organocuprate chemistry and the discovery that these copper species are versatile reagents for other types of synthetic transformations. Here zirconium alkenyls, normally inert to α,β-unsaturated ketones, have been activated toward conjugate addition by the addition of a reduced nickel catalyst system. Much of the chemistry of organozirconium reagent systems so activated remains to be studied. Further investigations in this area will undoubtedly uncover new methods for activation of organozirconium compounds. This, in turn, will enable development of other carbon–carbon bond forming reactions and extend the utility of these organometallic reagents.[46]

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(45) This is the same general method used by Stork and Isobe for preparation of **2a.**
(46) For example, **1a,** in the presence of $Ni(AcAc)_2$/DiBAH, reacts with methyl acrylate or 3-butyn-3-one to give the expected conjugate adduct in good yield.

Catalysis of Transimination by Rate-Limiting Proton Transfer to Buffer Bases[1]

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Abstract: General base catalysis of the hydroxylaminolysis of benzhydrylidenedimethylammonium ion gives a Brønsted plot that follows the Eigen curve expected for rate-determining trapping of the initially formed addition intermediate by proton transfer to a buffer base or water. The solvent deuterium isotope effects for catalysis by oxy anions exhibit a maximum at the break point of the Eigen curve, close to the estimated pK_a for the addition intermediate. This maximum can be accounted for by a partial change in rate-limiting step of the proton-transfer process near $\Delta pK = 0$. Water shows a positive deviation from the Brønsted plot and a solvent isotope effect of $k_{H_2O}/k_{D_2O} = 4.7$ that provide additional evidence for the trapping mechanism. The addition of glycerol increases the rate of the base-catalyzed reaction; much larger increases are observed with ethylene glycol and methanol. In contrast, the base-catalyzed hydrolysis of the cationic imine follows a linear Brønsted plot ($\beta = 0.24$), with a negative deviation for catalysis by water, and gives a constant value of $k_{H_2O}/k_{D_2O} = 1.9 \pm 0.2$. A concerted mechanism of base-catalyzed attack by water is suggested for this reaction.

Evidence for catalysis of the transimination of **1** through trapping the initial addition intermediate by buffer acids and bases was provided by the observation of a change in rate-determining step with increasing buffer concentration.[2] The relative catalytic activities of different acids and bases are consistent with trapping through simple proton transfer to or from the intermediate and with bifunctional acid–base catalysis by carboxylic acids, but it was not possible to obtain a satisfactory Brønsted plot for the reaction because of the change in rate-determining step.

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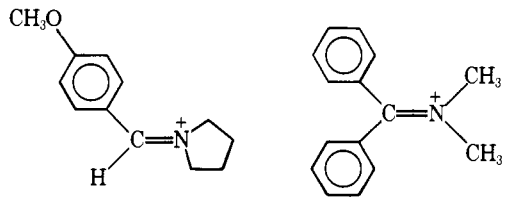


1 2

We have now examined catalysis of the transimination of **2** in order to obtain more information about catalysis by proton transfer in this relatively simple reaction. The transimination of **2** with hydroxylamine is subject to general base catalysis[3] and does not exhibit a change in rate-determining step with increasing buffer concentration up to 0.6 M, presumably because the attacking amine is expelled more rapidly from the initial addition compound in **2** than in **1**.[2] A stepwise mechanism of general base catalysis by proton transfer has been examined by Benkovic and co-workers for the related reaction of methoxyamine with an amidine.[4]

Experimental Section

Materials. Benzhydrylidenedimethylammonium ion (**2**) was prepared by the procedure of Hauser and Lednicer[5] with the addition of 3 drops of sulfuric acid as a catalyst. Ethylphosphonic acid was prepared from the diethyl ester.[6] Organic reagents, except for acetic acid and potassium acetate, were redistilled or recrystallized before use. Glycerol and ethylene glycol were refluxed for 2 h over sodium, vacuum-distilled twice, and stored at 4 °C. Stock solutions of 90% glycerol, ethylene glycol, and methanol were prepared by the addition of organic solvent to 10 mL of water to give 100 mL final volume. Acetonitrile was dried over molecular sieves. Glass-distilled water was used throughout.

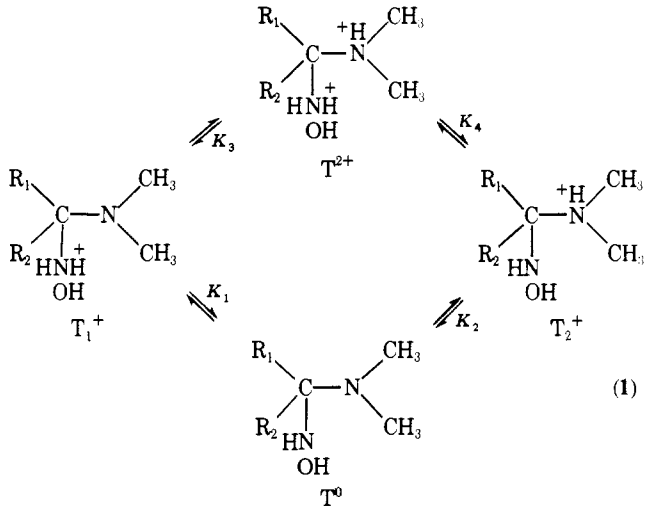
Methods. Reactions were followed spectrophotometrically at 300 nm after the addition of 0.05 mL of 0.006 M **2** in acetonitrile to 2.95 mL of reaction mixture that had been equilibrated in a thermostated cell holder at 25 °C. The ionic strength was maintained at 1.0 M with potassium chloride. Catalysis by buffers with <1 or >99% base was examined in reaction mixtures that were buffered by either hydroxylamine or 0.03 M methoxyacetate buffers. Solvent isotope effects were measured in parallel experiments in protium oxide and in deuterium oxide containing <2% water.

Pseudo-first-order rate constants were calculated from half-times obtained from semilogarithmic plots of $A - A_\infty$ against time, which were generally linear for 4 half-times. Experiments with **2** were carried out using a >20-fold excess and with **1** using a >14-fold excess of hydroxylamine. Rate constants for hydrolysis, k_{hyd}, were determined from parallel experiments in the absence of hydroxylamine and apparent second-order rate constants for the hydroxylamine reaction, k', were calculated from $k' = (k_{obsd} - k_{hyd})/[NH_2OH]_{fb}$. The concentration of hydroxylamine free base, $[NH_2OH]_{fb}$, was calculated from the total concentration of hydroxylamine added, the measured pH, and the pK_a of hydroxylamine hydrochloride under the conditions of the experiment. The apparent (uncorrected) pK_a values were found to be 6.17 in water, 6.27 in deuterium oxide, and in the range 6.17–6.42 in the aqueous-organic solvent mixtures at 25 °C, ionic strength 1.0 M (KCl). These values are based on pH-meter readings using a glass electrode that was calibrated with standard aqueous buffers.[7] Applying a correction of 0.4 to the pH-meter readings in deuterium oxide[8] gives $pK_a = 6.67$ for ND_3OD^+ and an isotope effect of $\Delta pK = 0.5$, similar to previously reported values of $\Delta pK = 0.45$ and 0.47.[9]

Catalytic constants based on total buffer concentration and hydroxylamine free base concentration, k_{cat}, were obtained from the slopes of plots of k' against the concentration of buffer. The same procedure was followed for hydroxylamine buffers, which gave nonlinear curves of k_{obsd} against buffer concentration.[1] Catalytic constants for the hydrolysis of **2**, k_h, were obtained from the slopes of plots of k_{hyd} against [buffer]; the intercepts gave k_0, the rate constant for "uncatalyzed" hydrolysis. Plots of k_h against the fraction base of different buffers gave k_H at 100% base for catalysis by the basic form of the buffer; no acid catalysis was observed.

The transimination of **1** with hydroxylamine was followed essentially as described previously.[2] The limiting second-order rate constants of the attack step, k_∞, were determined from a series of runs in 0.10–0.25 M hydrochloric acid. The curved plots of k' against buffer concentration were linearized by the relation $k_{cor} = k'/(1 - k'/k_\infty)$.[2] The slopes of plots of k_{cor} against total buffer concentration gave the apparent catalytic constants, k_{cat}.

Estimated pK_a Values of the Addition Intermediate. The pK_a values defined by eq 1 were estimated as described previously[2,10,11] using ρ_I



(1)

= 8.4 for the dissociation of substituted ammonium ions and published substituent constants.[11,12]

The value of pK_1 was estimated as 3.3, based on $pK_a = 5.96$ for $CH_3NH_2OH^+$.[13] The decrease of 2.7 pK units is caused by the substitution of two phenyl groups ($\sigma_I = 0.10$) and a methylamino group ($\sigma_I = 0.10$), and a correction of 0.02 for the additional methyl group, from the difference in the σ_I values of $CH(CH_3)_2$ and CH_2CH_3. The value of 6.6 for pK_2 was estimated from $pK_a = 9.76$ for $CH_3NH(CH_3)_2^+$,[14] corrected for the effects of two phenyl groups and a hydroxylamino group ($\sigma_I = 0.18$).[15] The value of $pK_4 = -1.5$ was obtained from $pK_1 = 3.3$ and an electrostatic effect of 4.8 units for the additional charge in T^{2+}.[11] The value of pK_3 is then 1.8, based on the same electrostatic correction.

Results

The disappearance of **2** in the presence of buffers and excess hydroxylamine follows the rate law

$$k_{obsd} = k_0 + k_H[A^-] + k_n[NH_2OH] + k_B[NH_2OH][A^-] \quad (2)$$

Catalysis of the hydroxylaminolysis reaction by acetate buffers in water and deuterium oxide is shown in Figure 1. There is significant catalysis by two ionic forms of phosphate, ethylphosphonate, and cacodylate buffers and the separation of the catalytic constants for the two forms is illustrated for cacodylate buffers in Figure 2. All of the other buffers examined, which have only a single ionization, show catalysis by the basic, but not the acidic, species of the buffer. The rate constant, k_n, for the "uncatalyzed" water reaction was determined from experiments at low hydroxylamine concentrations as shown in Figure 3. The value of k_n was found to be independent of pH in the range 3–7. Rate constants for the buffer-catalyzed hydrolysis of **2** were determined in a parallel series of experiments, as illustrated for methoxyacetate buffers in Figure 4. The results for catalysis of the hydroxylaminolysis reaction in water and deuterium oxide are shown in Tables I and II and catalytic constants for the hydrolysis of **2** are shown in Table III. The rate constant k_0, for the buffer-independent hydrolysis of **2**, was found to be independent of pH in the range of pH 3–6, in agreement with earlier results.[3]

Catalysis of the transimination reaction by ethylphosphonate dianion is slightly accelerated in the presence of 30% glycerol and greatly accelerated by 30% methanol (Figure 5). Similar results for catalysis by a series of ethylphosphonate buffers in aqueous-organic solvents are summarized in Table

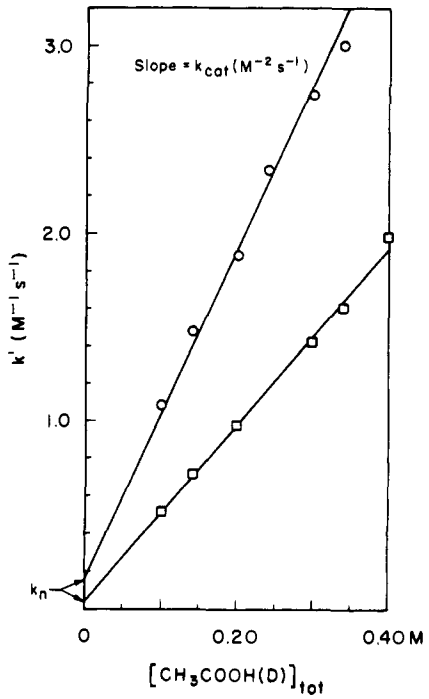


Figure 1. Dependence on the concentration of acetate buffer, 50% anion, of the second-order rate constant $k' = (k_{obsd} - k_{hyd})/[NH_2OH]_{fb}$ for the hydroxylaminolysis of **2** in water (○) and deuterium oxide (□) at ionic strength 1.0 M (KCl), 25 °C.

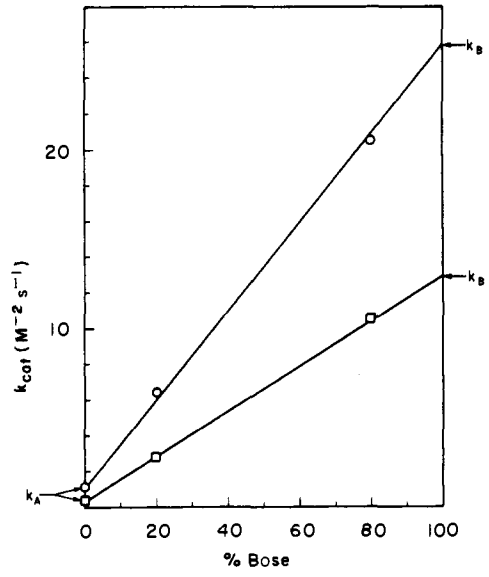


Figure 2. Dependence on buffer composition of the third-order rate constants for the hydroxylaminolysis of **2** catalyzed by cacodylate buffers in water (○) and deuterium oxide (□) at ionic strength 1.0 M (KCl), 25 °C.

IV. Similar, but somewhat smaller, rate increases in the presence of organic solvents occur with hydroxylamine as the catalyst (Table V).

Rate constants for the transimination of **1** were examined in acetate buffers in water, 45% glycerol, and 45% methanol. Rate constants for the buffer-independent attack step, k_∞, and for catalysis by acetic acid, k_A, and acetate ion, k_B, are shown in Table VI.

Discussion

The Brønsted plot for general base catalysis of the transimination reaction of **2** with hydroxylamine, shown in Figure

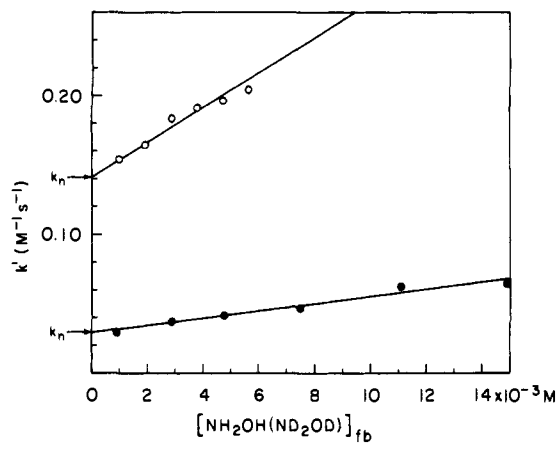


Figure 3. Dependence of k' for the hydroxylaminolysis of **2** on hydroxylamine concentration in water (○) and deuterium oxide (●) at ionic strength 1.0 M (KCl), 25 °C.

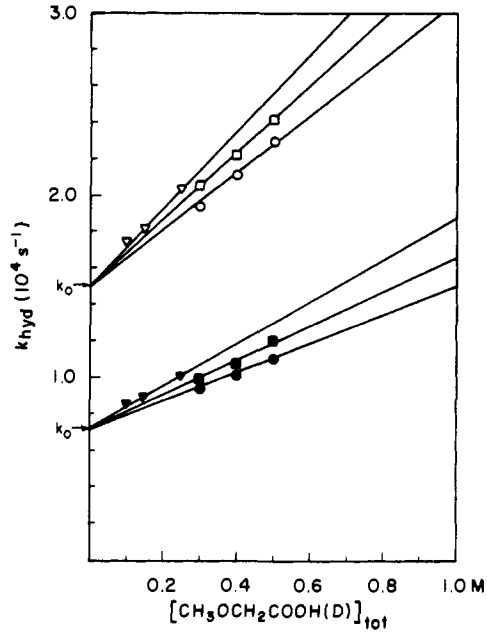


Figure 4. Dependence of the rate constants for the hydrolysis of **2** on the concentration of methoxyacetate buffers, 60 (circles), 80 (squares), and 90% (triangles) anion, in water (open symbols) and deuterium oxide (closed symbols) at ionic strength 1.0 M (KCl), 25 °C.

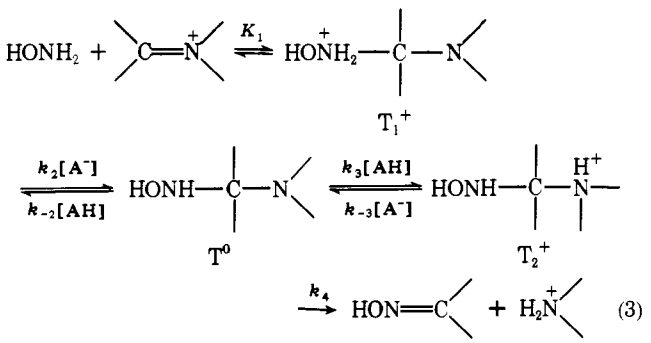
6, is nonlinear and has the shape that is expected for a simple proton transfer reaction between electronegative atoms in water, as described by Eigen.[16] The statistically corrected[17] rate constants show no significant deviations from the line for catalysts of differing structure or charge, except for a positive deviation of the point for water.[18] The rate constants for uncharged cacodylic acid and for the monoanions of phosphate and ethylphosphonate fit the Brønsted plot. Thus, catalysis by these species (Figure 2, Table II) can be accounted for by the same mechanism of general base catalysis as the other catalysts. There is no detectable general acid catalysis by any of the buffers examined. The lower curve in Figure 6 describes rate constants for the same catalysts in deuterium oxide.

These Brønsted curves support the mechanism of eq 3 in which the addition intermediate T_I^+ is formed in a rapid equilibrium step (K_1), the rate-limiting step is the trapping of this intermediate by proton removal (k_2) in order to prevent reversion to starting material (k_{-1}) and the protonation and expulsion of the leaving dimethylamine (k_3 and k_4) are fast. The observed rate constants for general base catalysis, k_B, are then equal to K_1k_2. An alternative mechanism in which the

Table I. General-Base-Catalyzed Transimination of **2** and Hydroxylamine[a]

catalyst	fraction base	concn range,[b] M	k_{cat} (H_2O), M^{-2} s^{-1}	k_{cat} (D_2O), M^{-2} s^{-1}	k_{cat} (H_2O)/ k_{cat} (D_2O)
Cl_2CHCOO^-	0.99[c]	0-0.44	0.21	0.11	1.91
	0.99[c]	0-0.44	0.14	0.07	2.00
F_2CHCOO^-	0.99[c]	0-0.70	0.18	0.10	1.80
	0.99[c]	0-0.70	0.20	0.12	1.67
$CNCH_2COO^-$	0.90	0.10-0.50	1.00	0.45	2.22
	0.95[d]	0-0.50	1.05	0.50	2.10
$ClCH_2COO^-$	0.80	0.14-0.34	1.35	0.55	2.45
	0.85	0.14-0.34	1.35	0.54	2.50
	0.85	0.10-0.50	1.55	0.60	2.58
	0.90	0.10-0.50	1.55	0.65	2.38
$CH_3OCH_2COO^-$	0.60	0.30-0.60	3.3	1.4	2.36
	0.80	0.30-0.60	4.0	2.0	2.00
	0.90	0.10-0.30	4.5	1.8	2.50
CH_3COO^-	0.20	0.10-0.40	3.5	1.8	1.94
	0.20	0.10-0.40	3.7	2.1	1.76
	0.50	0.10-0.40	8.4	4.4	1.91
	0.80	0.10-0.40	13.5	6.2	2.18
$(CH_3)_2AsO_2^-$	0.01[d]	0-0.74	1.10	0.34	
	0.20	0.10-0.40	6.4	2.8	
	0.80	0.04-0.20	19.0	10.0	1.90
$EtPO_3^{2-}$	0.10	0.03-0.08	5.6	3.0	1.86
	0.10	0.025-0.10	6.5		
	0.20	0.05-0.25	9.7		
	0.40	0.025-0.10	15.2		
	0.60	0.01-0.06	26.1	16.0	1.63
	0.80	0.025-0.10	29.0		
	0.90	0.025-0.10	39.3		
HPO_4^{2-}	0.003[d]	0-0.50	1.70	0.70	2.42
	0.005[e]	0.05-0.50	1.58		
	0.50	0.05-0.20	13.8		
NH_2OH	0.10	0.01-0.06	1.20	0.30[e]	4.0

[a] Ionic strength 1.0 M (KCl), 25 °C. [b] Range of total buffer concentration. [c] The pH was held constant with 0.50 M NH_2OH (ND_2OD), serving as both buffer and nucleophile. [d] The pH was held constant with 0.03 M methoxyacetate buffer. [e] 0.01-0.16 M [ND_2OD]; the pH was held constant with 0.03 M acetate buffer.



(3)

rate-limiting step is the protonation of T^0 by a buffer acid (k_3) is kinetically equivalent to this mechanism. However, the Eigen curve for a simple proton transfer reaction shows a break when the pK values of the catalyst and substrate are equal[16] and the break in the Brønsted curve of Figure 6 is at pK_a = 2.85, which is close to the estimated pK_a of 3.3 for T_1^+ (Experimental Section). This supports rate-limiting proton removal from T_1^+ rather than rate-limiting proton transfer to form T_2^+, which has an estimated pK_a of 6.6. This conclusion is in agreement with the generalization that rate-limiting proton transfer in this type of reaction will involve the step that is immediately adjacent (in time) to the attack or expulsion of the less basic amine molecule.[2]

The rate-limiting proton transfer step (k_2) can itself be divided into three steps, as described by Eigen:[16]

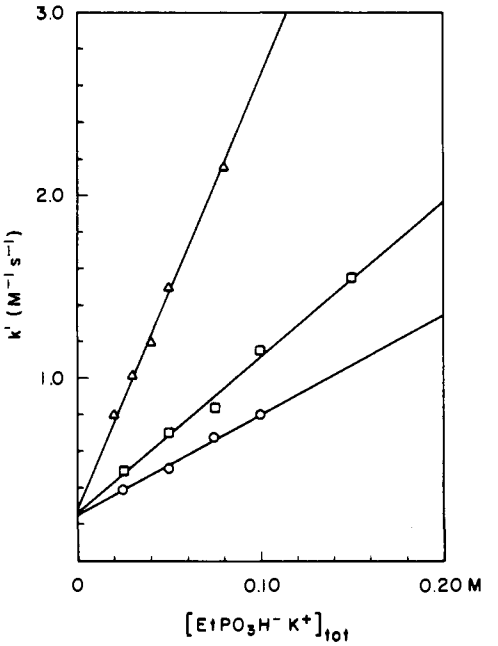


Figure 5. Dependence of k' for the hydroxylaminolysis of **2** on the concentration of ethylphosphonate buffer, 10% dianion, in water (○), 30% glycerol (□), and 30% methanol (△) at ionic strength 1.0 M (KCl), 25 °C.

Table II. Catalytic Constants and Isotope Effects for General Base Catalysis of the Transimination of **2** and Hydroxylamine[a]

catalyst	pK_a	k_B(H_2O), M^{-2} s^{-1}	k_B(D_2O), M^{-2} s^{-1}	k_B(H_2O)/ k_B(D_2O)
Cl_2CHCOO^-	1.03[b]	0.14-0.21	0.07-0.11	1.91-2.00
F_2CHCOO^-	1.13[c]	0.18-0.20	0.10-0.12	1.67-1.80
$H_2PO_4^-$	2.08[d]	1.70	0.70	2.42
$CNCH_2COO^-$	2.23[e]	1.11	0.50	2.22
$ClCH_2COO^-$	2.65[e]	1.71	0.70	2.44
$CH_3OCH_2COO^-$	3.33[e]	5.2	2.65	2.26
CH_3COO^-	4.60[e]	16.5	8.0	2.06
$(CH_3)_2AsO_2^-$	6.15[f]	26.1	12.9	2.02
$EtPO_3^{2-}$	7.60[e]	39.5	26.4	1.50[g]
H_2O	−1.74	2.5 × 10^{-3} [h]	0.47 × 10^{-3} [h]	4.67
$(CH_3)_2AsO_2H$	1.77[d]	1.10	0.34	3.23
$EtPO_3H^-$	2.23[e]	1.6-2.4	0.80	~2.2[i]
NH_2OH	6.17[j]	12.0	3.0	4.0

[a] Ionic strength 1.0 M (KCl), 25 °C. [b] Potentiometric titration. [c] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969,** *91,* 6353-6361. [d] Young, P. R.; Jencks, W. P. *Ibid.* **1978,** *100,* 1228-1235. [e] Rosenberg, S.; Silver, S. M.; Sayer, J. M.; Jencks, W. P. *Ibid.* **1974,** *96,* 7986-7998. [f] Sayer, J. M.; Jencks, W. P. *Ibid.* **1973,** *95,* 5637-5649. [g] Extrapolated to 100% dianion (Table I). [h] Third-order constant: $k_B = k_n/55.5$ M = 0.14/55.5 = 2.5 × 10^{-3} M^{-2}/s^{-1} (H_2O); k_B = 0.03/55.5 = 0.47 × 10^{-3} M^{-2} s^{-1} (D_2O). [i] Approximate value. [j] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968,** *90,* 2622-2637.

$$T_1^+ + A^- \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \left[T_1^+ \cdot A^- \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}} T^0 \cdot HA\right] \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} T^0 + HA \quad (4)$$

For strong bases proton transfer occurs at almost every properly oriented encounter, k_a is rate limiting, and the catalytic constants are independent of basicity. For weak bases the corresponding step, k_{-b}, is rate limiting in the reverse direction, k_b is rate limiting in the forward direction, and the Brønsted plot approaches a slope of 1.0. In the region near $\Delta pK = 0$ the k_p step becomes partly rate determining and the observed rate constants fall below a curve that is based on only the k_a and k_b

Table III. General Base Catalysis of the Hydrolysis of **2**[a]

catalyst	fraction base	concn range,[b] M	H_2O 10^4k_h, $M^{-1}\,s^{-1}$	H_2O 10^4k_H,[c] $M^{-1}\,s^{-1}$	D_2O 10^4k_h, $M^{-1}\,s^{-1}$	D_2O 10^4k_H,[c] $M^{-1}\,s^{-1}$	$k_H(H_2O)/k_H(D_2O)$
Cl_2CHCOO^-	0.90	0.20-0.40	0.50	0.56	0.25	0.27	2.1
$CNCH_2COO^-$	0.85	0.20-0.40	0.90	1.12	0.60	0.66-0.77	1.6
	0.90	0.20-0.40	1.0		0.70		
	0.95[d]	0.20-0.40	1.1				
$ClCH_2COO^-$	0.80	0.14-0.34	1.0	1.26	0.60	0.66-0.72	1.8
	0.85	0.14-0.34	1.0		0.60		
	0.90	0.20-0.40	1.2		0.50		
$CH_3OCH_2COO^-$	0.60	0.30-0.50	1.8	2.44	0.80	1.32	1.8
	0.80	0.30-0.50	1.9		1.0		
	0.90	0.10-0.25	2.2		1.2		
CH_3COO^-	0.50	0.14-0.34	1.25	2.70	0.50	1.27	2.1
	0.80	0.10-0.30	2.25		1.15		
$(CH_3)_2AsO_2^-$	0.20	0.20-0.40	3.2	10.5	1.3	5.76	1.8
	0.80	0.07-0.16	8.7		4.6		
$EtPO_3^{2-}$	0.10	0.03-0.07	5.3[e]	21.4[e]	4.3[e]	9.0[e]	
	0.60	0.01-0.05	13.0[e]		7.0[e]		
H_2O				0.027[f]		0.013[d]	2.1

[a] Ionic strength 1.0 M (KCl), 25 °C. [b] Range of total buffer concentration. [c] Obtained by extrapolation to 100% base form of catalyst. [d] The pH was held constant with 0.03 M methoxyacetate buffer. [e] Approximate values. [f] Second-order constants obtained as $k_H = k_0/55.5$ M $= 0.15 \times 10^{-3}/55.5 = 0.027 \times 10^{-4}\ M^{-1}\,s^{-1}$ (H_2O); $k_H = 0.071 \times 10^{-3}/55.5 = 0.013 \times 10^{-4}\ M^{-1}\,s^{-1}$ (D_2O).

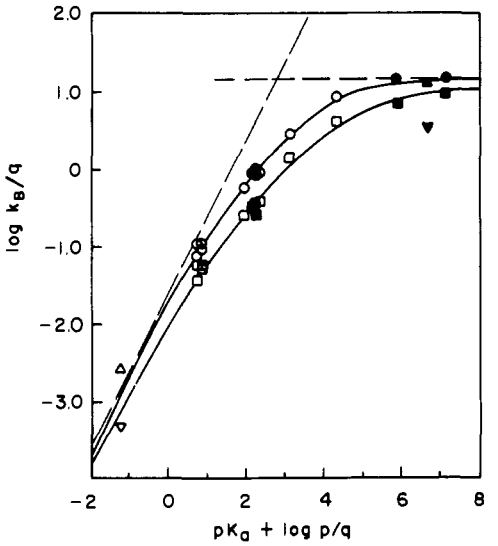


Figure 6. Brønsted plot for general base catalysis of the hydroxylaminolysis of **2** in water (upper line) and deuterium oxide (lower line) by carboxylate ions (○, □), other oxygen bases (●, ■), hydroxylamine (▲, ▼), water (△), and deuterium oxide (▽) at ionic strength 1.0 M, 25 °C. The solid lines were calculated from eq 5.

steps. This k_p step involves the proton transfer itself (which may take place through one or more intermediate water molecules) and any associated solvation changes. The upper line in Figure 6 was calculated[19] from the equation

$$k_B = \frac{K_1 k_a k_p k_b}{k_b k_p + k_{-a} k_b + k_{-a} k_{-p}} \qquad (5)$$

based on $K_1 = 1.34 \times 10^{-9}\ M^{-1}$, $k_a = k_b = 10^{10}\ M^{-1}\,s^{-1}$, $k_{-a} = k_b = 10^{11}\ s^{-1}$, $\log k_p = 10.3 + 0.5\Delta pK$, and $\log k_{-p} = 10.3 - 0.5\Delta pK$, with $\Delta pK = pK_{AH} - 2.85$. The calculated line shows good agreement with the observed catalytic constants.

The positive deviation of the rate constant for catalysis by water from the Brønsted line (Figure 6) and the large solvent isotope effect for water of $k_{H_2O}/k_{D_2O} = 4.7$ (Table II) provide additional evidence for the mechanism of eq 3 and 4. The rate-limiting step of the water-catalyzed reaction is the diffusional separation of H_3O^+ from T^0 with the rate constant k_b (eq 4); in the reverse direction this step is the diffusion-controlled encounter of H_3O^+ and T^0. Water generally falls on or below the Brønsted plot for most mechanisms of general base catalysis, but it is expected to fall above the line for simple rate-limiting proton transfer reactions because of the rapid rate of facilitated diffusion of the proton away from as well as toward a base[16] (it is readily shown that a positive deviation from a Brønsted plot of the rate constant for an acid in one direction of a reaction requires an equal deviation of the rate constant for the conjugate base in the other direction).

The large solvent deuterium isotope effect is expected from

Table IV. Effects of Solvents on the Catalytic Constants for the Ethylphosphonate-Catalyzed Transimination of **2** and Hydroxylamine[a]

solvent (v/v)	$EtPO_3^{2-}$ fraction base	k_{cat}, $M^{-2}\,s^{-1}$	k_B,[b] $M^{-2}\,s^{-1}$
30% glycerol	0.1	8.5	71
	0.4	29.0	
	0.6	43.4	
45% glycerol	0.1	11.9	88
	0.4	35.2	
	0.6	55.0	
60% glycerol	0.1	13.4	105
	0.4	51.1	
	0.5	59.3	
	0.6	59.3	
30% ethylene glycol	0.8	86	107[c]
45% ethylene glycol	0.8	138	172[c]
60% ethylene glycol	0.4	146	360[c]
10% methanol	0.2	13.0	48
	0.4	21.5	
	0.6	30.2	
30% methanol	0.1	23.1	137
	0.2	32.6	
	0.4	60.8	
45% methanol	0.1	47	339
	0.2	77	
	0.4	144	

[a] Ionic strength 1.0 M (KCl), 25 °C; the range of buffer concentration was 0.02-0.08 or 0.02-0.15 M. [b] Obtained by extrapolation to 100% base form of ethylphosphonate. [c] Determined from k_{cat} and an estimated third-order rate constant for catalysis by $EtPO_3H^-$

Table V. A Comparison of the Effects of Organic Solvents on the Transimination of **2** and Hydroxylamine Catalyzed by Ethylphosphonate and Hydroxylamine[a]

solvent	NH_2OH k_B/q,[b,c] $M^{-2}\,s^{-1}$	$EtPO_3^{2-}$ k_B/q,[c] $M^{-2}\,s^{-1}$
water	12.0	13.2
45% glycerol	21.4	29.4
45% methanol	52.9	113

[a] Ionic strength 1.0 M (KCl), 25 °C. [b] k_B determined as described in Figure 3. [c] Statistically corrected.[17]

Table VI. Effects of Solvents on Catalysis of the Transimination of **1** and Hydroxylamine by Acetate Buffers[a]

solvent	k_∞,[b] $M^{-1}\,s^{-1}$	fraction base	$10^{-3}k_{cat}$, $M^{-2}\,s^{-1}$
water	530	0 (k_A)[c]	3.3
		20	4.7
		50	7.5
		80	9.5
		100 (k_B)[d]	11.5
45% glycerol	887	0 (k_A)[c]	3.3
		20	5.3
		50	8.4
		80	11.5
		100 (k_B)[d]	13.7
45% methanol	1830	0 (k_A)[c]	5.0
		10	5.8
		20	13.8
		30	14.2
		40	17.5
		50	23.4
		100 (k_B)[d]	40.3

[a] Ionic strength 1.0 M (KCl), 25 °C. [b] Rate constant for the uncatalyzed addition step, determined in 0.1–0.25 M hydrochloric acid solutions. [c] Rate constant for buffer acid catalysis, obtained by extrapolation to 100% acid. [d] Rate constant for buffer base catalysis, obtained by extrapolation to 100% base.

the known equilibrium isotope effects for the dissociation of acids. The equilibrium isotope effect on the proton-transfer step $T_1^+ \rightleftharpoons T^0{\cdot}L_3O^+$ is expected to be similar to the value of $K_{H_2O}/K_{D_2O} = 3.2$ for the dissociation constants of NH_3OH^+ and ND_3OD^+. Since this step occurs before the rate-limiting separation of T^0 and L_3O^+ (k_b, eq 4), the equilibrium isotope effect for this step will appear in the observed rate constant. The difference between this value of 3.2 and the observed isotope effect of 4.7 probably reflects a decrease in the rate of facilitated diffusion in deuterium oxide. Water occupies a special position as a general base catalyst with respect to solvent isotope effects for this mechanism of catalysis, because there is little or no solvent isotope effect for the equilibrium transfer of a proton between a protonated intermediate and most other bases.

The solvent isotope effects for catalysis by carboxylate ions and other oxyanions exhibit a maximum near pK = 2.9 (Figure 7). The solid line in Figure 7 and the lower line in Figure 6 were calculated from eq 5 assuming a constant isotope effect of $k_{H_2O}/k_{D_2O} = 3.0$ for the k_p and k_{-p} steps and a 20% decrease in the rate constants for the diffusional steps in deuterium oxide.[20] The calculated line provides a satisfactory fit to the data for carboxylate catalysts (open circles, Figure 7), but only a limited quantitative significance should be attached to this agreement in view of the scatter of the data and the fact that the parameters in eq 5 can be varied somewhat without disturbing the agreement seriously.[21]

This solvent isotope effect maximum near the calculated pK of T_1^+ provides further evidence in support of the mechanism

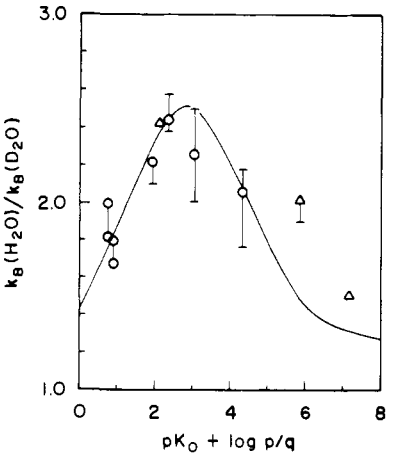


Figure 7. Solvent deuterium isotope effects on the general-base-catalyzed hydroxylaminolysis of **2** by carboxylate (○) and other oxy anion (△) catalysts. The bars represent the estimated errors for the determination of k_B from plots such as those in Figure 2 and the connected circles represent experimental points determined at 99% anion. The solid line was calculated from eq 5 as described in the text.

of eq 3 and 4 and suggests that the k_p step is kinetically significant. A similar isotope effect maximum has been observed for catalysis of the addition of methoxyamine to *p*-methoxybenzaldehyde by trapping the addition intermediate $T^\pm$ with general acids.[22] The isotope effects in these reactions can be accounted for entirely by a change in rate-limiting step with a constant isotope effect on the k_p step, which has its maximum effect on the observed catalytic constant at $\Delta pK = 0$. However, the results are also consistent with a maximum in the isotope effect for the k_p step itself with changing pK of the catalyst. Evidence for such a change in isotope effect has been obtained for general acid catalysis of the addition of methoxyamine to phenyl acetate through a preassociation mechanism.[23] The small limiting isotope effects that are approached for strong and weak base catalysts are consistent with predominantly rate-limiting diffusional steps, k_a and k_b, for these catalysts and a small or negligible equilibrium isotope effect for the addition of hydroxylamine to **2** in the K_1 step, which is expected to involve little or no change in the fractionation factors for the protons of hydroxylamine.[24] The solvent isotope effects for the uncharged bases hydroxylamine and cacodylic acid are larger than those for oxy anion bases of comparable pK (Table II). A similar difference between the isotope effects for nitrogen and oxy anion bases has been observed by Kresge and coworkers in the decomposition of nitramide catalyzed by strong bases, for which the proton-transfer step is believed to be partially rate determining.[25] It is not certain whether these differences are a consequence of the difference in the charge or the nature of the proton-accepting atom in these bases.

The absence of a change in rate-limiting step in the presence of up to 0.16 M cacodylate anion gives a value of $k_{-1} \geq 1.6 \times 10^9\ s^{-1}$ for expulsion of hydroxylamine from T_1^+, calculated as described previously[2] and taking $k_{-1} \geq 10k_a[A^-]$; this may be compared to a value of $k_{-1} \geq 4 \times 10^7\ s^{-1}$ for **1**.[2] Assuming equal values of k_a for cacodylate anion for the reactions of **1** and **2**, the ratio of the observed catalytic constants gives a more favorable value of K_1 for hydroxylamine addition to **1** by a factor of 5.8×10^2. This may be compared to an estimated difference of 7×10^4 between the equilibrium constants for hydration of benzaldehyde and benzophenone;[26] the *p*-methoxy substituent on **1** contributes to the smaller ratio for the hydroxylamine reaction with **1** and **2**.

Hydrolysis Reaction. General base catalysis of the hydrolysis of **2** presents an entirely different picture that is consistent with a concerted mechanism of catalysis, as suggested previously.[3]

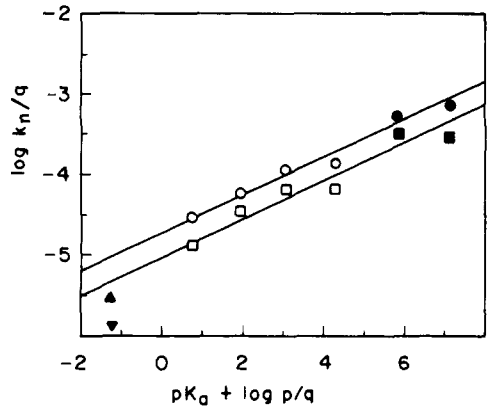


Figure 8. Brønsted plot for general base catalysis of the hydrolysis of **2** in water (upper line) and deuterium oxide (lower line) by carboxylate ions (○, □), other oxygen bases (●, ■), water (▲), and deuterium oxide (▼) at ionic strength 1.0 M, 25 °C.

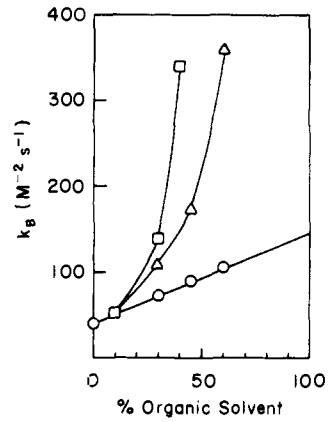
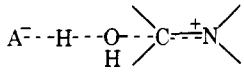


Figure 9. The effect of glycerol (○), ethylene glycol (△), and methanol (□) on k_B for catalysis of the hydroxylaminolysis of **2** by ethylphosphonate dianion at ionic strength 1.0 M, 25 °C.

The Brønsted plot for oxy anion bases is linear, rather than curved, with $\beta = 0.24$ (Figure 8). The solvent isotope effects are constant within experimental error at $k_{H_2O}/k_{D_2O} = 1.9 \pm 0.2$ and show no indication of a trend or isotope effect maximum with changing pK (Table III). The rate constant for catalysis by water shows a negative deviation from the Brønsted line, rather than the positive deviation that is observed in the hydroxylaminolysis reaction. This negative deviation could result from a favorable electrostatic interaction[27] of the oxy anion bases with the positively charged transition state for attack of water on **2**. All of these data are consistent with the transition state



for a concerted reaction mechanism. This appears to be the characteristic mechanism for general acid-base catalysis of the addition and expulsion of ROH at electrophilic carbon centers.[28] The constant Brønsted coefficient and isotope effect suggest a constant amount of proton transfer in the transition state, with changing acid strength, which is consistent with the behavior that is expected for the transition state of a concerted reaction on a three-dimensional reaction coordinate-energy diagram.[28]

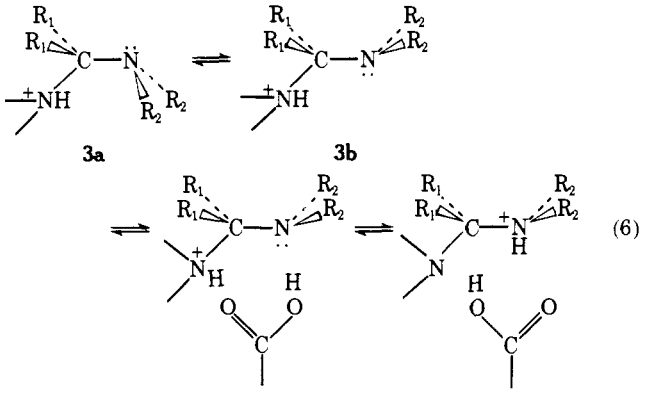
Solvent Effects. A comparison of the effects of glycerol, ethylene glycol, and methanol on the rate constants for catalysis by ethylphosphonate dianion of the reaction of **2** with hydroxylamine (Table IV) is consistent with the trapping mechanism of eq 3 and 4, but does not provide strong support for the mechanism because of the uncertainties introduced by large solvent effects on the rate. As shown in Figure 9, glycerol causes a small increase in the observed rate constants (open circles), rather than the expected decrease with increasing viscosity that is expected for a diffusion-controlled reaction. However, much larger increases in k_B are found with the less viscous ethylene glycol (triangles) and methanol (squares) as cosolvents. The ratios of the rate constants in glycerol and methanol at the same fraction organic solvent (v/v) follow approximately the expected inverse dependence on solvent viscosity that is expected for a diffusion-controlled reaction, but this result is of doubtful significance because it is unlikely that methanol is a satisfactory model for the "solvent effect" of glycerol on the rate in the absence of viscosity effects.

Catalysis of the reaction of **1** with hydroxylamine, which is also believed to proceed through a trapping mechanism,[2] shows similar behavior with little or no effect of 45% glycerol on the rate constant for catalysis by acetic acid and acetate ion, and a larger increase of these rate constants in the presence of 45% methanol (Table VI). Again, a clear-cut conclusion is difficult because of the small magnitude of the changes and the observation of somewhat similar effects of these solvents on the uncatalyzed step at high buffer concentrations (k_∞, Table VI). It is possible that diffusional steps are only partially rate limiting for these catalysts.

The rate increases in the presence of methanol and other organic solvents represent a stabilization of the addition intermediates, T^+, and the transition states for their reactions, relative to hydroxylamine and the cationic imines **1** and **2**, but the reason for this differential stabilization is not known. The intermediate T^+ is a protonated hydroxylamine derivative and some of the stabilization may reflect the stabilization of protonated "α-effect" compounds, by about 100-fold, relative to the free amine in methanol compared with water,[29] but only a small increase in the apparent pK of hydroxylamine itself was observed in the aqueous alcohol solutions examined here (Experimental Section). This stabilization may reflect, in part, a more favorable solvation of the protons on amine cations by alcohols than by water.[30] Pollack and co-workers have shown that cationic protonated imines are destabilized by up to 1000-fold relative to the uncharged imines in the presence of organic solvents, whereas there is a much smaller effect on the pK_a of the protonated parent amine.[31] The solvent effects are not caused by destabilization of the ethylphosphonate dianion, because similar effects are observed with the neutral base, hydroxylamine (Table V). It was also found that 45% methanol causes a fourfold increase in the pH-independent rate constant for the hydrolysis of **1**, which can be attributed to the same destabilizing effect of the organic solvent; however, 45% glycerol has no effect on this rate constant.

Acid Catalysis and Bifunctional Catalysis. In contrast to the transimination of **1** with hydroxylamine, the transimination reaction of **2** shows no detectable catalysis by the proton or carboxylic acids. Catalysis by carboxylic acids in the reaction of **1** was attributed to bifunctional acid-base catalysis of proton transfer after rotation or inversion of the initially formed product **3a** to **3b**, in which the proton donor and acceptor are on the same side of the molecule.[2] The formation of **3a** as the initial product is in agreement with the principle of stereoelectronic control, but the rapid isomerization to **3b** and the kinetically significant proton transfer step are inconsistent with other parts of this hypothesis.[32]

Inspection of molecular models shows that the *spp* conformation **3b** of the addition compound of **2** has unfavorable nonbonded interactions between the two phenyl groups and two methyl groups. This provides an explanation for the failure of the dimethylamino group to undergo rotation or inversion to this structure and, hence, for the absence of bifunctional catalysis. The absence of detectable acid catalysis may be at-



(6)

tributed to the difficulty of protonating the weakly basic, hindered dimethylamino group of T_1^+, so that base-catalyzed proton removal from the hydroxylammonium group of T_1^+ is the lowest energy, observed reaction pathway. The two phenyl groups interfere with the approach of an acid to the dimethylamino nitrogen atom and are likely to lower the pK_a of this group even below the estimated value of 1.8 by providing an unfavorable nonpolar environment to the protonated species in T^{2+}, so that protonation of the dimethylamino group occurs only after the deprotonation of T_1^+ to give the more basic T^0.

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Stereoelectronic Control in Acid and Base Catalysis of Amide Hydrolysis. A Theoretical Study

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Abstract: The intrinsic stereoelectronic properties of the protonated, $CH(OH)_2NH_3^+$, and deprotonated, $CH(OH)(NH_2)O^-$, model species for acid- and base-catalyzed decomposition of the tetrahedral intermediate in amide hydrolysis have been computed: nitrogen protonation leads to selective weakening of the C–N bond; hydroxyl deprotonation causes unselective weakening of both C–N and C–OH bonds; both effects are subject to strong conformational dependence. The conformational dependence of these effects is of the same magnitude as the effect of protonation itself. With respect to the neutral species, *acid catalysis* enhances both the reactivity and C–N/C–O selectivity of the C–N cleavage; on the other hand, *base catalysis* facilitates the cleavage of both the C–N and C–OH bonds but not the selectivity. Furthermore, the effects are larger for acid catalysis than for base catalysis. A limited study of the influence of binding to metal ions and of hydration has been performed. Coordination of Mg^{2+} to the nitrogen site of $CH_2(OH)NH_2$ leads to effects similar to protonation. Hydration of $CH_2(OH)NH_3^+$ by a water molecule slightly decreases the magnitude of the stereoelectronic effects. The results are discussed with respect to experimental results on amide hydrolysis and enzyme-catalyzed reactions. They also give information about the *stereochemistry of proton-transfer* reactions.

Amide hydrolysis, a reaction of fundamental importance in chemistry and biology, proceeds via a tetrahedral intermediate whose properties have been shown by previous experimental[1] and theoretical[2,3] work to be subject to control by conformation-dependent stereoelectronic effects.

The theoretical results for *neutral* aminodihydroxymethane, $CH(OH)_2NH_2$ (**1–15**)(T^0), show that bond lengthening and weakening occur in those conformations where the bond under

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