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Relative Reactivity of Amines and Oxyanions toward Proton Abstraction from Nitroethane. Electrostatic Effects and the Reactivity–Selectivity Principle

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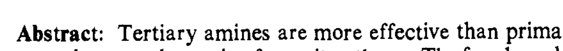
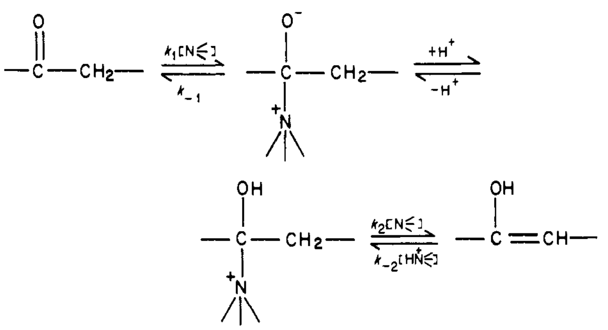
Abstract: Tertiary amines are more effective than primary and secondary amines which are more effective than oxyanions toward proton abstraction from nitroethane. The four homologous series of bases give rise to catalytic rate constants for nitroethane ionization that fall on three separate Brønsted plots: for tertiary amines $\beta = 0.45$, for primary and secondary amines $\beta = 0.60$, and for oxyanions $\beta = 0.71$. The increase in the Brønsted β value with decreasing reactivity is in accord with the reactivity–selectivity principle. In nitroethane ionization a tertiary amine with a conjugate acid of $pK_a = 10.0$ is 13-fold and one of $pK_a = 6.2$ is 130-fold more reactive than an oxyanion with a conjugate acid of the same pK_a. These are much smaller rate ratios than were observed in the enolization of oxaloacetate where tertiary amines were found to be 800-fold and 2200-fold more reactive than oxyanions of $pK_a = 10.0$ and 6.2, respectively, giving further support to the previously proposed nucleophilic addition–elimination mechanism for tertiary amine catalyzed enolization of oxaloacetic acid. The greater reactivity of tertiary amines compared to oxyanions is ascribed to energy-lowering and energy-raising electrostatic interactions between the catalyst and the anionic charge developing on the substrate in the transition state. With primary and secondary amines the degree of transition-state electrostatic stabilization is decreased by solvation. Electrostatic stabilization can also be affected by certain functional groups in the amine.

In a recent study of the base-catalyzed interconversion of the keto–enol tautomers of oxaloacetic acid we found that tertiary amines were much more effective catalysts than were oxyanions.[1] Depending on the pK_a, the second-order rate constants for catalysis by tertiary amines were from 800 ($pK_a = 10.0$) to 2200 ($pK_a = 6.2$) times greater than the oxyanion second-order rate constants. It has been well established that in the presence of oxygen bases keto–enol interconversion takes place by the general base catalyzed mechanism shown in eq 1. This mechanism involves rate-limiting proton removal from the α-carbon in the forward direction and rate-limiting proton donation to the α-carbon in the reverse direction. We believe that the rate acceleration observed in the presence of tertiary amines was too great to be attributed solely to the enhanced ability of tertiary amines in abstracting a proton from carbon. The surprisingly effective catalytic power of tertiary amines together with other kinetic evidence led us to propose that in the presence of tertiary amines keto–enol interconversion does not take place by the general base catalyzed mechanism of eq 1 but occurs instead by the nucleophilic addition–elimination mechanism of eq 2 in which the initial step is nucleophilic attack of the tertiary amine on the ketone carbonyl group rather than proton abstraction from the α-carbon.



$$-\overset{O}{\overset{\|}{C}}-CH_2- \underset{k_{-1}[B]}{\overset{k_1[B]}{\rightleftharpoons}} -\overset{O}{\overset{\|}{C}}-\underset{-}{CH}- \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} -\overset{OH}{\overset{|}{C}}=CH- \quad (1)$$



(2)

To substantiate our proposal for a change in the mechanism of keto–enol interconversion in the presence of tertiary amines, quantitative information was needed concerning the relative ease with which tertiary amines and oxyanions are able to remove a proton from carbon employing a system in which the amine is precluded from acting as a nucleophile. This paper describes the relative effectiveness of a series of oxyanions and primary, secondary, and tertiary amines as general base catalysts in the removal of a proton from nitroethane.

The reactivity–selectivity principle states that, within a series of similar reactions, reactivity and selectivity should exhibit an inverse correlation: a set of reagents exhibiting a high reactivity toward a given substrate (or a set of substrates exhibiting a high reactivity toward a given reagent) should show limited selectivity while those exhibiting low reactivity should be characterized by a higher selectivity.[2] Rarely, however, is the reactivity–selectivity principle experimentally realized, and as a consequence its fundamental validity has been frequently questioned.[3] Failure of the principle, however, has been attributed to unsatisfactory use of reactivity and selectivity parameters or to a reaction choice which lies outside the limitations of the principle, i.e., reactions in which more than one bond is broken and one bond is formed in the transition state, reactions involving a change in mechanism or a change in rate-limiting step, etc.[2c] The single one-step base-catalyzed removal of a proton from nitroethane employing four different homologous series of bases (primary amines, secondary amines, tertiary amines, and oxyanions) would appear to be a satisfactory reaction for investigation of the experimental applicability of the reactivity–selectivity principle.

Experimental Section

Materials. Nitroethane (Aldrich) and liquid amines were redistilled. Imidazole was recrystallized from acetone–petroleum ether and hydrazine hydrochloride from ethanol–ether. Other reagents used were the best available commerical grades. All solids were dried in a vacuum desiccator over P_2O_5.

Buffer Solutions. The buffer solutions were prepared immediately prior to use by the addition of standardized KOH to the amine hydrochloride or alcohol and standardized HCl to the amine free base.

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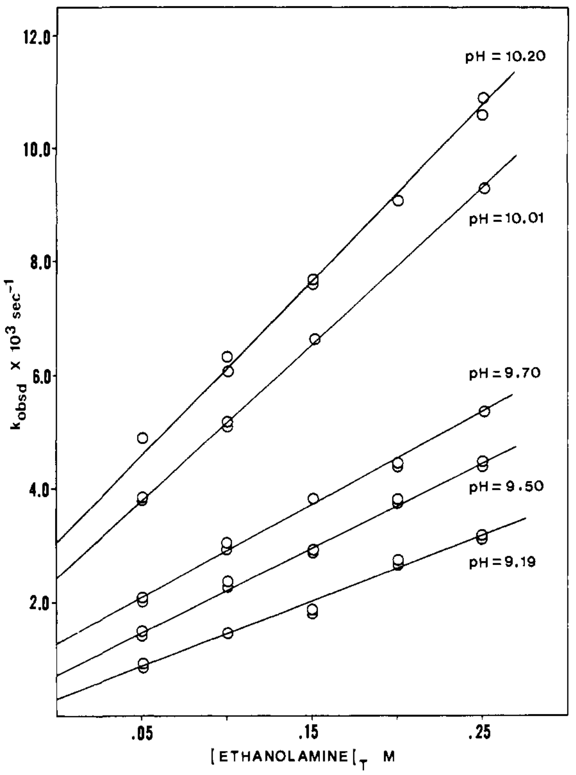

Figure 1. Plots of the observed first-order rate constants for removal of a proton from nitroethane by ethanolamine at five hydrogen ion concentrations vs. the total concentration of ethanolamine.

Phosphate buffer solutions were prepared by using KH_2PO_4 and 1.0 M KOH and carbonate buffer solutions by using K_2CO_3 and 1.0 M HCl. Doubly distilled water was used for all solutions. Buffer solutions were maintained at $\mu = 1.0$ (KCl) and contained 1×10^{-4} M EDTA to sequester extraneous metal ions. The pK_a of each of the buffers employed was determined from pH measurements of partially neutralized solutions at 30.0 °C and $\mu = 1.0$. The pH of the serial buffer dilutions agreed within ±0.03 pH unit. Readings of pH were determined on a Radiometer Type 26 pH meter.

Kinetic Measurements. A stock solution of nitroethane was prepared in peroxide-free dioxane. A 0.025-mL sample of the stock solution was added to 3 mL of a solution of the base at a pH within ±1 of its pK_a, allowing it to act as its own buffer. The reactions were carried out under the pseudo-first-order conditions of $[\text{buffer}]_T \gg [\text{nitroethane}]$; the concentration of nitroethane in the reaction mixture was 7×10^{-5} M. Reaction rates were determined at 30.0 °C by following the change in absorbance at 240 nm using either a Cary 16 or a Perkin-Elmer Lambda 3 spectrophotometer. Several buffers (quinuclidine, 3-quinuclidinol, *N*-methylmorpholine, 2-(diisopropylamino)ethanol, and propargyl alcohol) exhibited significant absorbance at 240 nm; in such cases the change in nitroethane absorbance was monitored at 250 nm. The rates of the most reactive bases were determined by using a Durrum D-110 stopped-flow spectrophotometer interfaced to a North-Star microcomputer for data digitation and storage employing an On-Line Instrument Systems 3820 stopped-flow program.[4] To minimize pH changes on mixing, uneven (1:5) mixing cylinders were used; the smaller cylinder contained an aqueous solution of nitroethane (2×10^{-4} M) and the larger cylinder the buffer solution. The pH of the reaction mixture was determined after mixing. The relative volumes of the mixing cylinders and the dead time of the spectrophotometer were checked by mixing 0.01 M $Fe(NO_3)_3$ in 0.1 N H_2SO_4 (large cylinder) and 0.05 M KSCN (small cylinder) solutions; the dead time was found to be less than 4 ms. A Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer was used to determine the second-order rate constant for hydroxide ion.[5] All spectrophotometers were thermostated.

Rate constants were calculated by manual digitation of rate traces using a Hewlett-Packard 9820A computer/9864A digitizer. Calculation of least-squares slopes and intercepts was done with the HP 9820A computer.

Table I. Second-Order Rate Constants and Equilibrium Constants for the Reaction of a Variety of Catalysts with Nitroethane in Water at 30 °C, $\mu = 1.0$

no.	catalyst	pK_a[b]	k_{gb}, M^{-1} s^{-1}	k_{ga}, M^{-1} s^{-1}	$pK_{a(NE)}$
1	quinuclidine	11.38	2.54		
2	triethylamine	11.08	1.37		
3	2-(diisopropylamino)ethanol	10.28	7.41×10^{-2}		
4	3-quinuclidinol	10.04	6.70×10^{-1}		
5	trimethylamine	10.00	7.40×10^{-1}		
6	3-chloroquinuclidine	8.96	2.57×10^{-1}	3.86×10^{-2}	8.14
7	*N*-methylmorpholine	8.07	6.26×10^{-2}	1.98×10^{-1}	8.57
8	Hepes[a]	7.57	1.81×10^{-2}	1.11×10^{-1}	8.36
9	3-quinuclidinone	7.46	4.48×10^{-2}	1.55×10^{-1}	8.00
10	*N*-methylimidazole	7.24	3.01×10^{-3}	2.06×10^{-2}	8.08
11	imidazole	7.18	1.65×10^{-3}	2.17×10^{-2}	8.30
12	arginine (guanidino group)	12.66	5.60		
13	guanidine	12.56	6.51		
14	piperidine	11.49	1.10		
15	diethylamine	11.37	8.94×10^{-1}		
16	ethylamine	11.12	6.00×10^{-1}		
17	dimethylamine	10.94	6.34×10^{-1}		
18	methylamine	10.63	3.75×10^{-1}		
19	proline	10.57	3.09×10^{-1}		
20	2-(methylamino)-ethanol	10.18	1.70×10^{-1}		
21	allylamine	9.97	9.48×10^{-2}		
22	ethanolamine	9.70	3.80×10^{-2}		
23	glycine	9.65	2.86×10^{-2}	2.19×10^{-3}	8.53
24	morpholine	9.28	1.49×10^{-1}	8.84×10^{-2}	9.05
25	arginine (amino group)	9.12	2.59×10^{-2}	3.07×10^{-3}	8.19
26	diaminopropane[c]	9.02	4.42×10^{-2}	4.24×10^{-3}	8.00
27	Tris[a]	8.30	6.70×10^{-3}	7.10×10^{-3}	8.33
28	glycylglycine	8.25	8.34×10^{-3}	8.92×10^{-3}	8.28
29	hydrazine[c]	8.03	6.92×10^{-3}	1.01×10^{-2}	8.19
30	Tricine[a]	7.98	9.27×10^{-3}	2.25×10^{-2}	8.37
31	glycine ethyl ester	7.58	7.04×10^{-3}	1.69×10^{-2}	7.96
32	hydroxide	15.75	8.91		
33	propargyl alcohol	13.55[d]	20.4		
34	trifluoroethanol	12.37[d]	2.27		
35	PO_4^{3-}	11.44	4.40×10^{-1}		
36	carbonate	9.66	3.37×10^{-2}		

[a] Hepes = *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid, Tricine = *N*-tris(hydroxymethyl)methylgylcine, Tris = tris(hydroxymethyl)aminomethane; see ref 7. [b] The pK_a of the conjugate acid was determined from pH measurements of partially neutralized solutions under the conditions of the kinetic experiments except where otherwise indicated. [c] No statistical corrections have been made. [d] Reference 8.

Results

The observed rate constants for base-catalyzed ionization of nitroethane (eq 3) can be expressed as in eq 4 where k_{ly} is the

$$CH_3CH_2NO_2 \underset{k_{ga}[HB]}{\overset{k_{gb}[B]}{\rightleftharpoons}} CH_3CH{=}NO_2^- \qquad (3)$$

$$k_{obsd} = k_{ly} + k_{gb}\frac{K_a}{K_a + a_H}[B]_T + k_{ga}\frac{a_H}{K_a + a_H}[B]_T \qquad (4)$$

rate of the lyate species catalyzed reaction, k_{gb} and k_{ga} are the second-order rate constants for general base and general acid catalysis, K_a is the acid dissociation constant of the buffer, a_H is the hydrogen ion activity determined at the glass electrode, and $[B]_T$ is the total concentration of buffer species present, i.e., [HB] + [B]. Plots of k_{obsd} vs. $[B]_T$ (Figure 1) give slopes which, when divided by the mole fraction of buffer present in the basic form $[K_a/(K_a + a_H)]$, give values of $k_{gb} + k_{ga}(a_H/K_a)$. Values of k_{gb} and k_{ga} are obtained from the intercepts and slopes, respectively, of plots of $[\text{slope}/K_a/(K_a + a_H)]$ vs. a_H/K_a. Such plots obtained with 3-quinuclidinone and glycylglycine buffers are shown in Figure 2. For catalysts whose conjugate acids have pK_a's > 9.5, $k_{gb} \gg k_{ga}$, and eq 4 simplifies to give eq 5. In such cases plots of k_{obsd} vs. $[B]_T$ give slopes which, when divided by $[K_a/(K_a + a_H)]$, give values of k_{gb} directly. For catalysts whose conjugate

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$$k_{\text{obsd}} = k_{\text{ly}} + k_{\text{gb}}\frac{K_a}{K_a + a_H}[\text{B}]_T \qquad (5)$$

acids have pK_a's < 7, $k_{ga} \gg k_{gb}$, and only the general acid term of eq 4 is detectable. Values of k_{gb} and k_{ga} are listed in Table I. Propargyl alcohol and trifluoroethanol exhibited a significant change in pH with buffer concentration and upon stopped-flow mixing with substrate. For these bases the pH of the reaction mixture was determined after reaction; the k_{gb} values were individually calculated from eq 5, employing values of k_{ly} and $[K_a/(K_a + a_H)]$ calculated from the final pH of the reaction mixture. The values of k_{gb} given in Table I for these two alcohols are the average of 10–15 such calculations. The second-order rate constant for hydroxide ion was (a) calculated from the intercept values of buffer dilution plots at zero buffer concentration and (b) determined in the absence of buffers with a pH-stat assembly.

The logs of the k_{gb} values for general base catalyzed removal of a proton from nitroethane are plotted in Figure 3 vs. the pK_a of the conjugate acid of the base. These values result in a Brønsted β value of 0.45 (correlation coefficient = 0.9985) for removal of a proton by tertiary amines (triangles), a β value of 0.60 (correlation coefficient = 0.9952) for removal of a proton by primary and secondary amines (circles), and a β value of 0.71 (correlation coefficient = 0.9976) for proton removal by oxyanions (squares). The second-order rate constants determined for glycine, arginine (pK_a = 9.12), ethanolamine, Tris, morpholine, hydroxide ion, triethylamine, 2-(diisopropylamino)ethanol, *N*-methylmorpholine, and Hepes were not used in the calculation of the β values, the first six for reasons explained in the Discussion and the last four because of steric hindrance. Although *N*-methylmorpholine exhibits only a small negative deviation from the Brønsted plot for tertiary amines, it was omitted in the calculation of the β value since it has been previously reported to exhibit steric hindrance toward proton removal.[6]

In Figure 4 are plotted the logs of the second-order rate constants for general acid catalyzed protonation of nitroethane anion vs. the pK_a of the general acid. The catalytic rate constants for protonation by primary ammonium ions and by imidazolium and *N*-methylimidazolium ions give rise to an α value of 0.41 (correlation coefficient = 0.9949). The ammonium ions of only two of the secondary amines and three of the tertiary amines investigated were of sufficiently low pK_a to exhibit a general acid catalytic term. Thus there are insufficient data to relate their acidity and catalytic activity particularly since one of the secondary amines is morpholine which exhibits anomalous behavior and two of the tertiary amines evidence steric hindrance in the Brønsted plot for general base catalysis.

The equilibrium constant for eq 3 is given by eq 6. The acid

$$K_{eq} = k_{gb}/k_{ga} = [\text{HB}][\text{CH}_3\text{CH}{=}\text{NO}_2^-]/[\text{B}][\text{CH}_3\text{CH}_2\text{NO}_2] \qquad (6)$$

dissociation constant for nitroethane ($K_{a(\text{NE})}$) can thus be calculated from eq 7 where K_a is the acid dissociation constant of the buffer

$$K_{a(\text{NE})} = K_a k_{gb}/k_{ga} \qquad (7)$$

species and k_{ga} and k_{gb} are the catalytic constants determined for that buffer. The calculated acid dissociation constants for nitroethane are listed in Table I. Excluding values obtained with amines whose second-order acid and/or base catalytic rate constants exhibit steric hindrance or other irregular behavior, the mean value of the kinetically determined pK_a of nitroethane is 8.15. The pK_a determined by half-neutralization at 30 °C has been reported to be 8.4.[9]

Discussion

A comparison of the reactivity of tertiary amines and oxyanions in the ionization of nitroethane clearly indicates that tertiary

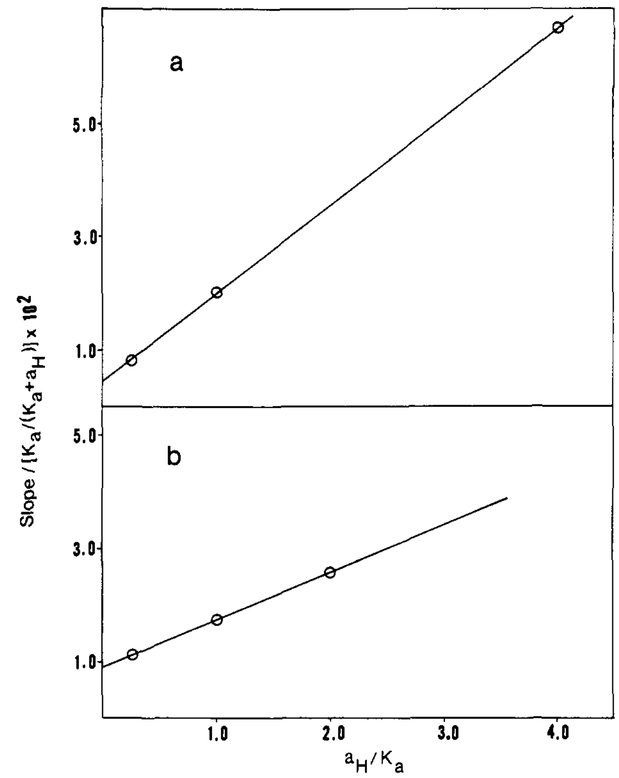

Figure 2. Plots of the slopes of buffer dilution plots divided by the mole fraction of buffer present in the basic form vs. the mole fraction of buffer present in the acidic form divided by the mole fraction of buffer present in the basic form: (a) 3-quinuclidinone buffer; (b) glycylglycine buffer.

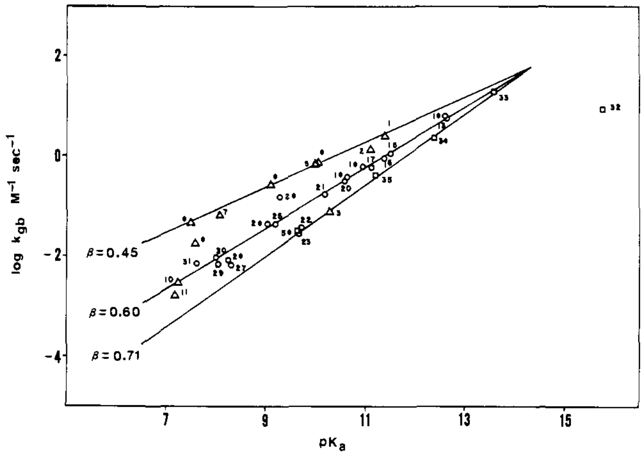

Figure 3. Brønsted plots for the general base catalyzed ionization of nitroethane employing tertiary amines (△), primary and secondary amines (○), and oxyanions (□) as catalysts.

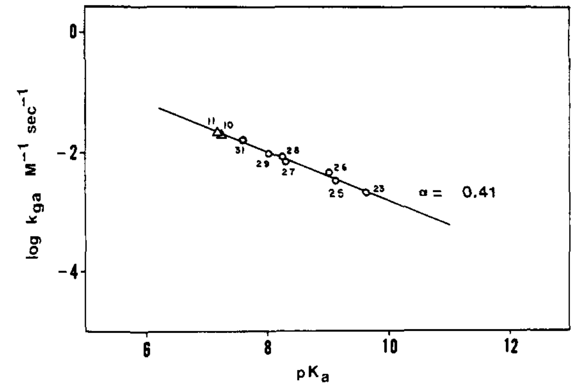

Figure 4. Brønsted plot for the general acid catalyzed protonation of nitroethane anion by primary ammonium ions (○) and by imidazolium and *N*-methylimidazolium ions (△).

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amines are more effective general base catalysts toward removal of a proton from carbon (Figure 3). A tertiary amine with a conjugate acid of $pK_a = 10.0$ is 13-fold more reactive toward proton abstraction from carbon than is an oxyanion with a conjugate acid of the same pK_a. If the reactivity difference at $pK_a = 6.2$ is compared, the amine is found to be 130-fold more reactive. These are very much smaller rate enhancements than were observed under the same experimental conditions in the enolization of oxaloacetic acid where tertiary amines were found to be 800-fold and 2200-fold more reactive than oxyanions with conjugate acids of $pK_a = 10.0$ and 6.2, respectively. Both nitroethane ionization and general base catalyzed enolization (eq 1) involve removal of a proton from carbon with the possibility of delocalization of the negative charge to a neighboring oxygen atom. In nitroethane ionization the amine can act only as a general base catalyst; in the enolization reaction the amine can act either as a general base (eq 1) or as a nucleophile (eq 2). The very large difference in rate acceleration evidenced by tertiary amines in the two reactions suggests that, while tertiary amines and oxyanions are both functioning as general base catalysts in nitroethane ionization, they are not both acting as general base catalysts in the interconversion of the keto–enol tautomers of oxaloacetic acid. This gives further substantiation to the proposal that tertiary amines catalyze the latter reaction via the nucleophilic addition–elimination mechanism of eq 2.[1]

The second-order rate constant for the reaction of 2-(diisopropylamino)ethanol with nitroethane falls on the Brønsted plot established for the oxyanion catalytic rate constants (Figure 3). Apparently the enhanced reactivity of the amine, compared to an oxyanion, toward proton removal is compensated by its decreased reactivity as a result of steric hindrance. Steric hindrance toward proton removal from carbon has been well documented.[6,10] In the study of the interconversion of the keto–enol tautomers of oxaloacetic acid, it was found that this amine exhibited behavior characteristic of oxyanions, and it was concluded that, unlike the other tertiary amines investigated, it catalyzed enolization by the general base catalyzed mechanism of eq 1. As in the present study, its second-order rate constant fell on the Brønsted plot with the oxyanion catalysts. Thus in both nitroethane ionization and in oxaloacetate enolization, the catalytic reactivity of 2-(diisopropylamino)ethanol is that expected for an oxyanion of the same pK_a. Steric factors cause 2-(diisopropylamino)ethanol to be 12-fold less reactive toward nitroethane ionization than would be expected for a nonhindered tertiary amine of the same pK_a. This same amine, however, was found to be more than 300-fold less reactive than a tertiary amine of similar pK_a participating in nucleophilic addition–elimination catalysis of keto–enol interconversion. For the sake of comparison, the steric factors associated with triethylamine were responsible for a 1.5-fold decrease in reactivity in nitroethane ionization and a 6-fold decrease in reactivity in enolization via the nucleophilic addition–elimination mechanism. This would suggest that the large decrease in the rate of enolization observed with 2-(diisopropylamino)ethanol is not due simply to steric hindrance but to a change in reaction mechanism, from the nucleophilic addition–elimination mechanism to the general base catalyzed mechanism, as a result of that steric hindrance as we have previously proposed.[1]

The Brønsted relationship for proton-transfer processes has been extensively studied and has been the subject of numerous reviews.[11]

The theoretical relationship initially proposed by Brønsted,[12] and subsequently expanded by Eigen,[11a,13] predicts that the slope of the linear free energy relationship should characterize the position of the transition state along the reaction coordinate. In a base-catalyzed proton-transfer reaction the position of the proton will be closer to the weaker base in the transition state. Thus, if a series of bases of a sufficiently large pK_a range are employed, the transition state should become progressively more product-like with decreasing basicity of the catalyst and the Brønsted β value should vary continuously between 0 and 1. Experimentally this has been difficult to verify since curvature in Brønsted plots can reflect differences other than in transition-state structures; differences in solvation and resonance, as well as structural differences in the basic catalysts, can give rise to nonlinear Brønsted relationships.[3a,14] Most proton-transfer reactions, however, even those investigated over a wide range of pK_a, are characterized by linear Brønsted plots, indicating an insensitivity of the transition state to changes in the strength of the donor or acceptor species.[3a,15]

The ionization of nitroethane catalyzed by four different homologous series of bases gives rise to catalytic rate constants that fall on three separate Brønsted plots, one for tertiary amines, one for primary and secondary amines, and one for oxyanions (Figure 3). When deviations attributable to steric factors and the unusual reactivity exhibited by morpholine, glycine, arginine ($pK_a = 9.12$), ethanolamine, Tris, and hydroxide ion are ignored, good correlations are obtained within a given base type between the strength and efficacy of the catalyzing base. These correlations can be expressed in terms of the following Brønsted equations:

tertiary amines

$$\log k_{gb} = -4.675 + 0.449pK_a \tag{8}$$

primary and secondary amines[16]

$$\log k_{gb} = -6.886 + 0.604pK_a \tag{9}$$

oxyanions

$$\log k_{gb} = -8.420 + 0.713pK_a \tag{10}$$

The Brønsted plots are linear, indicating that the transition state is insensitive to the strength of the catalyzing base in the limited pK_a range employed. The transition state, however, does exhibit a marked sensitivity to base structural type. Tertiary amines are the most reactive of the base catalysts and give rise to the smallest β value; primary and secondary amines which are less reactive exhibit a greater dependence on the pK_a of the amine; oxyanions which are the least reactive are characterized by a β value which suggests an even more product-like transition state. This pronounced increase in selectivity with decreasing reactivity is in agreement with the Bell–Polanyi–Hammond–Leffler–Thornton–Marcus hypothesis:[17] lowering the energy of the transition state

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(16) Statistical corrections were not employed in the generation of eq 9. When statistical corrections are employed (ref 11f, p 173), primary and secondary amines still fall on the same Brønsted plot and the Brønsted equation becomes $\log (k_{gb}/q) = -7.344 + 0.625(pK_a + \log p/q)$, where p is the number of equivalent protons and q the number of sites which can accept a proton. The corrected equation has a correlation coefficient of 0.9930; eq 9 has a correlation coefficient of 0.9952.

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relative to reactants should lead to a more reactant-like transition state, and, conversely, raising the energy of the transition state relative to reactants should result in a transition state occurring later on the reaction coordinate.

In studies of the reaction of a series of nitroalkanes with hydroxide ion, Brønsted exponents greater than 1 and less than 0 have been reported.[18] These observations of coefficients outside the usual range 0–1 have led to questions concerning the interpretation of the significance of Brønsted exponents in carbon acid ionizations. Several explanations have been subsequently offered to explain the anomalous behavior of nitroethanes. Among these are the occurrence of interactions with differing effects on the transition state than on either reactants or products.[19] variation in the intrinsic barrier for the reaction series,[20] the necessity for extensive nuclear rearrangements,[21] the formation of a transition state with little delocalization of the developing charge to the oxygen atom of the nitro group,[15b,18,22] and a variation in the work terms caused by a variation in hydrogen bond strengths with the free energy of proton transfer.[23] These explanations center around the postulation of a transition state for nitroethane ionization with considerable charge density on carbon resulting in different effects of substituents on the rate of proton transfer than on the equilibrium constant for nitroethane ionization where the charge density in the product is localized primarily on oxygen. Thus correlations employing a single base with a series of carbon acids can give rise to anomalous β values. In the present study, where the carbon acid is constant and the base is varied, normal Brønsted exponents are obtained for the proton-transfer process.

The observed sensitivity of nitroethane ionization to base structural type (Figure 3) is in agreement with the proposed carbanion-like transition state. Removal of a proton from nitroethane by tertiary amines leads to a transition state in which the developing negative charge on carbon is electrostatically stabilized by the developing positive charge on the nitrogen atom of the amine and $\beta = 0.45$. When, however, negatively charged oxygen bases are employed as catalysts, the electrostatic effects in the transition state become destabilizing. The decrease in the reactivity of oxyanions compared with tertiary amines is associated with an increase in selectivity. The Brønsted β value of 0.71 obtained for the ionization of nitroethane by oxyanions is similar to β values (0.7,[14c] 0.75[14a]) previously reported for reactions involving oxyanion-catalyzed removal of a proton from a carbon acid. An interesting consequence of the reactivity–selectivity principle is the existence of an isokinetic pK_a beyond which the reactivity of the two base structural types must reverse: an oxyanion will be more reactive than a tertiary amine of the same pK_a. The isokinetic pK_a for nitroethane ionization is 14.3.

Primary and secondary amines fall on the same Brønsted plot.[24] They are less reactive than tertiary amines and more reactive than oxyanions, and the Brønsted exponent is also intermediate between that found for the other two series of bases. The Brønsted β value of 0.60 is similar to that (0.61) recently reported for the ionization of 2-nitropropane employing five primary amines.[25] Pearson and Williams reported a β value of 0.65 for the reaction of primary amines with nitroethane.[26] Apparently the transition state experiences less intermolecular electrostatic stabilization when the reacting base is a primary or secondary amine than when it is a tertiary amine. This may be due to a decrease in the concentration of positive charge on the amino nitrogen in the transition state as a result of hydrogen bonding by solvent to the adjacent proton(s). Hydrogen bonding could also occur with a second molecule of amine in a termolecular transition-state complex. However, no second-order dependence on amine concentration was detected at total amine concentrations up to 0.25 M.

Ethanolamine, Tris, glycine, and arginine exhibit negative deviations from the Brønsted plot for primary and secondary amines. Only the α-amino group of arginine exhibits a negative deviation; the guanidino group shows normal behavior. These four amines are primary amines possessing either a hydroxyl group (ethanolamine and Tris) or a carboxylate group (glycine and arginine) capable of forming an intramolecular hydrogen bond with one of the protons on the attacking nitrogen atom. Thus the observed negative deviations may be due to a decrease in positive charge density on the nitrogen atom in the transition state as a result of this hydrogen bonding, resulting in a decrease in electrostatic stabilization and a retardation in rate. In a study of the ionization of 2-nitropropane, postively charged primary amines have been found to give positive deviations and negatively charged primary amines negative deviations from the Brønsted plot defined by neutral primary amines. This has been attributed to a through-space electrostatic interaction between the developing negative charge on the substrate and the charged group of the catalyst.[25] A similar explanation can be used to account for the negative deviations observed in the present study for glycine and arginine but not those observed for ethanolamine and Tris. Secondary amines containing similarly positioned hydroxyl or carboxylate groups (proline, Tricine, and 2-(methylamino)ethanol) do not exhibit negative deviations from the Brønsted plot, perhaps because of unfavorable entropy changes. Positive deviations similar to the one observed here for morpholine have been observed for this amine in a variety of studies.[27] We have no satisfying explanation to account for the anomalous behavior of this amine.

The tertiary amines *N*-methylimidazole andd imidazole are about 50-fold less reactive than predicted by the Brønsted plot for tertiary amines. The second-order rate constants for these amines fall on the Brønsted plot defined by primary and secondary amines. The decreased reactivity of these amines is presumably attributable to a decrease in transition-state electrostatic stabilization as a result of a decrease in the concentration of positive charge on the attacking nitrogen by resonance delocalization to the other ring nitrogen. These amines have also been found to be less reactive than saturated tertiary amines in the dedeuteration of isobutyraldehyde-2-*d*[10b] and in the base-catalyzed elimination of hydrogen chloride from 9-fluorenylmethyl chloride.[6b] However, they exhibit reactivity characteristic of saturated tertiary amines in the base-catalyzed elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-2-decalone[28] and from 4-methyl-4-acetoxy-2-pentanone.[6a] It may be that the reactivity of imidazole and *N*-methylimidazole compared to the reactivity of saturated tertiary amines in proton transfer reactions is dependent on the nature of the transition state. Proton-transfer reactions in which imidazole and *N*-methylimidazole are less effective catalysts than saturated tertiary amines may be those with transition states possessing carbanion-like character, and thus the reactivity differences arise from differences in electrostatic stabilization. On the other hand, proton-transfer reactions in which imidazole and *N*-methylimidazole exhibit reactivity characteristic of tertiary amines may be those in which the transition state possesses little or no formal

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charge, i.e., E_2-like transition states.

Hydrazine, the only α-effect nucleophile investigated, falls on the Brønsted plot defined by primary and secondary amines. This is in agreement with the study of Pratt and Bruice which showed that there was no α-effect for proton abstraction from carbon.[29]

The positioning of catalysts on Brønsted plots according to charge type has been noted previously in reactions involving proton transfer. In the base-catalyzed decomposition of nitramide, dipositive, neutral, negative, and dinegative catalysts fall on four separate Brønsted plots.[30] In the hydrolysis of vinyl ethers, under conditions where proton donation is rate limiting, a cationic charge is developing on the substrate in the transition state, and thus the direction of catalytic efficacy is, as expected, the opposite of what is observed in nitroethane ionization; negatively charged acid catalysts are the most reactive and positively charge acid catalysts are the least reactive.[31] Reactivity differences between positively charged, neutral, and negatively charged acids have been reported for the general acid catalyzed cleavage of *N*-(*p*-nitrophenyl)-carbamate[32] and for the general acid catalyzed decarboxylation of carboxyimidazolidone.[33] None of these reactions, however, conforms to the reactivity–selectivity principle. In nitramide decomposition and in carbamate cleavage the Brønsted plots are parallel while in vinyl ether hydrolysis the least reactive homologous series of catalysts define a Brønsted plot with the smallest slope. In a study of the catalysis of α-hydrogen exchange, Hine found that saturated tertiary amines were more effective catalysts than were pyridines and oxyanions of similar pK_a.[10c] Although no explanation was offered to account for this observation, it may be yet another example of transition-state electrostatic effects in a proton-transfer reaction.

From the above it is apparent that, for reactions in which a charge is being generated on the substrate in the transition state, systematic deviations from Brønsted relations are expected to occur when nonhomologous series of catalysts are employed. If a negative charge is developing on the substrate, positively charged catalysts will experience energy lowering intermolecular interactions and negatively charged catalysts energy raising interactions. If, on the other hand, a positive charge is developing on the substrate, it will be the positively charged catalysts that will evidence negative deviations from a Brønsted plot based on neutral catalysts. The use of an inappropriate value for the acidity constant of the hydronium ion has been offered to account for the negative deviation that is frequently observed for this species in Brønsted plots describing general acid catalysis.[34] If however, the Brønsted correlation is defined by neutral acids, unfavorable electrostatic interactions may be responsible for a sizable portion of the deviation. Similarly, hydroxide ion would be expected to show a negative deviation from a Brønsted plot defined for neutral bases in a reaction where a negative charge is developing on the substrate. In the present study, however, hydroxide ion evidences a large negative deviation from the Brønsted plot defined by other negatively charged catalysts (Figure 3). This negative deviation is presumably attributable to a combination of solvation effects and a change in transition-state structure.[14a,c]

The Brønsted plot for general acid catalyzed protonation of nitroethane anion by primary ammonium ions is shown in Figure 4, $\alpha = 0.41$. The imidazolium and *N*-methylimidazolium ions fall on the plot with the primary amines similar to what was found in the reverse base catalyzed reaction.

In several studies comparing the relative effectiveness of primary, secondary, and tertiary amines as general base catalysts, the three classes of amines were found to fall on three separate and parallel Brønsted plots with tertiary amines being the most reactive and primary amines the least reactive.[6b,35] This has been attributed to the relative ability of the three classes of ammonium ions to be stabilized by solvation.[26,36] Tertiary ammoium ions are relatively poorly solvated and thus are less apt to exist in the ammonium ion form; they, therefore, are more effective general base catalysts than their pK_a's would predict. This has been substantiated by studies relating amine gas-phase basicities and free energies of protonation in water in which the three classes of amines were also found to fall on three separate and parallel plots.[37] In the present study primary and secondary amines fall on the same plot, and the plot of tertiary amines exhibits a substantially different slope. Thus, in nitroethane ionization, electrostatic effects in the transition state are apparently more important than the ground-state stabilities of the ammonium ions.

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