bifunctional buffers efficiently catalyze the expulsion of amine from the tetrahedral intermediate generated by hydration of imidate ester III. Rate enhancements of up to 300-fold have been calculated from a comparison of the effects of bifunctional catalysts to those of a series of monofunctional general acid and general base catalysts. No single factor (pK_a of the acidic or basic groups, catalyst geometry, ring size of a cyclic transition state) has been identified as primarily responsible for high catalytic activity. In the region of catalyst $pK > 7$, monofunctional oxy acids are about eight times better general acid catalysts than monofunctional nitrogen acids.

In 1952, Swain and Brown reported that the mutarotation of tetramethylglucose in benzene was efficiently catalyzed by 2-pyridone, and proposed a mechanism involving bifunctional acid-base catalysis via a cyclic transition state.[1b] Their suggestion that polyfunctional catalysis may account, at least in part, for the high catalytic activity of enzymes has received continued attention, though few unequivocal examples of such catalysis in model systems have been described.[2-6] Bifunctional catalysis has been proposed to occur in a number of reactions carried out in *aprotic solvents*. These include the reaction of amines with 2,4-dinitrofluorobenzene,[7] the aminolysis of *p*-nitrophenyl acetate,[8] the addition of amines to isocyanates,[9] and the isomerization of cholestenone,[10] as well as additional studies on the mutarotation of tetramethylglucose.[8,11,12] Among the catalysts for which special effectiveness has been claimed have been carboxylic acids, pyrazole, 1,2,4-triazole, ureas, amides, and various phosphorus oxy acids.

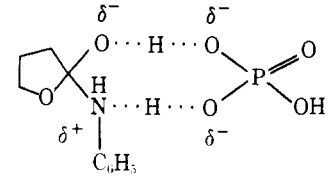
In water, 2-pyridone loses its unusual catalytic properties, and is no better a catalyst for the mutarotation of glucose than other general bases of similar pK.[12] Presumably, the ability of water to act as a proton donor and acceptor suppresses the need for special catalytic pathways for proton transfer in this reaction. Nevertheless, there are known several reactions carried out in aqueous medium in which the enhanced reactivity of some general acid-base catalysts (usually phosphate, arsenate, or bicarbonate ions) has been ascribed to bifunctional catalysis. Among these are the hydrolysis of amides,[13] imidate esters,[14] and amidines,[15] the aminolysis of esters[16] and thiol esters,[17] the decomposition of the adduct of hydrogen peroxide and aldehydes,[18] the addition of urea to formaldehyde,[19] the hydration of pteridine,[20] and a transimination reaction.[21]

The experiments described in this paper were undertaken to define more closely the relationship between the structure of an acid-base catalyst and its ability to function effectively as a bifunctional catalyst in aqueous solution. The reaction chosen for this purpose was the hydrolysis of an imidate ester, earlier studies having shown that the nature of the hydrolysis products is markedly affected by the presence of general acid-base catalysts.[14,16a,22] Thus, the yield of aniline obtained on hydrolysis of the cyclic imidate I is increased by increasing concentrations of phosphate or imidazole buffers at constant pH (eq 1a). Despite the fact that the $H_2PO_4^-$-HPO_4^{2-} and the imidazole-imidazolium buffers have approximately the same pK_a, phosphate buffer is at least 200 times as effective as imidazole buffer in catalyzing the expulsion of aniline from the intermediate shown in eq 1a. The unusual reactivity of



(1a)

phosphate ions has been ascribed to their bifunctional character, which enables them to participate in more or less simultaneous proton transfers, as in transition state II.[14] It



II

should be noted that catalytic effects on the breakdown of the intermediate are seen as a change in the product distribution, with little or no change in the rate of the overall reaction. Under

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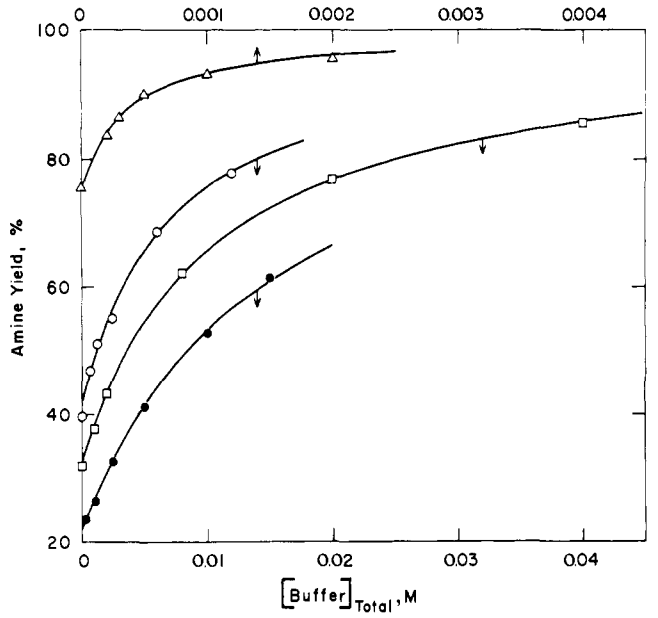


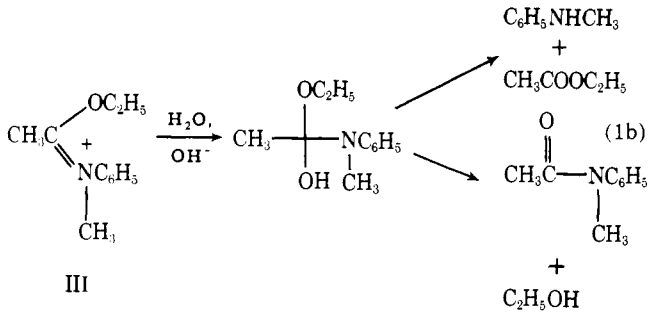
Figure 1. Effects of bifunctional buffers on yield of *N*-methylaniline formed on hydrolysis of imidate ester III. All reactions contain Tris buffer at indicated concentration: Δ, arsenate, pH 7.18 (0.012 M Tris); ○, phenylphosphonate, pH 8.02 (0.012 M Tris); □, hexafluoroacetone hydrate, pH 8.40 (0.04 M Tris); ●, phosphate, pH 9.11 (0.064 M Tris). Curves are calculated from equation for rectangular hyperbola given in note 42, using values of K'_{app} listed in Table I.

most conditions, the rate-determining step is the formation of the intermediate, which is followed by rapid, product-determining steps.

The high sensitivity of imidate hydrolysis to the presence of low concentrations of bifunctional buffers makes this reaction an attractive system for the study of the phenomenon of bifunctional acid-base catalysis. Also, the tetrahedral addition intermediate that is generated from imidate esters is closely related to the intermediates believed to be formed in the aminolysis of esters and the alcoholysis of amides,[13b,16a,23,24] so that conclusions drawn from the study of catalysis in the hydrolysis of imidates are important to the understanding of the mechanism of acid-base catalysis of these acyl transfer reactions.

Results

Kinetic data on the hydrolysis of imidate ester III (eq 1b) have been reported previously, as part of a detailed study of



the effect of monofunctional general acids and bases on the breakdown of the corresponding tetrahedral intermediate.[1a] In the present work, the ability of bifunctional catalysts to enhance the expulsion of *N*-methylaniline was examined. In all cases, the dependence of amine yield on catalyst concentration followed a rectangular hyperbola, and the yields invariably approached 100% at high buffer concentration (Figure 1). Many of the catalysts used were so effective at low

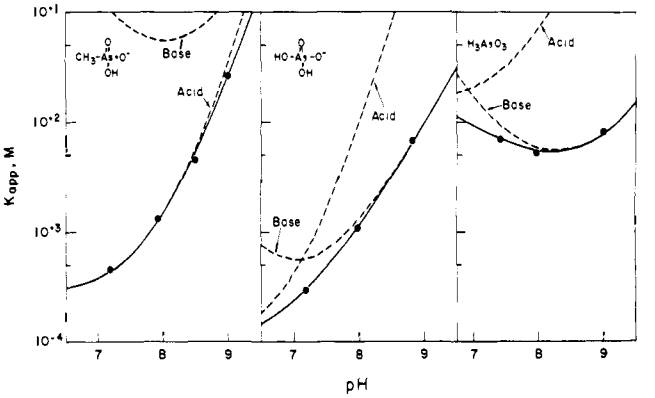
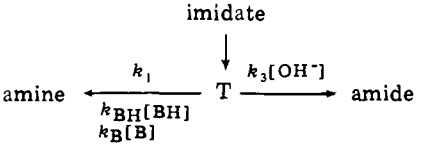


Figure 2. pH dependence of the effectiveness of buffers in catalyzing the formation of *N*-methylaniline from III. Solid curve is calculated using eq 3, and constants of Table II. Dashed curves are for acid or base catalysis only, and are calculated from eq 3, with k_B and $k_{BH} = 0$, respectively. $pK' = 7.49$.

Scheme I



concentration that a second buffer had to be employed to maintain constant pH.

The results of experiments with 15 catalysts are given in Table I. The treatment of the data has been described in detail,[1a] and is briefly summarized here. According to Scheme I, the tetrahedral intermediate T derived from the imidate ester is converted to amine in a solvent-catalyzed reaction (k_1) and in reactions catalyzed by buffer acids (BH) and bases (B). Use was made of the steady-state assumption for the intermediate T to derive eq 2, which describes the dependence of the amine

$$\%\ \text{amine} = \frac{\dfrac{k_1([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T}{\dfrac{(k_1 + k_3[OH^-])([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T} = \frac{\dfrac{k_1([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T}{K_{app} + [B]_T} \quad (2)$$

yield on the total concentration $[B]_T$ of a buffer whose acid dissociation constant is K_a. The constant K_{app} is equivalent to the buffer concentration which gives half the maximum possible increase in amine yield over the yield at zero buffer concentration, and is thus a direct measure of the catalytic ability of a given buffer. Values of K_{app} were obtained from data such as those of Figure 1 as described earlier[1a] and are given in Table I. When a second buffer kept at fixed concentration is used to maintain constant pH, the hyperbolic dependence of amine yield on the concentration of the variable buffer gives a constant K'_{app} which must be corrected for the effect of the second buffer.[1a] Comparison of the last two columns of Table I shows that the corrections are not large.

The expression for K_{app} in eq 2 can be rewritten as

$$K_{app} = \frac{k_1}{k_{BH}}\left(\frac{[H^+] + K'}{[H^+]}\right)\left(\frac{[H^+] + K_a}{[H^+] + \dfrac{k_B K_a}{k_{BH}}}\right) \quad (3)$$

where $K' = k_3 K_w / k_1$ (K_w is the ion product of water) and pK'

Table I. Buffer Catalysis of Amine Formation from Hydrolysis of Imidate[a]

buffer	pH[b]	concn range, M	no. of points	2nd buffer[c] conc, M	K'_{app}, M[d]	K_{app}, M[d]
phosphite (PF)	7.19	0.0002-0.0020	5	0.012	0.0011	9.1×10^{-4}
	7.78[e]	0.0064-0.064	4	0.015	0.0074	0.0066
	8.00	0.002-0.016	7	0.020	0.014	0.012
	8.52[e]	0.015-0.060	5	0.020	0.11	0.10
	8.85[e]	0.016-0.096	4	0.025	0.29	0.28
phosphate (PA)	6.96	0.0001-0.010	7	0.020	4.2×10^{-4}	2.9×10^{-4}
	7.35	0.0004-0.010	4	0.010	5.7×10^{-4}	4.9×10^{-4}
	8.75	0.0005-0.010	4	0.032	7.0×10^{-3}	6.8×10^{-3}
	9.11	0.000 25-0.015	6	0.064	0.015	0.015
phenylphosphonate (PP)	6.87	0.000 12-0.0036	6	0.012	4.0×10^{-4}	3.2×10^{-4}
	7.28	0.0002-0.0020	5	0.012	0.0013	0.0011
	8.02	0.0006-0.012	6	0.012	0.0073	0.0068
	8.63[e]	0.006-0.090	6	0.05	0.063	0.059
	9.04[e]	0.016-0.096	5	0.04[f]	0.46	0.44
methylphosphonate (MP)	7.31	0.0002-0.0060	6	0.012	8.5×10^{-4}	7.1×10^{-4}
	8.06	0.0016-0.0080	4	0.012	0.0044	0.0041
	8.61[e]	0.0032-0.032	5	0.05	0.037	0.034
	9.05	0.0064-0.032	4	0.04[f]	0.13	0.12
arsenate (ANA)	7.18	0.0001-0.0020	6	0.012	3.7×10^{-4}	3.0×10^{-4}
	7.98	0.0002-0.0020	5	0.020	0.0012	0.0011
	8.82	0.001-0.010	6	0.025	0.0069	0.0068
methylarsonate (MAN)	7.18	0.0001-0.0010	5	0.012	5.6×10^{-4}	4.7×10^{-4}
	7.94	0.0005-0.0020	4	0.020	0.0015	0.0014
	8.49	0.0005-0.0040	5	0.020	0.0048	0.0046
	9.00	0.001-0.040	7	0.030	0.029	0.029
arsenite (ANI)	7.42	0.001-0.020	6	0.012	0.0080	0.0069
	7.98	0.001-0.020	6	0.020	0.0060	0.0054
	8.99	0.001-0.040	7	0.030	0.0084	0.0082
hexafluoroacetone hydrate (HF)	7.13	0.0002-0.0020	5	0.012	0.0015	0.0012
	7.55	0.0004-0.0040	5	0.012	0.0020	0.0018
	8.40	0.001-0.04	7	0.040	0.010	0.0093
	8.90	0.004-0.060	7	0.080	0.029	0.027
tetrafluoroacetone hydrate (TF)	7.42	0.0062-0.123	7	0.010[g]	0.022	0.019
	7.98	0.0024-0.060	6	0.015[g]	0.023	0.022
	8.85	0.008-0.040	4	0.020	0.040	0.040
trifluoroacetone hydrate (TRF)	7.40	0.0384-0.307	6	0.012	0.58	0.50
	7.88	0.0317-0.190	5	0.020	0.60	0.53
	8.31	0.0396-0.317	6	0.040	0.64	0.57
	9.05	0.0537-0.430	6	0.060	0.72	0.70
selenite (SE)	8.02	0.000 08-0.0040	7	0.020	0.0015	0.0013
	9.00	0.0064-0.096	7	0.020	0.044	0.043
bicarbonate (BC)	7.49	$(0.4\text{-}4.0)10^{-4}$	4	0.020[g]	3.2×10^{-4}	2.8×10^{-4}
	8.00	$(0.8\text{-}8.0)10^{-4}$	4	0.020[g]	6.0×10^{-4}	5.5×10^{-4}
	9.00	$(6\text{-}120)10^{-4}$	4	0.010[h]	0.0043	0.0042
	9.25	0.003-0.03	4			0.0087
	9.73	0.009-0.03	4			0.029
acetone oxime (AO)	7.73[i]	0.0012-0.024	6	0.015	0.0092	0.0081
	8.25[j]	0.002-0.04	6	0.020	0.021	0.019
	8.85[k]	0.025-0.20	6	0.020	0.078	0.077
2-pyridone (PD)	7.92	0.01-0.30	5	0.012	0.16	0.14
	8.55	0.08-0.32	5	0.020	0.39	0.38
6-chloro-2-pyridone (CPD)	7.90	0.0004-0.04	7	0.015	0.0028	0.0025
	8.38	0.002-0.16	7	0.020	0.016	0.016
	8.98[e]	0.012-0.24	7	0.020	0.18	0.18

[a] At 30 °C, 0.5% CH_3CN-H_2O, μ = 0.5. [b] ±0.02, except where stated. [c] Tris, except where noted. [d] See text. [e] ±0.03. [f] 2-Amino-2-methylpropane-1,3-diol. [g] *N*-Methylmorpholine. [h] Sodium borate. [i] Contained 0.095 M acetone. [j] Contained 0.10 M acetone. [k] Contained 0.105 M acetone.

is the pH at the inflection point of the sigmoid curve which describes the variation in amine yield with pH at zero buffer concentration. For imidate III, pK' = 7.49.[1a] The dependence of K_{app} on pH is illustrated in Figure 2 for three arsenic-containing buffers and in Figure 3 for two ketone hydrates. The solid lines in Figures 2 and 3 were calculated from eq 3, using the values of k_{BH}/k_1 (= k_{AH}) and k_B/k_1 (= k_A) given in Table II. The dashed lines in the figures represent the separate contributions of acid and base catalysis to the overall buffer catalysis of amine formation from the tetrahedral intermediate. It should be noted that, the lower the value of K_{app}, the higher the catalytic effect of the given buffer or buffer component. Thus, the left-hand panel of Figure 2 indicates that catalysis by methylarsonate buffer proceeds largely via the conjugate acid, while catalysis by arsenite buffer involves mainly the conjugate base of the buffer (Figure 2, right-hand panel). The intersection of the dashed lines occurs at the pH where general acid and general base catalysis contribute equally to the observed buffer catalysis. Values of k_{AH} and k_A derived from similar data for other buffers are presented in Table II.

The fluorinated ketones tri-, tetra-, and hexafluoroacetone exist in aqueous solution almost completely as the ketone hy-

Table II. Constants for General Acid and General Base Catalysis of Amine Formation in Imidate Hydrolysis

buffer	pK_a	p, q^a	k_{AH}, M^{-1}	k_A, M^{-1}
phosphite (PF)	6.20[b]	1, 3	1.6×10^4	47
phosphate (PA)	6.60[b]	2, 3	7.3×10^3	2.9×10^3
phenylphosphonate (PP)	6.93[b]	1, 3	6.0×10^3	60
methylphosphonate (MP)	7.33[b]	1, 3	4.4×10^3	220
arsenate (ANA)	6.60[b]	2, 3	1.1×10^4	3.4×10^3
methylarsonate (MAN)	8.56[b]	1, 3	3.6×10^3	360
arsenite (ANI)	9.10[c]	3, 1	65	9.7×10^3
hexafluoroacetone hydrate (HF)	6.46[c]	2, 1	2.5×10^3	1.0×10^3
tetrafluoroacetone hydrate (TF)	8.86[c]	2, 1	59	1.2×10^3
trifluoroacetone hydrate (TRF)	10.44[c]	2, 1	2.4	1.4×10^3
selenite (SE)	8.02[b]	1, 3	6.3×10^3	130[d]
bicarbonate (BC)	9.75[b]	1, 3	1.0×10^4	*e*
acetone oxime (AO)	12.24[c]	1, 1	340	*e*
2-pyridone (PD)	11.62[c,f]	1, 1	30	*e*
6-chloro-2-pyridone (CPD)	7.45[c]	1, 1	5.1×10^3	51

[a] Statistical correction factors; see ref 29. [b] For conversion of monoanion to dianion. [c] For conversion of neutral species to monoanion. [d] Upper limit. [e] Not observed, [f] Reference 31.

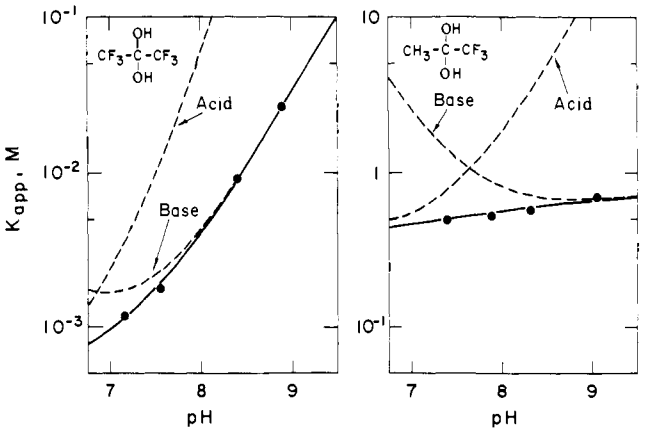


Figure 3. pH dependence of the effectiveness of buffers in catalyzing the formation of *N*-methylaniline from III. For calculation of curves, see legend to Figure 2.

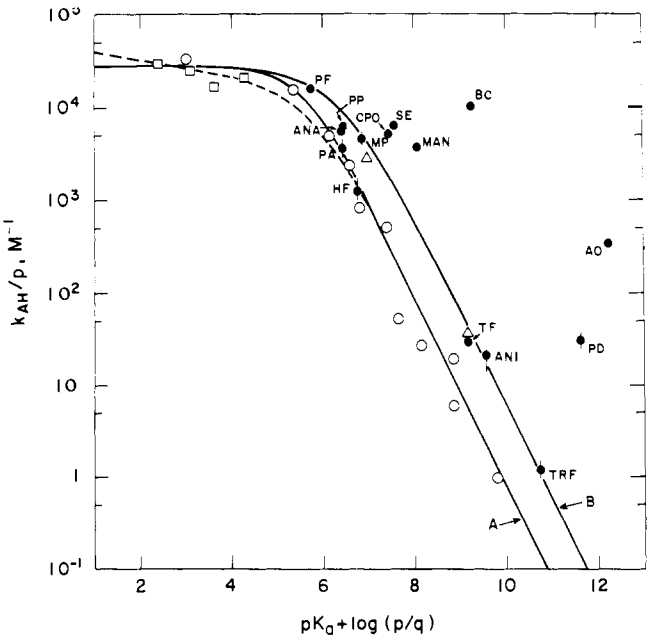


Figure 4. Brønsted plot for general acid catalysis of amine formation from III. Error bars are estimated variation in catalytic constant assuming that K_{app} values are accurate to ±10%. Closed circles refer to bifunctional catalysts. Abbreviations are listed in Table II. Open symbols refer to monofunctional catalysts (data taken from ref 1a): □, carboxylic acids; ○, amines; △, alcohols. The solid lines refer to the mechanism of Scheme II and the dashed line to the mechanism of Scheme III. Their calculation is described in the text.

drate. The equilibrium constant for the hydration of hexafluoroacetone has been estimated to be 1.2×10^6 in favor of hydration. Even with the much less electrophilic 1,1,1-trifluoroacetone, the hydrate is the predominate species in water, the equilibrium constant of 35 at 25 °C indicating that no more than 3% of the added ketone hydrate is present in the keto form.[25]

To repress the possible formation of hydroxylamine in experiments with acetone oxime as the catalyst, the reactions were carried out in the presence of ca. 0.1 M acetone. Under these conditions, the ratio of oxime to free hydroxylamine is about 10^5 at equilibrium, so that no interference is expected from nucleophilic or general acid-base reactions of hydroxylamine with the imidate ester.[26]

The possibility that a significant part of the observed catalysis by arsenite buffer could result from contamination by the highly reactive arsenate ion is ruled out by the finding of <0.2% arsenate in the sodium arsenite preparation used. For example, the addition of 0.02 M arsenite buffer at pH 7.98 causes an increase of 20% in amine yield over the yield at zero buffer concentration. The presence of arsenate at a level of 0.2% would result in an increase of only 2% over the yield in the absence of buffer.

Discussion

The hydrolysis of imidate ester III is subject to concurrent catalysis by monofunctional acids and bases. Catalysis occurs via separate transition states for general acids and general bases, and there is no evidence for the existence of a transition state containing both a general acid and a general base (other than solvent species). The general acid-base catalytic pathways previously suggested for this imidate consist of (a) the general-base-catalyzed conversion of a cationic intermediate (T^+) to a zwitterionic intermediate ($T^\pm$) (step k_{-d} in Scheme II); this is kinetically equivalent to the general-acid-catalyzed reaction of a neutral intermediate; (b) the general-acid-catalyzed conversion of an anionic intermediate (T^-) to ester and amine (step k_{-f}'' in Scheme II), which is kinetically indistinguishable from the interaction of a general base with a neutral intermediate.[1a]

Support for these conclusions is derived from the Brønsted plots for general acid and general base catalysis by monofunctional catalysts. The biphasic Brønsted plot for acid catalysis (Figure 4, open symbols) is in accord with expectation for a kinetically important proton-transport step,[27] while the

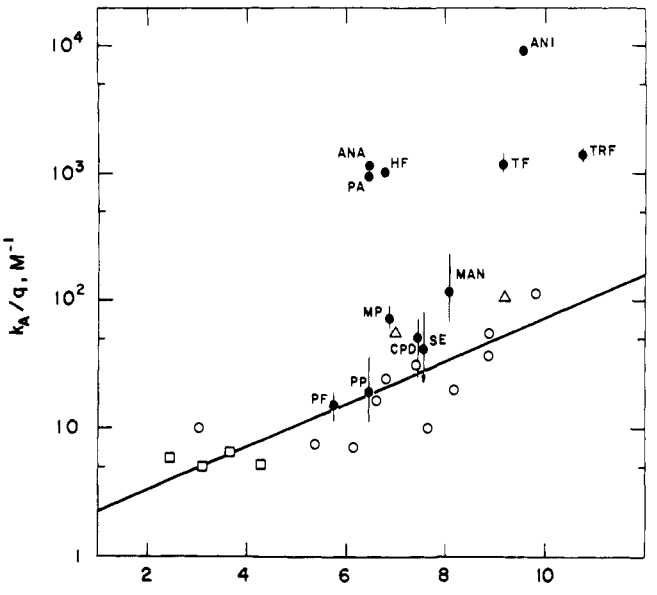


Figure 5. Brønsted plot for general base catalysis of amine formation from III. Error bars are estimated variation in catalytic constant assuming that K_{app} values are accurate to ±10%. Closed circles refer to bifunctional catalysts. Abbreviations are listed in Table II. Open symbols refer to monofunctional catalysts (data taken from ref 1a): □, carboxylic acids; ○, amines; △, alcohols. Least-squares line is based on points for monofunctional catalysts and has slope = 0.17. Point for selenite (SE) is upper limit only.

Brønsted plot for base catalysis (Figure 5, open symbols) with $\beta = 0.17$ over 7 units of pK suggests the occurrence of a proton transfer concerted with the expulsion of amine from the tetrahedral intermediate.[28] There exists, however, a serious objection to some aspects of the mechanism of Scheme II (see below).

On the basis of earlier studies,[8,14,22] it seemed likely that, in general, amphoteric buffers of type IV and V would effectively catalyze the conversion of T^0 to $T^{\pm}$ and thus provide a new pathway for the breakdown of the tetrahedral intermediate to amine. The availability of a lower energy transition state should manifest itself as a positive deviation from the

Scheme II

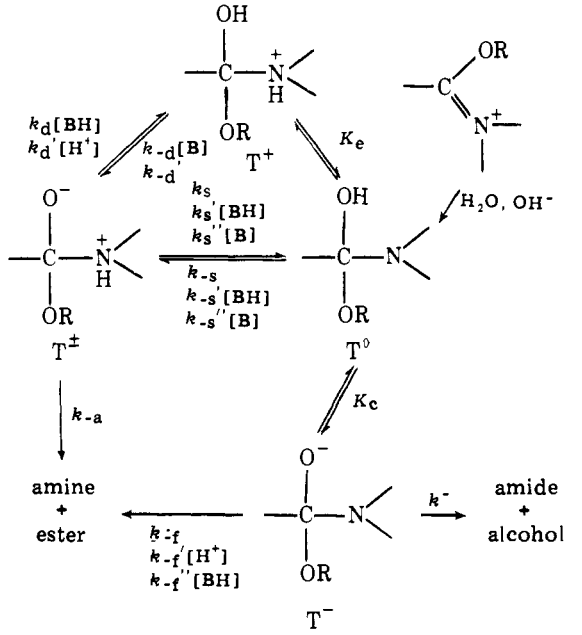


Table III. Representative Structures of Bifunctional and Monofunctional Catalysts[a]

catalyst	acid form	base form
phosphate	(7.2) HO—P(=O)(OH)—O⁻ (2.2)	(12.3) HO—P(=O)(O⁻)—O⁻ (7.2)
methylphosphonate	(7.1) HO—P(=O)(CH₃)—O⁻ (2.4)	O⁻—P(=O)(CH₃)—O⁻
phosphite	(6.7) HO—P(=O)(H)—O⁻ (1.8)	⁻O—P(=O)(H)—O⁻
arsenite	HO—As(OH)—OH	(13.8) HO—As(OH)—O⁻ (9.1)
hexafluoroacetone hydrate	(CF₃)C(OH)₂—CF₃	(CF₃)C(OH)(O⁻)—CF₃ (6.5)
selenite	(8.3) HO—Se(=O)—O⁻ (2.6)	⁻O—Se(=O)—O⁻

[a] For bifunctional species, pK values of acidic and basic groups are indicated. In the case of basic groups, numbers refer to pK_a of conjugate acid form. Values are from ref 34, except for methylphosphonate (ref 44) and hexafluoroacetone hydrate (this study). For the latter compound, pK_2 is not available and is probably >12.[46]

appropriate Brønsted plot. Possible catalysts include compounds where X = carbon, phosphorus, arsenic, sulfur, and selenium, while atoms Y and Z will generally be oxygen or nitrogen. The structures of some of the catalysts considered are shown in Table III, where the conjugate acid and base species listed are those of greatest concentration in the narrow pH range (pH 7-9) suitable for study of the products of the hydrolysis of imidate III.[1a] Disregarding for the moment more subtle catalytic requirements, it is possible to divide the catalysts into three groups, with the following characteristics: (a) both the conjugate acid and base forms may act as bifunctional catalysts (phosphate, arsenate); (b) only the acid form is bifunctional (phosphonates, arsonates, selenite, bicarbonate, pyridones, carboxylic acids); (c) only the conjugate base form is bifunctional (arsenite, fluoro ketone hydrates).

$$\underset{\text{IV}}{Y{=}X{-}ZH} \qquad \underset{\text{V}}{Y{-}X{-}ZH}$$

General Acid Catalysis. The statistically corrected[29] constants k_{AH} for acid catalysis by a series of bifunctional buffers (Figure 4, closed circles) may be compared to the Brønsted line defined by monofunctional general acids. For several buffers, there exists an ambiguity in the choice of the appropriate Brønsted plot. For example, the catalyst $H_2PO_4^-$ can be considered an acid of pK = 6.6, or the conjugate base of an acid of p$K \simeq 2$. The former interpretation leads to the conclusion that $H_2PO_4^-$ is no more reactive than monofunctional acids of similar strength (Figure 4), while the latter interpretation suggests that this ion is extraordinarily reactive as a general base (cf. the Brønsted line for general bases, Figure 5). In general, the Brønsted plot selected for comparison to the bifunctional catalyst was that from which the given catalyst deviated the least.

The constants k_{AH} for catalysis by $H_2PO_4^-$, $H_2AsO_4^-$, methyl- and phenylphosphonate monoanions, and phosphite monoanion are not significantly different from those of monofunctional catalysts of similar pK_a. Although these catalysts

all contain the adjacent acidic and basic groups which are necessary for bifunctional catalysis, according to Scheme II monofunctional catalysis in this pK region is approaching the diffusion-controlled limit (Figure 4), and there appears not to be any advantage gained by the introduction of an additional pathway for proton transfer.[16b,17,24] This point is perhaps easier to understand by considering the reverse reaction, which would involve true general acid catalysis of the conversion of $T^{\pm}$ to T^{+}. With general acids of low pK, the rate-determining step in the protonation of $T^{\pm}$ is the diffusion-controlled encounter of the reactants since the proton transfer is thermodynamically favorable. Bifunctional catalysts of low pK would be expected to react at the same diffusion-controlled rate as monofunctional acids, and, if no rate enhancement is seen in the direction of protonation, none would be observed in the reaction between the buffer conjugate base and T^{+}. The observed reactivity of bicarbonate ion is about 300 times greater than expected and may be taken as evidence for the existence of a bifunctional mechanism in the hydrolysis of III. Biselenite ion and methylarsonate monoanion also show appreciable positive deviations from the Brønsted line.

The conjugate acid forms of the fluoro ketone hydrates and of arsenious acid (Table III) do not have a basic group and their catalytic constants should fall on a line defined by monofunctional acids. This expectation was confirmed by experiment (Figure 4, curve B). It appears that monofunctional acids generate two different lines of unit slope, depending on whether the acidic proton is attached to nitrogen (Figure 4, curve A) or to oxygen (curve B). The values of k_{AH} previously obtained[1a] for two monohydric alcohols (Figure 4, triangles) are consistent with the values now reported for tri- and tetrafluoroacetone hydrates and arsenious acid. It is not clear why the point for hexafluoroacetone hydrate (HF) shows a negative deviation from curve B. Phosphorus oxy acids such as the monoanions of methyl- and phenylphosphonate, and of phosphite, also fit well on curve B, though phosphate monoanion falls somewhat below the line.

2-Hydroxypyridine exists in water predominantly in its tautomeric form 2-pyridone, with approximately a value of 10^3 for the ratio of the two tautomers.[30] When compared to oxy acids, 2-pyridone is about 300 times as reactive as predicted for monofunctional catalysts and 1500 times as reactive as predicted for a nitrogen acid of the same pK. The latter comparison appears justified owing to the high ratio of pyridone to pyridine structure in aqueous solution. The reactivity of 2-pyridone in the hydrolysis of III stands in contrast to its weak catalysis of the mutarotation of glucose in water,[12] and is reminiscent of its effectiveness as a catalyst for the mutarotation of tetramethylglucose in benzene.[1b] Owing to its very low basicity (pK_a for cationic 2-pyridone is 0.75)[31] it is unlikely that the neutral 2-pyridone is reacting as a nucleophile toward III. It has not been excluded, however, that general bases of pK_a as low as 0.75 might still show appreciable reactivity. If linear extrapolation of the Brønsted line (Figure 5) to such low pK values is warranted, a general base of pK = 0.75 would have $k_A = 2\ M^{-1}$, so that 2-pyridone would be only 15 times as reactive as expected. The possibility that the reactivity of 2-pyridone is in large measure the result of a nonspecific solvent effect seems ruled out by the fact that the presence of 0.32 M 2-pyridone at pH 8.5 causes a 26% increase in amine yield, while 0.5 M *tert*-butyl alcohol leads to an increase of <2% in amine yield at the same pH.[1a] Organic solvents of higher dielectric constant are even less effective than *tert*-butyl alcohol in increasing the yield of amine from III. The much more acidic 6-chloro-2-pyridone, which exists to the extent of 86% as the pyridone form in water,[30] shows little rate enhancement when compared to oxy acids, and is about 17-fold better a catalyst than comparable nitrogen acids.

The catalysis by carboxylic acids of several reactions carried out both in aprotic[8,11,12] and aqueous[14,21,22,32] solvent has been ascribed to a bifunctional mechanism. In the hydrolysis of III, catalysis by carboxylic acids has reached the diffusion-controlled limit, so that bifunctional catalysis leads to no further rate increases (Figure 4).

Acetone oxime is an unusually effective general acid catalyst for the dehydration of acetaldehyde hydrate, its catalytic constant being some 100 times greater than expected from the Brønsted plot defined by other general acids.[33] An explanation based on the lack of charge delocalization in the oxime anion has been advanced.[33b] The positive deviation of acetone oxime from the Brønsted line for the hydrolysis of III is even larger, the oxime being 8700 times a better catalyst than predicted for an oxy acid of similar pK. It is conceivable that the remarkable reactivity of the oxime is the result of bifunctional catalysis (see below).

General Base Catalysis. All the compounds whose conjugate bases contain both an acidic and a basic group (Table III), and which were considered likely to act as bifunctional catalysts, show pronounced positive deviations from the Brønsted plot for general base catalysis (Figure 5). Although the remaining hydroxyl group of phosphate dianion is a very weak acid (pK_a = 12.3 at 25 °C),[34] its presence is sufficient to make phosphate dianion 50 times a better catalyst than phenylphosphonate dianion. Arsenate and phosphate dianions exhibit equal reactivities, as do the corresponding monoanions (Figure 4). In contrast, the next lower oxoacids of phosphorus (H_3PO_3) and arsenic (H_3AsO_3) have markedly different catalytic properties. Phosphorous acid is a divalent acid (pK_1 = 1.2, pK_2 = 6.7),[34] whose monoanion is bifunctional, and whose dianion bears no acidic proton (Table III).[35,47] Arsenious acid (pK_1 = 9.1) is a much weaker acid, whose structure corresponds to $As(OH)_3$,[36] and whose monoanion is bifunctional while the neutral species has no basic group. The observed reactivities of these two catalysts are in accord with their pK_a and with expectation based simply on the availability of acidic and basic groups. While the catalytic effect of $H_2PO_3^-$ has reached the diffusion-controlled limit, arsenious acid is no more effective than the monofunctional hexafluoro-2-propanol (Figure 4). On the other hand, the monoanion $H_2AsO_3^-$ is the most reactive of the basic catalysts encountered in this study.

Comparison of K_{app} values for phosphate and imidazole catalysis of the hydrolysis of III indicates less dramatic differences than were seen in the hydrolysis of the iminolactone I.[14] With the latter compound, it was estimated that, at pH 7.3, phosphate buffer was 240 times more effective than imidazole buffer in catalyzing the expulsion of aniline from the tetrahedral intermediate. In that study, insufficient data were available to determine the separate contribution of imidazolium ion and of imidazole free base to the total imidazole catalysis. With imidate III, the ratio of phosphate to imidazole catalysis rises from 7 at pH 7 to 67 at pH 9, and approaches a limiting value of 90 at a pH which is sufficiently basic so that the reactions involve solely HPO_4^{2-} and imidazole free base.

Reaction Mechanism. The reaction mechanism that was previously proposed[1a] to account for the effect of monofunctional general acids and general bases is now modified by the addition of pathways k_s', k_{-s}' and k_s'', k_{-s}'' to include catalysis by bifunctional buffers (Scheme II). The main features of this mechanism are as follows: (a) the rate-determining step in the hydrolysis of the imidate is the addition of water or hydroxide ion to form the uncharged tetrahedral intermediate T^0, which is in equilibrium with cationic (T^+) and anionic (T^-) species; (b) in the absence of buffers, T^0 is converted to a zwitterionic intermediate $T^{\pm}$ by a solvent-mediated proton switch; (c) $T^{\pm}$ breaks down rapidly to the amine and ester products, to which T^- is also converted in part; (d) general acid catalysis of amine formation (Scheme I, step k_{BH}) is in fact the kinetically

equivalent reaction of buffer bases with T^+; (e) general base catalysis of amine formation (Scheme I, step k_B) is proposed to be the kinetically equivalent reaction of buffer acids with T^-; (f) bifunctional buffer acids or bases catalyze the conversion of T^0 to $T^\pm$.

Use was made of the assumption that the steady-state approximation applies to the four tetrahedral intermediates to derive eq 4 which describes the dependence of amine yield on pH and total buffer concentration $[B]_T$ (where $[B]_T = [BH] + [B]$; $K_a = [B][H^+]/[BH]$); $K_c = [T^-][H^+]/[T^0]$; $K_d = [T^\pm]\cdot[H^+]/[T^+]$; $K_e = [T^0][H^+]/[T^+]$). It was also assumed that $k_{-a} \gg k_s + k_d'[H^+] + k_d[BH] + k_s'[BH] + k_s''[B]$, and that $k_{-s} \gg k_{-d}'[H^+]/K_c$. The first assumption states that $T^\pm$ breaks down to amine and ester faster than it reverts to other forms of the intermediate; the second assumption indicates that the main pathway to amine in neutral or acidic solution (in the absence of buffer) is via T^0 and $T^\pm$, not through T^+. The left-hand term in the denominator is equal to K_{app} (cf. eq 2) and may be rearranged to eq 5, which has the same form as eq 3, and where $k' = (k_{-f} + k^-)K_c/(k_{-s} + k_{-f}'K_c)$. It follows that k_{AH} and k_A and given by eq 6 and 7. These constants represent the rates of buffer-catalyzed pathways for amine formation *relative* to solvent-catalyzed pathways. The equations for k_{AH} and k_A each contain two terms. The right-hand terms refer to monofunctional catalysis and indicate that the rate constants for the apparent general acid and general base catalysis (Scheme I) are proportional respectively to $k_{-d}K_a$ and k_{-f}'/K_a. The left-hand terms consist of the contribution of bifunctional catalysis to the process of amine formation.

$$\% \text{ amine} = \frac{([H^+] + K_a)\dfrac{k_{-s} + k_{-f}K_c/[H^+] + k_{-f}'K_c}{k_{-s}'[H^+] + k_{-s}''K_a + k_{-d}K_a[H^+]/K_e + k_{-f}''K_c} + [B]_T}{([H^+] + K_a)\dfrac{k_{-s} + k_{-f}K_c/[H^+] + k_{-f}'K_c + k^-K_c/[H^+]}{k_{-s}'[H^+] + k_{-s}''K_a + k_{-d}K_a[H^+]/K_e + k_{-f}''K_c} + [B]_T} \quad (4)$$

$$K_{app} = \left(\frac{k_{-s} + k_{-f}'K_c}{k_{-s}' + k_{-d}K_a/K_e}\right)\left(\frac{[H^+] + K'}{[H^+]}\right) \times \left(\frac{[H^+] + K_a}{[H^+] + \dfrac{(k_{-s}''K_a + k_{-f}''K_c)K_e}{(K_e k_{-s}' + k_{-d}K_a)K_a}K_a}\right) \quad (5)$$

$$k_{AH} = \frac{k_{-s}'}{k_{-s} + k_{-f}'K_c} + \frac{k_{-d}K_a}{K_e(k_{-s} + k_{-f}'K_c)} \quad (6)$$

$$k_A = \frac{k_{-s}''}{k_{-s} + k_{-f}'K_c} + \frac{k_{-f}''K_c}{(k_{-s} + k_{-f}'K_c)K_a} \quad (7)$$

The curves which describe the dependence of k_{AH} for monofunctional general acid catalysis (Figure 4, curves A and B) on the pK_a of the catalysts were calculated by means of eq 8 for amines (curve A) and eq 9 for alcohols (curve B).[27,37,38a] The calculation of curve A is based on the assumption that $\Delta pK = 0$ at $pK_a = 5.5$, while ΔpK was assumed to be equal to zero at $pK_a = 6.4$ for the calculation of curve B. The rate constant k_{-a} for the breakdown of the encounter complex (note 38a, eq *a*) was taken as 10^{10} s^{-1} and $\log k_p = 10 + 0.5\Delta pK$. The effect of assuming that $k_p \approx k_{-a}$ in the calculation of curve B is to produce a more gradual transition between the regions of slope one and zero. The acceptable fit of the data to the theoretical Brønsted curves serves mainly to demonstrate that the proposed product-determining proton transfer in imidate hydrolysis is reasonable. Although not too much importance should be attached to the values assigned to the constants of eq 8 and 9, it should be noted that the different values selected for the point where $\Delta pK = 0$ change in the direction expected for going from a symmetrical proton transfer (oxygen bases abstracting a proton from the hydroxyl group of T^+, curve B) to the unsymmetrical process where neutral reactants form charged products (nitrogen bases abstracting a proton from the hydroxyl group of T^+, curve A).[27]

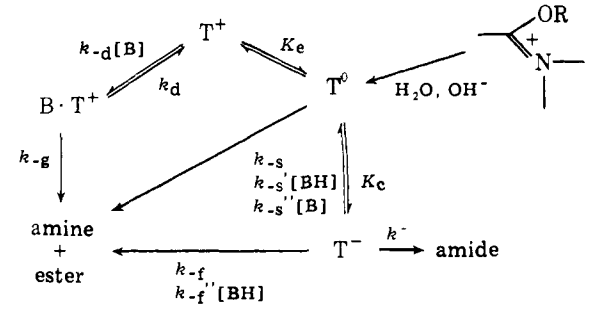
$$k_{AH} = \frac{k_{-d}K_a}{K_e(k_{-s} + k_{-f}'K_c)} = \frac{k_aK_a}{K_e(k_{-s} + k_{-f}'K_c)(1 + 10^{-\Delta pK})} = \frac{(8.57 \times 10^9)K_a}{1 + 10^{-\Delta pK}} \quad (8)$$

$$k_{AH} = \frac{k_aK_a}{K_e(k_{-s} + k_{-f}'K_c)\left(1 + \dfrac{k_{-a}}{k_p} + 10^{-\Delta pK}\right)} = \frac{(6.8 \times 10^{10})K_a}{1 + \dfrac{k_{-a}}{k_p} + 10^{-\Delta pK}} \quad (9)$$

Although the mechanism given in Scheme II appears to be quantitatively consistent with the Brønsted plots for general acid and general base catalysis, the following considerations suggest that it requires modification. The proposal that the protonation of T^- by general acids is concerted with the expulsion of amine is not likely to be valid for acids of $pK < 5$, which are expected to carry out the thermodynamically favorable conversion of T^- to $T^\pm$ at diffusion-controlled rates (pK_a for $T^\pm \rightleftharpoons T^- + H^+$ is ~6.1).[1a] The absence of a break at about $pK = 6$ in the Brønsted plot (Figure 5) speaks against a stepwise process in the breakdown of T^- to amine. A possible solution to this dilemma is outlined in Scheme III, which is based on the assumption that the zwitterionic intermediate $T^\pm$ is too unstable to exist. The principal features of this mechanism are as follows: (a) General acid catalysis of amine formation (Scheme I, step k_{BH}) consists of a two-step process, the rate-limiting step with strongly basic catalysts being the encounter-controlled formation of the complex $B\cdot T^+$ (slope $\beta = 0$ or $\alpha = 1$); with weakly basic catalysts, the rate-determining step is the breakdown of the complex to amine in a reaction concerted with proton transfer (slope $\beta = 0.9$ or $\alpha = 0.1$). (b) General base catalysis of amine formation (Scheme I, step k_B) occurs as protonation of T^- concerted with the expulsion of amine ($\beta = 0.17$ or $\alpha = 0.83$); the concerted pathways for the breakdown of $B\cdot T^+$ and T^- may be considered to be enforced by the negligible lifetime of $T^\pm$.[28b] (c) Bifunctional catalysts accelerate the concerted breakdown of T^0 to amine.

The mechanism of Scheme III is similar to that advanced for general acid–base catalysis in the reaction of methoxyamine with acetyltriazole,[38b] where the rates of catalysis by strong acids or bases were independent of the pK of the catalysts, while catalysis by weaker acids or bases was correlated by Brønsted slopes of 0.6–0.7. With imidate III, the proposed

Scheme III



mechanism requires that the cleavage of T^+ catalyzed by weak bases exhibit a Brønsted slope $\beta < 1.0$, which in terms of Figure 4 is equivalent to $\alpha > 0.0$ in the region of catalyst $pK < 6$.

For Scheme III, the steady-state rate law for the dependence of amine yield on pH and buffer concentration is given by eq 10. The left-hand term in the denominator of eq 10 is equal to K_{app}, and may be rearranged to eq 11, where $K' = (k_{-f} + k^-)K_c/k_{-s}$. Comparison of eq 11 to eq 3 shows that k_{AH} and k_A are given by eq 12 and 13, respectively. The right-hand terms in eq 12 and 13 represent the contributions of monofunctional catalysis to the observed catalytic constants.

$$\% \text{ amine} = \frac{\dfrac{([H^+] + K_a)(k_{-f} + k_{-s}[H^+]/K_c)}{\dfrac{k_{-g}k_{-d}[H^+]^2K_a}{K_cK_e(k_{-g} + k_d)} + \dfrac{k_{-s}'[H^+]^2}{K_c} + k_{-f}''[H^+] + \dfrac{k_{-s}''K_a[H^+]}{K_c}} + [B]_T}{\dfrac{([H^+] + K_a)(k_{-f} + k_{-s}[H^+]/K_c + k^-)}{\dfrac{k_{-g}k_{-d}[H^+]^2K_a}{K_cK_e(k_{-g} + k_d)} + \dfrac{k_{-s}'[H^+]^2}{K_c} + k_{-f}''[H^+] + \dfrac{k_{-s}''K_a[H^+]}{K_c}} + [B]_T} \tag{10}$$

$$K_{app} = \left(\frac{k_{-s}K_e(k_{-g} + k_d)}{k_{-g}k_{-d}K_a + k_{-s}'K_e(k_{-g} + k_d)}\right)\left(\frac{[H^+] + K'}{[H^+]}\right)\left(\frac{[H^+] + K_a}{[H^+] + \dfrac{(k_{-f}''K_c + k_{-s}''K_a)K_e(k_{-g} + k_d)}{[k_{-g}k_{-d}K_a + k_{-s}'K_e(k_{-g} + k_d)]K_a}K_a}\right) \tag{11}$$

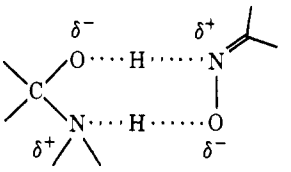
$$k_{AH} = \frac{k_{-s}'}{k_{-s}} + \frac{k_{-g}k_{-d}K_a}{k_{-s}K_e(k_{-g} + k_d)} \tag{12}$$

$$k_A = \frac{k_{-s}''}{k_{-s}} + \frac{k_{-f}''K_c}{k_{-s}K_a} \tag{13}$$

The theoretical curve for the dependence of k_{AH} on catalyst pK for monofunctional catalysts (Figure 4, dashed line) was calculated from eq 12 (with $k'_{-s} = 0$). Values of k_{-g} were obtained from the Brønsted relationship $\log k_{-g} = 0.9pK_a + 5.78$, and assumed values of $k_d = 10^{11}$ s^{-1} and $k_{-d} = 10^9$ M^{-1} s^{-1} were used. A value of $k_{-s} = 1.5$ s^{-1} was derived from the experimental points in the pK region where $\alpha = 1.0$, where it is assumed that $k_{-g} \gg k_d$. The observed values of k_{AH} fit reasonably well to the theoretical curves calculated either for Scheme II or III and neither mechanism can be favored on this basis alone. It is probable, however, that the involvement of $T^{\pm}$ as a discrete species (Scheme II) can be ruled out on the basis of the argument given above.

Bifunctional Catalysis. The rate enhancements observed with bifunctional catalysts are summarized in Table IV. Although the relative efficiencies of these catalysts (obtained by comparison to monofunctional catalysts) vary widely, the absolute values of the terms k_{AH} and k_A are clustered in the range of 10^3-10^4 M^{-1}, with the exception of 2-pyridone. Bifunctional catalysis seems to be almost independent of the pK_a of the catalyst. This is seen particularly clearly with the three fluoroacetone hydrates (Figure 5), whose catalytic constants are nearly identical, although their pK_a values vary from 6.5 to 10.4. For the same reason, it is unlikely that the effect of the fluoroacetone hydrates on the amine yield is the result of a nucleophilic reaction between the catalyst and the imidate ester. This conclusion is supported by the observation that the anion of hexafluoro-2-propanol, which is as basic as the anion of tetrafluoroacetone hydrate, falls on the Brønsted line defined by other general bases. The Brønsted plot for the reaction of methoxyamine with phenyl acetate shows a small dependence of rate on the pK_a of bifunctional catalysts ($\alpha = 0.16$) over a wide range of pK_a values.[16b] The more structurally heterogeneous group of bifunctional catalysts (Figure 4) whose pK_a varies from 6.6 (phosphite monoanion) to 9.8 (bicarbonate) also shows little dependence of k_{AH} on pK_a, although the data exhibit some scatter.

With the exception of acetone oxime, all the bifunctional catalysts employed in this study contain an acidic group and a basic group in a 1,3 relationship (cf. IV and V), so that the cyclic transition state which is required for the concerted transfer of two protons would consist of an eight-membered ring (cf. II). Arguments have been presented to the effect that an eight-membered ring is energetically favored over a six-membered ring in a cyclic transition state involving proton transfer.[39] In the case of acetone oxime, a seven-membered ring (VI) would be formed. The inability to achieve a cyclic transition state for proton transfer may explain why compounds like imidazole (free base), which possesses acidic and basic groups in the desired 1,3 relationship but is sterically unsuited for a cyclic proton transfer, do not show unusual catalytic effects.



VI

$$Y{=}X{-}ZH \rightleftharpoons HY{-}X{=}Z$$

VII

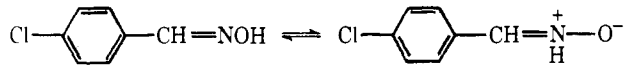
The transition state for bifunctional proton transfer seems not to have a stringent requirement for a particular geometry around the central atom of the catalyst. Catalysts with tetrahedral (fluoro ketone hydrates, phosphate[35]), planar (bicarbonate), and pyramidal (arsenite)[36] structures all have high reactivity.

The term "tautomeric catalysis" has been introduced to describe a bifunctional proton transfer during which the catalyst is transformed from one tautomeric form to another (VII).[8] It has also been suggested that the electronic rearrangement which accompanies this process is in some manner connected with the effectiveness of the catalysis.[5,6b] That the interchange of σ and π bonds is not an absolute requirement for effective bifunctional catalysis is demonstrated by the reactivity of fluoro ketone hydrate and arsenite monoanions. In the case of tautomeric catalysis as defined in VII, the relative thermodynamic stability of the two tautomers is important in determining whether catalysis will be observed.[5] If one of the two tautomeric forms is highly unstable relative to the other, the energy of the transition state for catalysis might become high enough so that bifunctional catalysis will not occur. These considerations may be applied to the catalysis by acetone oxime. It has been estimated that *p*-chlorobenzaldehyde oxime

Table IV. Relative Effects of Bifunctional and Monofunctional Catalysts on the Formation of Amine from Imidate III

acid catalyst[a]	rate ratio[b]	base catalyst[c]	rate ratio[b]
$HSeO_3^-$	4.3	HPO_4^{2-}	52
$(CH_3)HAsO_3^-$	7.4	$HAsO_4^{2-}$	61
HCO_3^-	290	$H_2AsO_3^-$	150
acetone oxime	8700	$CF_3C(OH)O^-CF_3$	47
6-chloro-2-pyridone	17	$CHF_2C(OH)O^-CHF_2$	22
2-pyridone[d]	1460	$CF_3C(OH)O^-CH_3$	14
		2-pyridone[d]	15

[a] Values of k_{AH} for bifunctional catalysts are compared to values for monofunctional oxy acids (Figure 4, curve B), except for the pyridones, which are compared to curve A. In the pK region of unit slope, monofunctional catalysts which fall on curve B react 8 times faster than those correlated by curve A. [b] Rate constants and pK_a values have been statistically corrected. [c] Values of k_A for bifunctional catalysts are compared to values for monofunctional catalysts of the same pK (Figure 5, line). Interpolations are made by means of the equation $\log k_A/q = 0.17[pK_a + \log (p/q)] + 0.18$. [d] 2-Pyridone is compared both to monofunctional acids and bases (see text).



VIII

exists to the extent of 1–2% in the zwitterionic form VIII in aqueous solution,[40] and the corresponding ratio for acetone oxime should not be very different, so that the zwitterionic form of acetone oxime is a viable intermediate in oxime catalysis.

With regard to the timing of the proton transfers involving bifunctional catalysts, there exists evidence that, in systems where $T^{\pm}$ has a finite lifetime, the solvent-mediated proton switch which converts T^0 to $T^{\pm}$ occurs as a stepwise process in which the thermodynamically more favorable proton transfer takes place first.[24,41] This mechanism is a reasonable possibility for the operation of bifunctional catalysts, even if $T^{\pm}$ does not exist as a discrete species. The second proton transfer would occur before the diffusion of the catalyst out of the solvent cage. The choice between proton donation to or proton abstraction from T^0 as the first event in a (at least partially) stepwise proton transfer may be made by considering the magnitude of ΔpK_a between the weakly basic nitrogen atom of the intermediate ($pK_a \simeq 1.1$)[1a] and the acid group of the catalyst, as well as between the weakly acidic hydroxyl group of T^0 ($pK_a \simeq 12.3$)[1a] and the basic center of the catalyst (Table III). Most of the bifunctional catalysts possess an exceedingly weak acidic or basic group. It must be kept in mind, however, that the second proton transfer becomes increasingly favorable as the first proton transfer progresses, owing to pK_a changes both in the catalyst and the tetrahedral intermediate. This is true both for sequential proton transfer (regardless of whether the catalyst first donates or abstracts a proton) and for a largely concerted mechanism.

Experimental Section

Imidate ester III, acetonitrile, and monofunctional buffers were materials from a previous study.[1a] Other compounds were obtained from commercial sources and were used without further purification, with the exception of 2-pyridone and 6-chloro-2-pyridone, which were recrystallized. Methylphosphonic acid was a gift from Dr. J. Chlebowski. Acid–base titration was carried out on the following compounds at 30 °C and ionic strength 0.5: sodium arsenite ($NaAsO_2$, J. T. Baker), sodium methylarsonate ($CH_3AsO(ONa)_2 \cdot 6H_2O$, Alfa), sodium phosphite ($Na_2HPO_3 \cdot 5H_2O$, Fisher), sodium selenite (Na_2SeO_3, Alfa), and 6-chloro-2-pyridone (Aldrich). The curves obtained conformed to theory. End points were all within 1% of the calculated values except for sodium arsenite, which was found to contain 2% of a strong acid. Values of pK for other catalysts were taken as the pH of half-neutralized solutions, whose concentrations were high enough so that the pH was not changed when the buffer was diluted by half. Sodium arsenite was found to contain <0.2% arsenate. The assay used was based on a procedure in which arsenate oxidizes HI to I_2 in the presence of concentrated HCl.[43] The absorbance at 515 nm of CCl_4 extracts was linearly dependent on arsenate concentration (up to at least 0.02 M), and was not affected by the presence of 0.4 M arsenite. Colorimetric assay[45] showed that phenylphosphonate and methylphosphonate contained <0.2% inorganic phosphate.

Product Analysis. For most of the catalysts studied, the yield of N-methylaniline produced on hydrolysis of the imidate salt in 0.5% acetonitrile–water at 30 °C and ionic strength 0.5 (KCl) was determined by colorimetric assay.[1a] For experiments in which the buffers interfered with the colorimetric assay, amine yields were determined from the UV absorbances at completion of reaction. The wavelengths used were 283 (N-methylaniline, ϵ 1540; N-methylacetanilide, ϵ negligible) or 240 nm (N-methylaniline, ϵ 8880; N-methylacetanilide, ϵ 2430), the choice of the wavelength depending on the absorbance of the buffer in use. The extinction coefficients of N-methylaniline and N-methylacetanilide appeared to be slightly affected by the buffer and therefore were determined for each experimental condition. The catalysts which interfered with the colorimetric assay were phenylphosphonate (>0.03 M), methylphosphonate (>0.09 M), and selenite (>0.02 M). Although arsenate and phosphate at >0.015 M also interfered with the colorimetric assay, the assay was still employed because the highest concentration used for these catalysts did not exceed 0.015 M.

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$$HX + Y \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} XH \cdots Y \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}} X \cdots HY \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} X + HY \quad \text{(a)}$$

$$k_f = \frac{k_a k_p k_b}{k_p k_b + k_b k_{-a} + k_{-a} k_{-p}} \quad \text{(b)}$$

Assuming that $k_p \gg k_{-a}$, $k_{-a} \simeq k_b$, and $\log K_p = \Delta pK$ [where ΔpK = pK(catalyst) − pK(Intermediate)] gives

$$k_f = \frac{k_a}{1 + 10^{-\Delta pK}} \quad \text{(c)}$$

Setting $k_f = k_{-d}$ (in eq 6) and $k'_{-s} = 0$ yields eq 8. The same method was used for the derivation of eq 9, except that it was assumed that $k_p \approx k_{-a}$, giving

$$k_f = \frac{k_a}{1 + \frac{k_{-a}}{k_p} + 10^{-\Delta pK}} \quad \text{(d)}$$

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Host–Guest Complexation. 14. Host Covalently Bound to Polystyrene Resin for Chromatographic Resolution of Enantiomers of Amino Acid and Ester Salts[1,2]

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Abstract: A host, $CH_3OCH_2PSCH_2OED(CH_3)_2(OEOEO)_2D$ ((*R,R*)-**12**), was synthesized for preparative or analytical chromatographic resolution of racemic amino acids and esters. In (*R,R*)-**12**, PS is cross-linked polystyrene, ~12% of whose phenyl groups are substituted in the para position with a CH_3OCH_2 group, and 0.8% with a spacer unit ($CH_2OCH_2CH_2$), which in turn is attached to a designed complexing site. This site is a macrocycle composed of two 1,1′-dinaphthyl or D units of the same *R* configuration attached to one another at their 2,2′ positions by two OEOEO units (E is CH_2CH_2). The spacer is attached to the remote 6 position of that D unit which contains two methyl groups substituted in its 3,3′ positions. Columns of this material were used in chromatographic resolutions in $CHCl_3$–CH_3CN of racemic mixtures of $C_6H_5CH(CO_2H)NH_3ClO_4$, p-$HOC_6H_4CH(CO_2H)NH_3ClO_4$, $C_6H_5CH_2CH(CO_2H)NH_3ClO_4$, $C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, $(CH_3)_2CHCH(CO_2H)NH_3ClO_4$, $C_2H_5(CH_3)CHCH(CO_2H)NH_3ClO_4$, $(CH_3)_3CCH(CO_2H)NH_3ClO_4$, $CH_3CH(CO_2H)NH_3ClO_4$, $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$, p-$HOC_6H_4CH(CO_2CH_3)NH_3ClO_4$, p-$CH_3O_2CC_6H_4CH(CO_2CH_3)NH_3ClO_4$, p-$ClC_6H_4CH(CO_2CH_3)NH_3ClO_4$, $C_6H_5CH_2CH(CO_2CH_3)NH_3ClO_4$, and p-$HOC_6H_4CH_2CH(CO_2CH_3)NH_3ClO_4$. Separation factors ranged from 26 to 1.4, and resolution factors from 4.5 to 0.21. Host of the *R,R* configuration bound D guest more firmly than L guest by from 1.8 to 0.18 kcal/mol in all cases. A column packed with 9.5 g of (*R,R*)-**12** containing the equivalent of 0.42 g of complexing site gave base-line separation of enantiomers of $C_6H_5CH(CO_2H)NH_3ClO_4$ in runs that involved as much as 15 mg to as little as 0.013 mg of racemate. A host similar to (*R,R*)-**12** in which the two methyl groups are absent, $CH_3OCH_2PSCH_2OED(OEOEO)_2D$ ((*R,R*)-**11**), was found to give lower separation factors than (*R,R*)-**12**. The results are discussed in terms of complementary vs. noncomplementary stereoelectronic diastereomeric relationships between host and guest.

Amino ester salt racemates as a family have been resolved preparatively by solid–liquid and liquid–liquid chromatography that involved designed host–guest complexation. Separation factors varied from 1.52 to 6.4.[4] Derivatives of amino acid racemates have been resolved analytically as gases on long capillary columns of very high plate value in which optically active, derivatized peptides served as liquid phases. Separation factors between enantiomers as high as 1.7 have been observed.[5] Sephadex, covalently bound to L-arginine as a solid phase, was used to resolve preparatively solutions of 3,4-dihydroxyphenylalanine with a separation factor of 1.6. A complementary relationship between ion-pairing sites of the bound amino acid and one enantiomer of the racemate was envisioned.[5c]

This paper reports the first example of the synthesis of designed solid phase hosts useful for both preparative and analytical chromatographic resolution of amino acid and ester racemates as a family.[2] Macromolecules (*R,R*)-**11** and (*R,R*)-**12** (Chart I) are composed of a macroreticular cross-linked polystyrene *p*-divinylbenzene resin on which have been grafted the chiral hosts (*R,R*)-**1** and (*R,R*)-**2**, respectively. About 0.8% of the para positions of the C_6H_5 groups available

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