of the hydronium ion contribution found for prostacyclin at low $[H^+]$ must mean that the accelerative effect of the carboxylate group operates chiefly only in the hydronium ion reaction: there is little or no corresponding acceleration of general-acid-catalyzed pathways. This would seem unlikely if the carboxylate group were acting electrostatically, for that group should exert its effect in transition states formed from general acids as well as those from the hydronium ion. An electrostatic acceleration, if present, should in fact be especially prominent in reactions of positively charged general acids such as the *N*-methylmorpholinium ion studied here, but general-acid catalysis by this species was found to be barely detectable. Electrostatic effects, moreover, on proton-transfer reactions in aqueous solution are ordinarily quite small; they are of a magnitude approaching the present rate acceleration only when the proton is completely transferred and the charge is completely developed at the rate-determining transition state,[27] and in cases of partial proton transfer such as vinyl ether hydrolysis they are an order of magnitude smaller.[15c]

It has been suggested by a reviewer that the rate acceleration shown by prostacyclin in its carboxylate form may have effected a change in mechanism of this reaction from the conventional scheme for vinyl ether hydrolysis, in which carbon protonation is rate determining, to one where this step is reversible and subsequent reaction of the alkoxycarbocation intermediate is rate determining. We believe that this has not happened, for such a preequilibrium process should give an inverse hydronium ion isotope effect, $k_{H^+}/k_{D^+} < 1$, as has indeed been reported for the single example of such a mechanism for vinyl ether hydrolysis found to date.[28] We are nevertheless exploring this mechanistic possibility and will report our findings separately.

Rate accelerations attributable to intramolecular catalysis are commonly expressed as effective molarities. An effective molarity can be estimated for the present case by comparing the rate constant for the intramolecular step of the present reaction, $k_{intra} = k_{H^+}'K_a = 0.53\ s^{-1}$ (cf. eq 7), with the specific rate of hydrolysis of prostacyclin in the carboxylic acid form catalyzed by an external carboxylic acid of the same pK_a. Such a value is not available, but the similarity of the rates of hydrolysis of prostacyclin and its methyl ester noted above and evident in Figure 1 suggests that the ester may be a good model, and the rate constant for the hydrolysis of that substance by acetic acid is available: $k_{HOAc} = 0.93\ M^{-1}\ s^{-1}$. Use of this result leads to an effective molarity of 0.57 M for the present intramolecular reaction. This is a rather small value, but effective molarities for general-acid- and general-base-catalyzed reactions do tend to be small, with the important exception of the hydrolysis of certain acetals.[29]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. D_2, 7782-39-0; H_3O^+, 13968-08-6; HCO_2H, 64-18-6; $HOCH_2CO_2H$, 79-14-1; CH_3CO_2H, 64-19-7; $C_2H_5CO_2H$, 79-09-4; $CH_2ClPO_3H^-$, 54947-16-9; $CH_3PO_3H^-$, 39863-50-8; $NH_3^+(CH_2)_2NH_3^+$, 22534-20-9; D_3O^+, 24847-51-6; CH_3CO_2D, 758-12-3; $H_2PO_4^-$, 14066-20-7; $D_2PO_4^-$, 69976-02-9; prostacyclin, 35121-78-9; prostacyclin methyl ester, 61799-74-4.

Supplementary Material Available: Tables of rate data (15 pages). Ordering information is given on any current masthead page.

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Hydrogen Bonding between Solutes in Aqueous Solution[1]

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Abstract: Hydrogen bonding between protonated amines and substituted phenolate ions in water has been measured from the increase in phenolate absorbance with increasing concentration of amine buffers, at pH values below the pK_a of the phenol. This method permits measurement of hydrogen bonding between phenolate ion and acids of lower pK_a than phenol. Hydrogen bonding is weak, with an association constant of $K_{AB} = 0.81\ M^{-1}$ for the complex of phenolate ion and ethylenediamine dication at ionic strength 2.0 M (KCl), 25 °C. The absorption spectra of the hydrogen-bonded complexes are similar to those of the corresponding phenolate ions in water. This shows that the hydrogen-bonded proton in the complex is in a double-minimum energy well, with a significant barrier for transfer in the thermodynamically favorable direction. Hydrogen bonding to phenolate ion increases with increasing strength of the acid and follows a Brønsted correlation with $\alpha = 0.15$ for substituted ammonium cations. Values of K_{AB} for complexes with ethylenediamine dication increase with increasing basicity of substituted phenolate ions and are consistent with a Brønsted slope of $\beta = 0.10$. The results may be described by a Hine interaction coefficient of $\tau = \partial\alpha/\partial pK_{BH} = \partial\beta/-\partial pK_{AH} = 0.013$. Thiol anions and *p*-nitrophenolate anion exhibit weaker hydrogen-bonding ability.

The importance of hydrogen bonding for maintaining the structure of biological macromolecules and in general acid-base catalysis is well known, but remarkably little is known about the strength of hydrogen bonds between solutes in aqueous solution. The formation of such hydrogen bonds requires that competition from hydrogen bonding of the donor and acceptor to 55 M water must be overcome (eq 1), but it has not been generally appreciated

$$B{\cdot}HOH + H_2O{\cdot}HA \rightleftharpoons B{\cdot}HA + H_2O{\cdot}HOH \quad (1)$$

what is necessary in order to overcome this competition. It is clear that intermolecular hydrogen bonding in water is generally weak, with association constants that are often not significantly larger than that expected for the formation of random-encounter complexes.[2-5] An exception is the hydrogen bifluoride ion, FHF^-,

(1) This paper is dedicated to Jack Hine. The research was supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 81-17816).
(2) Farrer, H. N.; Rossotti, F. J. C. *Acta Chem. Scand.* **1963**, *17*, 1824-1825.
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with an association constant[6] of 4 M^{-1}.

Reported values of association constants for hydrogen-bonded complexes in water vary widely. They include values of 0.47 M^{-1} for phenol–acetate,[7] 0.25 M^{-1} for formic acid–formate,[4] 0.1 and 0.4 M^{-1} for acetic acid–acetate,[2,8] and 5.6 M^{-1} for dihydrogen phosphate self-association.[9] However, direct measurements by laser Raman spectroscopy gave values of only 0.6 ± 0.3 M^{-1} for dihydrogen phosphate and 0.3 ± 0.1 M^{-1} for monohydrogen phosphate,[10] which may include a favorable contribution from bifunctional hydrogen bonding. The value for acetic acid–acetate has also been challenged and attributed to an activity coefficient or liquid-junction potential effect;[3,11] furthermore, no curvature suggestive of hydrogen bonding has been observed for catalysis by acetic acid–acetate buffers up to 2.0 M.[4] The available data suggest that methods based on the direct observation of hydrogen-bonded complexes are more reliable and often give smaller association constants than indirect methods that are based on pH measurements, colligative properties, or activity coefficient effects.

In order that hydrogen bonding between solute molecules be detectable in water there must be an increase in the strength of hydrogen bonding with increasing acidity and basicity of the reactants, as described by Brønsted α and β values, respectively. In order to overcome the competition by water, it is necessary that the α value increase with increasing basicity of the base and that the β value increase with increasing acidity of the acid. Hine has proposed an equation with an interaction coefficient, τ, that describes these relationships.[12]

It has generally been assumed that the most favorable experimental situation for detecting hydrogen bonding involves a conjugate acid–base pair such as acetic acid and acetate ion. However, this is not the case if one component of the system is present at very low concentration. We describe here an examination of hydrogen bonding of the basic phenolate ion to protonated amines, including compounds with pK_a values several units below the pK_a of ~10 for phenol. Hydrogen-bonded complexes have been observed that show an increase in stability with increasing acidity of the proton donor and increasing basicity of the proton acceptor. The association constants are small and not of high precision, but they are adequate to provide an estimate of the interaction coefficient τ for intermolecular hydrogen-bond formation in aqueous solution.

Experimental Section

Materials. Reagent-grade inorganic salts were used without further purification. Organic compounds were recrystallized or distilled before use. Absorbance was measured on Cary 118 or Zeiss PM6 spectrophotometers in thermostated cells at 25 °C. Solution pH was measured with a Radiometer GK 2321C electrode and an Orion Model 701A pH meter. The electrode was free of the anomalous ionic strength effects reported by Illingworth.[13]

Equilibrium Constants. The apparent pK of each amine buffer was determined by titration or calculated from the pH of the most dilute buffer solution in each experiment. The pK of each substituted phenol was measured spectrophotometrically at 2 M ionic strength in dilute buffers of known pH.

Association constants for hydrogen-bonded complexes were measured by the following procedure. Stock solutions of amine buffers were prepared by neutralizing the hydrochloride or dihydrochloride salt to the desired fraction base with a concentrated potassium hydroxide solution and filtering through a sintered-glass funnel. Aliquots of the phenol solution were mixed in 10-mL volumetric flasks with various dilutions of the amine buffer and a sufficient amount of a potassium chloride solution to maintain ionic strength at 2 M. The stoppered flasks were brought to constant temperature in a water bath at 25 °C. The total absorbance of each sample was measured against water as reference, and any small contribution of buffer absorbance was determined separately and subtracted. Alternatively, each sample was read against a reference solution containing an identical buffer concentration in the absence of the phenol. Wavelengths were chosen at which the absorbance of the phenol is small or negligible, and the absorbance of the phenolate ion is large, as close to the λ_{max} as feasible. At the end of the experiment, the pH of a fresh aliquot from each flask was measured in small plastic cups that were maintained at 25 °C by a circulating water bath.

This procedure was modified for experiments with thiols and with *p*-methoxyphenol after initial experiments showed time-dependent absorbance changes. Stock solutions of these compounds were first temperature equilibrated, and the absorbance was measured immediately upon their dilution into buffer. Following a small initial change, the absorbance remained constant for at least 15 min. All solutions used in experiments involving thiols were flushed with argon. The absorbance of all other substituted phenols was stable over time.

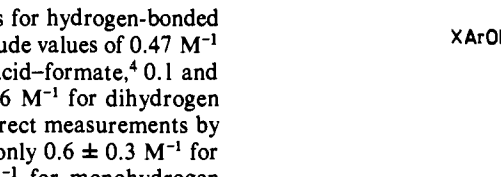
Solutions of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid were prepared by injecting a solution of the compound in acetonitrile into a rapidly stirring aqueous solution containing 1.5 equiv of potassium hydroxide. The final amount of acetonitrile in the experimental solutions was constant and generally <2%.

Calculation of K_{buff}. The changes in absorbance of the substituted phenolate ion as a function of buffer concentration were used to calculate a value of K_{buff}, which is the apparent association constant defined on the basis of the total concentration of buffer. The value of K_{buff} is equal to the quotient of the slope and intercept derived from plots of the absorbance of the substituted phenolate ion against the concentration of buffer (eq 2). In this equation, A is the absorbance at a given concentration

$$K_{buff} = \frac{A - A_0}{A_0[\text{buffer}]} \qquad (2)$$

of buffer and A_0 is the intercept at the y axis. An equation describing the complete interaction of both the acidic and basic components of the buffer with both the substituted phenol and phenolate ion is derived in the Appendix (eq 13). Equation 2 is a simplified form of this equation, which is valid when the concentration of the substituted phenol is in large excess over that of the substituted phenolate ion.

Scheme I



Results

The equilibrium constant K_{AB} for the formation of a hydrogen-bonded complex of phenolate ion and a protonated amine (Scheme I) was determined by measuring the increase in the UV absorbance of total phenolate ion in the presence of increasing concentrations of amine buffer at constant ionic strength. The experiments were generally carried out at a constant pH value that is several units below the pK_a of phenol, so that there is a large pool of nonionized phenol. Consider as a first approximation that medium effects are negligible, the pH is constant at constant ionic strength, and K_{AB} is the only equilibrium constant for hydrogen bonding that is important. The concentration and absorbance of XArO⁻·HOH will then remain essentially constant as the buffer concentration is increased. Any increase in the absorbance of phenolate ion will result from formation of the hydrogen-bonded complex.

Figure 1 shows the increase in the absorbance of phenolate ion in the presence of increasing concentrations of ethylenediamine buffers, 50% dication, at ionic strength 2.0 M maintained with potassium chloride. An association constant for formation of the hydrogen-bonded complex of K_{buff} = 0.50 M^{-1}, based on total buffer concentration, is obtained from the fractional increase in phenolate absorbance divided by the buffer concentration (eq 2). Extrapolation of this value and values of K_{buff} obtained at other buffer ratios to 100% dication, as shown in the upper line of Figure 2, gives a value of K_{AB} = 0.81 M^{-1} for hydrogen bonding of phenolate ion to ethylenediamine dication. The results of experiments with less acidic protonated diamines are also shown in Figure 2. Values of K_{buff} and K_{AB} for a larger series of proton

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(5) Scott, R. L. *J. Phys. Chem.* **1971**, *75*, 3843–3845.
(6) Haque, R.; Reeves, L. W. *J. Am. Chem. Soc.* **1967**, *89*, 250–252. Schaumberg, K.; Deverell, C. *J. Am. Chem. Soc.* **1968**, *90*, 2495–2499.
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(12) Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766–5771.
(13) Illingworth, J. A. *Biochem. J.* **1981**, *195*, 259–262.

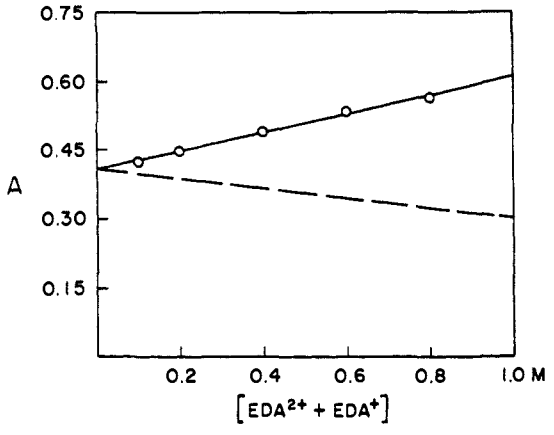


Figure 1. Change in the absorbance of phenolate ion at 300 nm with increasing concentration of ethylenediamine (EDA) buffer, 50% dication, at 25 °C and ionic strength 2 M (KCl). The absorbance of the phenol (0.05 M) is negligible at this concentration and wavelength. The solid line is the least-squares fit to the data points. The dashed line is the absorbance change predicted from the measured change in pH (see text).

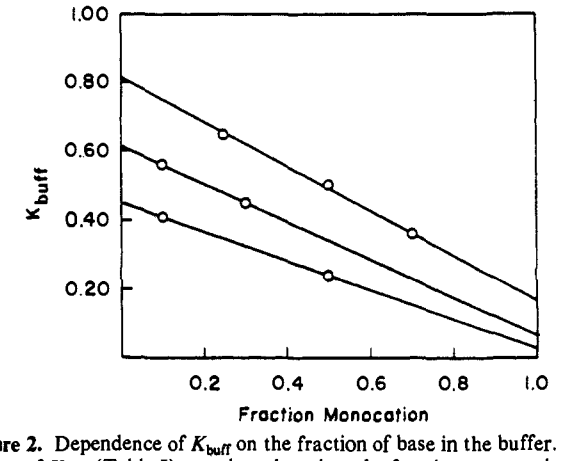
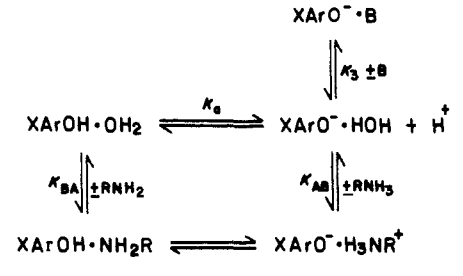


Figure 2. Dependence of K_{buff} on the fraction of base in the buffer. The values of K_{buff} (Table I) are plotted against the fraction monocation for dicationic buffers of ethylenediamine (top), 2-hydroxy-1,3-diaminopropane (middle), and 1,3-diaminopropane (bottom).

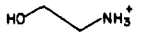
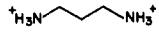
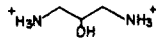
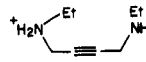
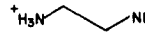
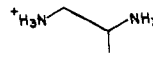
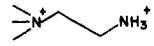
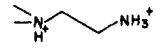
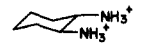
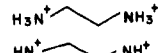
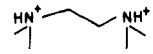
Scheme II



donors were obtained in similiar experiments and are summarized in Table I. The results of a series of experiments to measure the hydrogen bonding of a series of substituted phenolate ions and other bases to ethylenediamine dication are reported in Table II.

Scheme II includes the equilibrium constants K_{BA}, for hydrogen bonding of phenol to the buffer base, and K_3, for hydrogen bonding of phenolate ion to the acidic protons on the monocation of diamines. These equilibrium constants are expected to be smaller than K_{AB} because the pK values of the reacting species are less favorable for hydrogen bonding. Under some conditions formation of the XArOH·NH_2R complex could decrease the size of the XArOH pool and, therefore, decrease the absorbance from the XArO⁻·H_3NR^+ complex and the value of K_{buff}. However, it is shown in the Appendix that under the conditions of these experiments there is no error from formation of this complex when the values of K_{buff} are extrapolated to 100% dication. The concentration of the XArOH·NH_2R complex approaches zero as the fraction of buffer base approaches zero.

Table I. Equilibrium Constants for Formation of a Hydrogen-Bonded Complex between Phenolate Ion and Substituted Ammonium Ions at Ionic Strength 2 M (KCl) and 25 °C (Absorbance Measurements: 300 nm Unless Otherwise Noted)

acid	pK_a[a]	f_B[b]	K_{buff}, M^{-1}	K_{AB}, M^{-1}	K_B, M^{-1}
	9.94	0.1	0.15	0.20	−0.28[c]
	9.30	0.1 0.5	0.41 0.24[d]	0.45	0.03
	8.47	0.1 0.3	0.56 0.45	0.62	0.07
	8.32	0.25	0.28		
	7.65	0.25 0.5 0.7	0.65 0.50 0.36	0.81	0.17
	7.38	0.5	0.53		
	7.34	0.5	0.32	(0.58)	(0.06)[e]
	7.13	0.5	0.37		
	7.09	0.5	0.23		
	6.78	0.6	0.41		
	6.63	0.5 0.7	0.14 0.05	0.37	−0.09
	6.18	0.6 0.8	0.40 0.23	0.91	0.06
^+H_3NOH	6.12	0.5 0.5 0.75	0.43 0.47 0.28	0.79	0.11

[a] Apparent pK measured at 2 M ionic strength. [b] Fraction base in the buffer. [c] The values of K_{AB} and K_B were calculated by using eq 13 in the Appendix from the results of an experiment at $f_B = 0.7$ in which the concentration of phenolate ion decreased with increasing buffer concentration. [d] Determined at 295 nm. [e] The value of K_{AB} in parentheses was estimated by calculating a value of K_B as the mean of the values found for other diamines in the table and drawing a line from the calculated value of K_B through the measured point to the y axis in a plot of K_{buff} against f_B.

The positive intercepts on the right side of Figure 2, K_B, reflect the relatively weak hydrogen bonding of the acidic protons of ethylenediamine monocation and other diamine monocations to phenolate ion (K_3 in Scheme II). Values of K_B for these and other amines are included in Table I. The K_B term also includes the effect of hydrogen bonding to ArOH by the basic site of diamine monocations to form ArOH·NH_2R (K_{BA} in Scheme II), which causes a decrease in the concentration of ArO^-. The negative values of K_B in Table I are attributed to this term. The relationship of these equilibrium constants to the experimental results is described in the Appendix. However, we have not systematically investigated the effect of the basic component of the buffer because of its small magnitude.

Replicate determinations of K_{buff} were generally found to agree within ±0.05 M^{-1}. We estimate that the values of K_{AB} are accurate to within ±0.2 M^{-1} or better. Equation 13 (Appendix) was used to calculate K_{buff} for experiments in which the concentration of the substituted phenol was not in large excess over that of the substituted phenolate ion.

While the above observations are consistent with the formation of a hydrogen-bonded complex, changes in pH, the apparent pK of the substituted phenol, or the absorbance spectra of substituted phenols and phenolate anions as the buffer and counterion are exchanged at constant ionic strength could result in either an increase or a decrease in absorbance. The following experiments were carried out in order to evaluate the influence of these medium effects on the experimental system.

Spectra of the Hydrogen-Bonded Complex and Medium Effects on the Spectra. The values of K_{AB} reported in Tables I and II are based on the assumption that the extinction coefficients of

Table II. Equilibrium Constants for the Formation of a Hydrogen-Bonded Complex between Ethylenediamine Dication and Substituted Phenolate Ions at Ionic Strength 2 M (KCl) and 25 °C

base	pK^a	$f_B{}^b$	λ, nm	K_{buff}, M^{-1}	K_{AB}, M^{-1}	K_B, M^{-1}
3,5-di-*tert*-butyl-4-hydroxybenzoate dianion	10.67	0.5	310	1.31		
		0.7		0.92	2.37	0.26
		0.8		0.67		
p-methoxyphenolate	10.20	0.3	325	0.72		
		0.4		0.58		
		0.5		0.60	0.88	0.29
		0.5		0.58		
		0.7		0.47		
phenolate	9.85	0.25	300	0.65		
		0.5		0.50	0.81	0.17
		0.7		0.36		
m-hydroxybenzoate dianion	9.63	0.5	330	0.71	(1.22)	(0.18)[c]
5-nitrosalicylate	9.60	0.7	450	0.34	(0.64)	(0.18)[c]
p-chlorophenolate	9.34	0.1	310	0.63		
		0.25		0.54	0.69	0.11
		0.5		0.40		
p-hydroxybenzoate dianion	8.93	0.25	300	0.90	(1.22)	(0.17)[c]
		0.5	300	0.42[d]		
m-nitrophenolate	8.10	0.3	400	0.48		
		0.5		0.37	0.61	0.14
		0.7		0.29		
p-hydroxyacetophenone anion	7.99	0.25	320	0.50	0.60	0.20
		0.5		0.40		
p-nitrophenolate	7.10	0.25	400	<0.1	<0.2[e]	
		0.5		<0.1		
mercaptoacetate dianion	9.87	0.5	265	0.53		
		0.5		0.55		
		0.5		0.70		
2-mercaptoethanol anion	9.57	0.25	245	<0.1	<0.2[e]	
		0.50		<0.1		
benzoate	3.99	0	290	≤0.11	≤0.11[f]	

[a] Apparent pK determined at 2 M ionic strength. [b] Fraction base in the buffer. [c] Values for K_{AB} in parentheses were estimated by calculating a value for K_B by linear regression of K_B against pK for the other substituted phenolates in this table. The value of K_{AB} was derived by drawing a line from the calculated value of K_B through the measured point to the y axis in a plot of K_{buff} against f_B. [d] The buffer used in this measurement was *N,N,N*-trimethylethylenediamine dication, which has an apparent pK of 7.34. [e] The upper limits for K_{buff} were determined by assuming that a 5% absorbance increase could have gone undetected over the range of buffer concentration studied. The upper limit of K_{AB} was calculated by assuming that the value of K_{buff} at $f_B = 0.5$ was 0 and the value of K_{buff} at $f_B = 0.25$ was 0.1 M^{-1}. [f] The value of K_{AB} for benzoate and ethylenediamine dication was determined by a modification of the usual method. A constant concentration of methoxyamine buffer, 35% base, was used to maintain the pH, and ethylenediamine dication was exchanged for KCl at constant ionic strength. The amount of complex formed was estimated from the observed decrease of the benzoic acid absorbance, which has λ_{max} at a longer wavelength than benzoate anion.

phenolate ions are the same when they are hydrogen bonded to water or to the proton donor in the hydrogen-bonded complex. Any error in this assumption gives a corresponding error in the value of K_{AB}. The changes in extinction coefficient upon the net formation of hydrogen-bonded complexes in different solvents are not large,[14] and the differences, and corresponding errors, for exchange of one hydrogen bond for another in the same solvent should be even smaller.

Figure 3 shows the spectrum of 0.075 mM *p*-hydroxyacetophenone in the presence of 0.1 M (a) and 0.8 M (b) ethylenediamine buffer, 50% dication, at ionic strength 2 M (KCl). The difference spectrum for curves a and b is shown in the inset. There is an increase in absorbance in the region of ArO^- absorption and a decrease in absorbance in the region of ArOH absorption with increasing buffer concentration. The observed decrease in absorbance in the region of ArOH absorption at 265 nm is 0.055, which may be compared with a decrease of 0.045 calculated from the observed increase in ArO^- absorbance at 320 nm, assuming identical extinction coefficients for ArO^- hydrogen bonded to water and to the buffer acid. The difference spectrum has a maximum at 320 ± 2 nm, which is close to the maximum at 324 nm for the ArO^- ion in water. Similar results were obtained for unsubstituted phenol in 0.1–0.8 M 1,3-diaminopropane buffers, 50% dication (not shown). The difference spectrum shows a maximum at 284 ± 2 nm, which is close to the maximum at 287 nm for phenolate ion in water. It is possible that these small shifts in λ_{max} toward λ_{max} for the phenol reflect a slightly larger amount of proton transfer to the oxygen anion from the relatively acidic buffer acid,

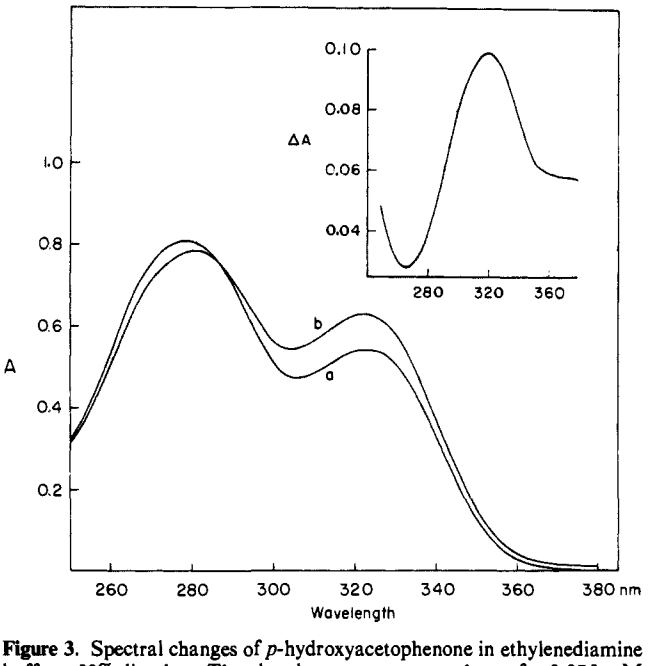
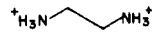
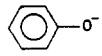
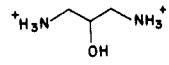
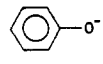
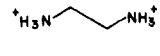
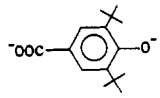
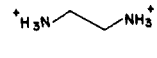
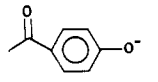
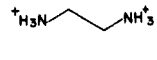
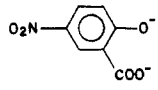


Figure 3. Spectral changes of *p*-hydroxyacetophenone in ethylenediamine buffers, 50% dication. The absorbance spectra are shown for 0.075 mM *p*-hydroxyacetophenone in 0.1 M (a) and 0.8 M (b) ethylenediamine buffer at 25 °C and ionic strength 2 M (KCl). The inset shows the difference spectrum of b and a.

compared with water.[14] If so, the small magnitude of the shift suggests that there is a correspondingly small change in the ex-

(14) Sawicki, E.; Hauser, T. R.; Stanley, T. W. *Anal. Chem.* **1959**, *31*, 2063–2065. Parker, A. J.; Brody, D. *J. Chem. Soc.* **1963**, 4061–4068.

Table III. Variation in K_{buff} with Wavelength for Complex Formation of Dicationic Diamines with Substituted Phenolate Anions at Ionic Strength 2 M (KCl) and 25 °C

acid	base	f_B[a]	λ, nm	K_{buff}, M^{-1}
		0.1	295	0.63
			298	0.56
			300	0.50
			303	0.46
		0.3	295	0.57
			300	0.45
			303	0.39
		0.8	305	0.68
			310	0.67
			315	0.60
		0.25	320	0.50
			340	0.42
		0.5	320	0.40
			340	0.33
		0.7	450	0.34
			455	0.32
			460	0.27

[a] Fraction of base in the buffer.

tinction coefficient of the phenolate ion toward that of the phenol.

Table III shows the results of determinations of K_{buff} at different wavelengths for a series of substituted phenolate ions. The differences in K_{buff} at different wavelengths are larger than the estimated errors of the individual determinations, but smaller than the estimated uncertainty of the overall equilibrium constants. The trends represent, in part, interference from changes in the absorbance of the phenol that are caused by medium effects (see below). The values reported in Tables I and II were obtained by using wavelengths at which this absorbance is small. There is little or no absorbance of phenol at 300 nm under the conditions of the experiments described in Table I.

Neutral and charged organic compounds and inorganic ions often cause small shifts in the λ_{max} of substituted phenol and phenolate ions in aqueous solutions that result in absorbance changes that are maximal on either side of λ_{max} and negligible near the λ_{max}.[15] Typical difference spectra, for *p*-nitrophenolate and phenolate anions, are shown in Figure 4. The changes in absorbance are almost always <10% in 1 M buffer at the wavelengths used for the determination of equilibrium constants; the similar changes brought about by potassium chloride will result in still smaller changes for experiments maintained at constant ionic strength. Tetramethylammonium chloride was found to cause larger changes in absorbance and was not used to maintain constant ionic strength.

Phenol and anisole were found to show almost identical difference spectra between 1 M potassium chloride and 0.8 M semicarbazide buffer, 50% cation at ionic strength 1.0, with 4% maximal increases in absorbance at 280 and 279 nm, respectively. This result suggests that the polarizability of the solvent affects λ_{max} through nonspecific interactions that do not involve the phenolic proton.[15,16]

The strongest evidence that nonspecific solvent effects are not responsible for the increase in phenolate absorption that is ascribed to the formation of hydrogen-bonded complexes is provided by the dependence of K_{AB} on the acidity of the proton donor and the basicity of the substituted phenolate ion (Tables I and II). The small changes in absorbance that are observed with weakly acidic proton donors and weakly basic phenolate ions provide the best controls to show that medium effects are small.

Changes in Apparent pH and p*K* with Buffer Concentration. The interpretation of increases in phenolate absorbance with increasing buffer concentration (e.g., Figure 1) as a measure of hydrogen bonding of phenolate ion to the acidic component of the buffer requires that the amount of phenolate ion that is hydrogen bonded to water remain constant as the buffer concentration increases. In other words, it requires that medium effects upon substituting buffer for potassium chloride at a constant ionic strength of 2.0 M do not cause changes in the pH or the apparent p*K* of the phenol that change the concentration of phenolate ion. In fact, the apparent pH does decrease significantly with increasing concentration of ethylenediamine buffer. The dashed line in Figure 1 shows the decrease in absorbance of phenolate ion that would be expected from the observed decrease in apparent pH. Similar decreases were observed with other diamine buffers.

Figure 5 shows that the decrease in apparent pH is larger as the fraction of the dication in the buffer increases. If this decrease in pH were real, it would lead to an underestimation of K_{AB}.

The following evidence indicates that changes in pH and the apparent p*K* values of phenols are small or negligible under the conditions of these experiments. The changes in apparent pH presumably represent changes in the reference electrode junction potential.[17,18]

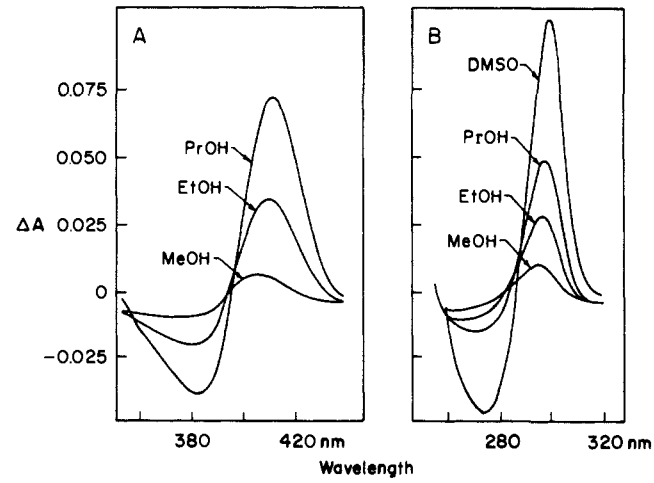


Figure 4. Medium effects on the spectra of *p*-nitrophenolate and phenolate anions. Difference spectra are shown in which the reference cuvette contained either 0.05 mM *p*-nitrophenolate anion in 10 mM potassium hydroxide and 2 M potassium chloride (A) or 0.7 mM phenolate anion in the presence of 9.3 mM potassium hydroxide and 2 M potassium chloride (B). The sample cuvette contained the same solution in addition to 1 M methanol, ethanol, 1-propanol, or dimethylsulfoxide. The absorbance of phenolate ion at this concentration is 0.63 at 300 nm and 1.8 at 287 nm. The absorbance of *p*-nitrophenolate ion at this concentration is 0.91 at 400 nm and 0.69 at 420 nm.

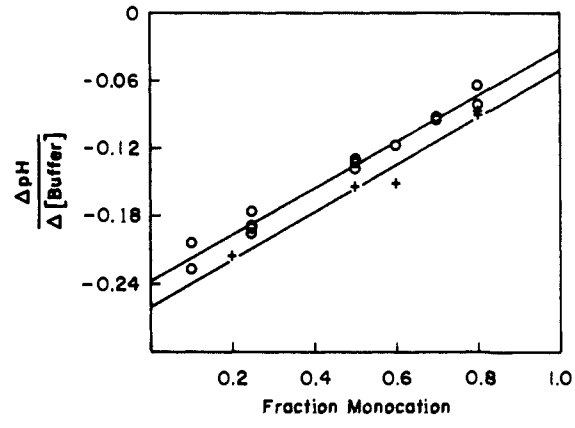


Figure 5. Change in the apparent pH with the concentration (*M*) and fraction monocation of the buffer. The pH of various concentrations of dicationic buffers containing ethylenediamine (O) or piperazine (+) was measured with a glass electrode at 25 °C and ionic strength 2 M (KCl) as described in the Experimental Section. The slopes of linear plots of ΔpH against buffer concentration are plotted against the fraction monocation in the buffer. The lines shown were determined by linear regression.

(15) McRae, E. G. *J. Phys. Chem.* **1957**, *61*, 562–572.
(16) Wetlaufer, D. B.; Edsall, J. T.; Hollingworth, B. R. *J. Biol. Chem.* **1958**, *233*, 1421–1428. Yanari, S.; Bovey, F. A. *J. Biol. Chem.* **1960**, *235*, 2818–2826.

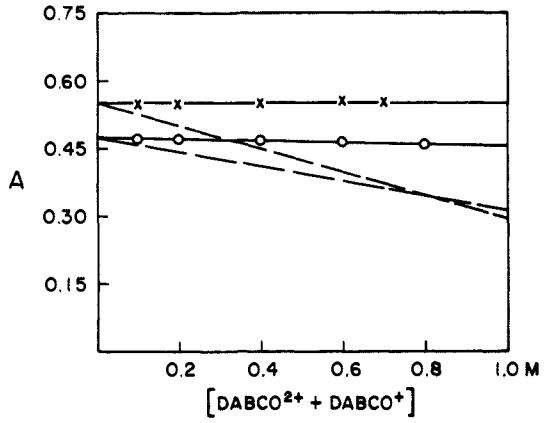


Figure 6. Absorbance of 2-chloro-4-nitrophenolate anion and aniline in Dabco buffers. The absorbance at 430 nm is shown for solutions containing 0.3 mM 2-chloro-4-nitrophenol and various concentrations of buffer, 50% dication (O). The absorbance at 280 nm is shown for solutions of aniline in various concentrations of buffer, 80% dication (×). The measured pH decreased linearly with buffer concentration with slopes of −0.17 and −0.25 unit/M buffer for 50% and 80% dication, respectively. The dashed lines show the absorbance decrease expected from the apparent change in pH. Only a small fraction of each indicator was present in the basic form, and the acidic form has negligible absorbance at these wavelengths.

(1) Figure 6 shows that there is no detectable change in the absorbance of 2-chloro-4-nitrophenolate anion and of aniline near λ_{max} with increasing concentrations of Dabco (1,4-diazabicyclo-[2.2.2]octane) buffers, 50% and 80% dication, respectively. The dashed lines in Figures 6 show the decrease in absorbance that would be observed if the concentrations of the basic species of these indicators changed according to the changes in observed pH. The absence of a significant change in absorbance and the identical behavior of the uncharged and anionic indicators suggest that medium effects on the apparent pK values are negligible in this system.

(2) The absorbance of *p*-nitrophenolate ion at 425 nm was found to change by <2% in buffers containing 0.05–1.0 M total hydroxylamine, methoxyamine, or semicarbazide, 7.5% free base, at ionic strength 1.0 M (KCl); in each case the apparent pH decreased by 0.15 pH unit. There was also no detectable absorbance change in similar experiments with buffers containing piperazine or Dabco dications. The identical behavior with buffers of different pK_a suggests that there is no significant hydrogen bonding to the anion by the buffer acid that might compensate for a medium effect.

Discussion

The principal conclusion of this work is that intermolecular hydrogen bonding between solute molecules in water is weak, even under exceptionally favorable conditions. The association constant K_{AB} is only 0.81 M^{-1} for hydrogen-bond formation between phenolate anion (pK_a 9.85) and ethylenediamine dication (pK_a 7.65), in spite of the favorable ΔpK between the proton donor and acceptor of 2.2 units and the favorable statistical factor from the six acidic protons in this system. With a less favorable ΔpK and a smaller statistical factor, hydrogen bonding becomes difficult or impossible to detect. The conjugate acid of ethanolamine, with $\Delta pK \sim 0$ and three acidic protons, has K_{AB} = 0.2 M^{-1} for hydrogen bonding to the phenolate anion.

This conclusion supports and extends the conclusion of Klotz and Franzen and of Susi and Timasheff that intermolecular hydrogen bonding between amide or peptide groups in aqueous solution is very weak because of competition from the high concentration of liquid water.[19] This does not mean that hydrogen bonding is not an important driving force for the maintenance of the native structure of proteins and nucleic acids. Most of the hydrogen bonds in proteins and other macromolecules are formed in intramolecular reactions, so that the equilibrium constants for hydrogen-bond formation can be much more favorable than for bimolecular reactions because of the smaller loss of translational and rotational entropy in intramolecular reactions.[20] Unfortunately, these differences in entropy are not known, so that the results reported here cannot be used directly to estimate the contribution of hydrogen bonding to the stability of macromolecules.

Requirements for Hydrogen Bonding in Water. The factors that are necessary for the development of significant hydrogen bonding between solutes in water are not widely appreciated. It is not sufficient that hydrogen bonding becomes stronger with increasing strength of the acid or the base, for example. All intermolecular hydrogen bonding between solutes in water involves *competition* between hydrogen bonding to water and to a solute, so that if the strength of hydrogen bonding increases with increasing acidity of HA, there will be no increase in hydrogen bonding to a solute B if there is an equal increase in the strength of the hydrogen bonds to B and to water. Significant hydrogen bonding to B requires that there be an interaction term such that an increase in the acidity of HA increases the strength of hydrogen bonding to B more than to water.

The dependence of K_{AB} for hydrogen-bond formation upon the acidity of HA and the basicity of B is described by the Brønsted coefficients α and β (eq 3 and 4). Brønsted coefficients are first

$$\alpha = \frac{\partial \log K_{AB}}{-\partial pK_{AH}} \quad (3)$$

$$\beta = \frac{\partial \log K_{AB}}{\partial pK_{BH}} \quad (4)$$

derivatives of the experimental quantity log K_{AB}. Significant intermolecular hydrogen bonding in water requires a *change* in α and β with changing pK_a of the base and acid, respectively, as described by eq 5–8. These changes are second derivatives of

$$\frac{\partial \beta}{-\partial pK_{AH}} = \frac{\partial \alpha}{\partial pK_{BH}} = \tau \quad (5)$$

$$\alpha = -\tau(pK_{H_3O^+} - pK_{BH}) \quad (6)$$

$$\beta = -\tau(pK_{AH} - pK_{HOH}) \quad (7)$$

log K_{AB}. They are equal to the same interaction coefficient, τ. The complete expression for this interaction coefficient, eq 8, was

$$\log K_{AB} = \tau(pK_{AH} - pK_{HOH})(pK_{H_3O^+} - pK_{BH}) - 2.04 \quad (8)$$

derived by Hine using an electrostatic model.[12] However, the same or a similar equation must describe any measurable hydrogen bonding between solutes in water that follows the Brønsted relations. Equation 8 differs from the equation proposed by Hine in the constant log 110 = 2.04, instead of log 55 = 1.74. This term is a correction for the concentration of liquid water, in which we have included a statistical factor of 2 for the two protons of water.[21]

Figure 7 shows the behavior that is described by eq 3–8 and that is required in order for intermolecular hydrogen bonding to

(17) Bates, R. G. *Determination of pH: Theory and Practice*; Wiley: New York, 1973. Olin, A.; Svanstrom, P. *Acta Chem. Scand., Ser. A* **1978**, *A32*, 283–288. Westcott, C. C. *pH Measurements*; Academic: New York, 1978.

(18) Since similar results were observed with a hydrogen electrode, it is unlikely that the proton-sensitive glass membrane is responsible for the effect: Everett, D. H.; Pinsent, B. R. W. *Proc. R. Soc. London* **1952**, *A215*, 416–429.

(19) Klotz, I. M.; Franzen, J. S. *J. Am. Chem. Soc.* **1962**, *84*, 3461–3466. Susi, H.; Timasheff, S. N.; Ard, J. S. *J. Biol. Chem.* **1964**, *239*, 3051–3054.

(20) Brant, D. A.; Miller, W. G.; Flory, P. J. *J. Mol. Biol.* **1967**, *23*, 47. Go, M.; Go, N.; Scheraga, H. A. *J. Chem. Phys.* **1971**, *54*, 4489. Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 316–317.

(21) Hine's original equation was modified as described in the text to include a statistical factor of 2 for water protons. It might be argued that a statistical correction should be made for both the acidic and the basic sites of water, giving a factor of 2 × 2 = 4. Different electron pairs are not ordinarily included in a statistical correction, but if both protons of water are hydrogen bonded to other water molecules, stoichiometry requires that there must be an equal number of basic sites. However, water is a liquid at 25 °C, and all possible hydrogen bonds are not formed. We have, therefore, chosen an arbitary statistical factor of 2.

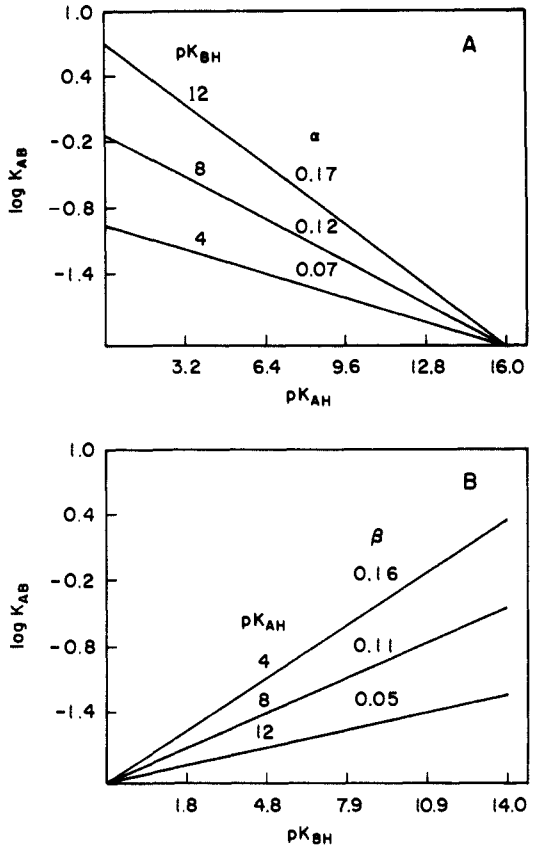


Figure 7. Dependence of α on pK_{BH} and of β on pK_{AH} according to the Hine equation (8). Statistically corrected values used in the calculation were $\tau = 0.013$, $pK_{HOH} = 16.04$, and $pK_{H_3O^+} = -1.26$.

be significant in aqueous solution. The increase in α and β with increasing basicity of B and acidity of AH, respectively, is described by a value of $\tau = 0.013$ and is required in order for intermolecular hydrogen bonding to compete effectively with hydrogen bonding to water. Figure 7 shows that hydrogen bonding will be strongest when the pK values of the acid and base are as far removed from the pK_a values of the reference compounds H_2O and H_3O^+ as possible.

The values of the interaction coefficient τ are small, but small changes in τ have large effects. The upper limit that is possible for τ in water is 0.057.[12] Hine estimated a value of $\tau = 0.024$ for hydrogen bonding in methanol,[12] and a crude electrostatic calculation gave a value of $\tau = 0.013$ in water.[22] A measurement of equilibrium constants for the exchange of substituted aliphatic alcohols with ethers of ring-substituted 1-phenylethanols in 50% and 10% trifluoroethanol–water gave an electrostatic interaction term that corresponds to a value of $\tau = 0.014$ for hydrogen bonding.[23]

Figure 8 shows that the statistically corrected values of log K_{AB} for hydrogen bonding of protonated amines to the phenolate anion fit a Brønsted correlation with a slope of $\alpha = 0.15$.

There is considerably more scatter in this correlation if the data are not statistically corrected. This is consistent with the behavior expected for hydrogen bonding, but it would not be expected for a simple electrostatic interaction between the oppositely charged acids and base. There is no difference in the fit of monocations and dications to the line. The least-squares line for the buffer acids falls close to the point for water, using the statistically corrected value of log $(K_{AB}/p) = -2.04$. The value of K_B for hydrogen bonding of phenolate ion to ethylenediamine monocation (Table I), obtained from extrapolation of the values of K_{buff} to

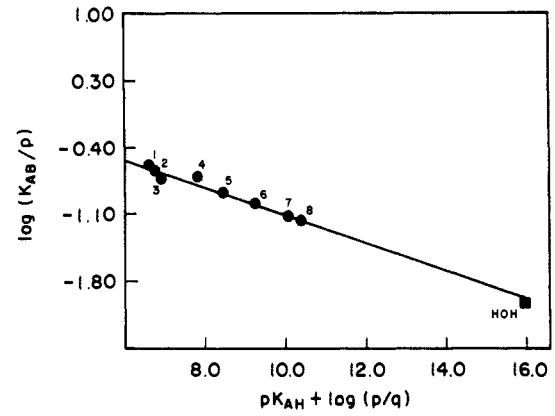


Figure 8. Brønsted plot for the formation of hydrogen-bonded complexes of substituted ammonium cations with phenolate anion. The values of K_{AB} and pK are statistically corrected.[32] The value for *N*-(trimethyl)-ethylenediamine (eq 4) was measured at only one buffer ratio. The line with slope $\alpha = 0.15$ is the least-squares fit to the experimental points. The calculated value of log K_{AB} for an acid with a pK equal to that of water (eq 8) is indicated by a square. The numbered points refer to (1) hydroxylammonium ion, (2) piperazine dication, (3) *sym*-tetramethylethylenediamine dication, (4) *N,N,N*-trimethylethylenediamine dication, (5) ethylenediamine dication, (6) 2-hydroxy-1,3-diaminopropane dication, (7) 1,3-diaminopropane dication, and (8) (2-hydroxyethyl)ammonium ion.

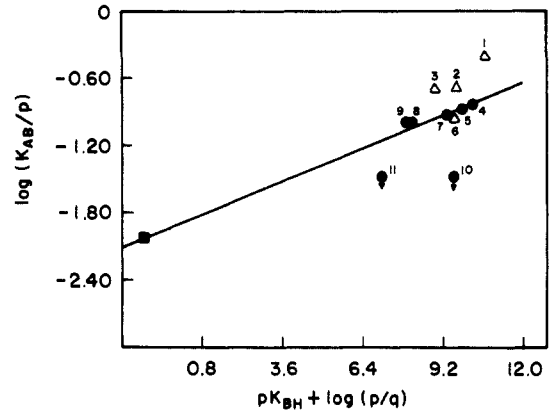


Figure 9. Brønsted plot for the formation of hydrogen-bonded complexes of substituted phenolate anions with ethylenediamine dication. The open symbols are estimates of K_{AB}, as described in Table II, and the triangles are dianions. The calculated value of log K_{AB} for a substituted phenolate anion whose conjugate acid has a pK equal to that of H_3O^+ (eq 8) is indicated by a square. The line with slope $\beta = 0.1$ was drawn to intersect this point; the values shown with arrows are upper limits. The numbered points refer to (1) 3,5-di-*tert*-butyl-4-hydroxybenzoate dianion, (2) *m*-hydroxybenzoate dianion, (3) *p*-hydroxybenzoate dianion, (4) *p*-methoxyphenolate, (5) phenolate, (6) 5-nitrosalicylate dianion, (7) *p*-chlorophenolate, (8) *m*-nitrophenolate, (9) *p*-hydroxyacetophenone anion, (10) 2-mercaptoethanol anion, and (11) *p*-nitrophenolate.

100% ethylenediamine monocation, agrees well with the value of K_{AB} that is expected for an acid of this pK from the Brønsted plot of Figure 8.

Figure 9 shows that the equilibrium constants for hydrogen bonding of a series of substituted phenolate anions to ethylenediamine dication tend to increase with increasing basicity of phenolate ions with similar overall structure. The data are consistent with a line of slope $\beta = 0.10$ that passes through the point for water. The points for dianions, 1–3, show significant positive deviations of ~0.3 log unit (twofold) compared with those for monoanions. This is consistent with an electrostatic effect that becomes significant only for the interaction of dianions with dications; ion-pair formation between doubly charged ions in water is significant even at ionic strength 1–2 M.[24,25] No hydrogen

(22) Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 6708–6714 and ref 25.
(23) Rothenberg, M. E.; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340–1346.
(24) Davies, C. W. *Ion Association*; Butterworths: Washington, DC, 1962; pp 169–170.

bonding was detected for the anions of *p*-nitrophenolate and 2-mercaptoethanol, and the upper limits of log K_{AB} for these anions, 10 and 11 in Figure 9, fall significantly below the line.

The Brønsted correlations of Figures 8 and 9, with a slope of $\alpha = 0.15$ for hydrogen bonding to a base of pK = 9.9 and a slope of $\beta = 0.10$ for hydrogen bonding to an acid of pK = 7.7, correspond to a value of $\tau = 0.013$ (eq 6 and 7, calculated from statistically corrected equilibrium constants). These values of α and β are in the range that has been attributed to stabilization of the transition state in general acid–base catalysis by hydrogen bonding to the catalyst.[26] The value of $\tau = 0.013$ and an observed value of α or β for general acid–base catalysis could be used with eq 6 and 7 to provide a rough estimate of the pK_a of a reacting group in the transition state that is stabilized by hydrogen bonding to an acid or base catalyst.

It may be surprising, at first sight, that the Hine equation is adequate to describe intermolecular hydrogen bonding in water within the accuracy of our measurements. Equation 8 was derived from a simple electrostatic model, assuming a rigid system with no changes in bond lengths.[12] The success of this model is consistent with the view that electrostatic interactions provide the primary driving force for hydrogen-bond formation and that the covalent contribution is relatively small.[27] However, there is no doubt that there are changes in bond length upon hydrogen-bond formation and that the A–H bond length increases with increasing strength of the base, B.[28,29] The consequences of such changes are included in the observed value of τ.

Similarly, the interaction coefficients that describe substituent effects on the equilibrium constants for interconversion of ring-substituted 1-phenylethyl ethers and substituted aliphatic alcohols measure the electrostatic interaction between polar substituents on the aromatic ring and the alcohol[23] but may also reflect a significant change in bonding that arises from a resonance contribution of the nonbonded structure ArCH(Me)$^{+}$·$^{-}$OR. There is evidence from X-ray diffraction for changes in bond lengths and angles that arise from such contributions in several systems of this kind.[30] Therefore, the observed values of τ cannot be interpreted entirely in terms of a simple electrostatic interaction in a rigid system with constant covalent bonding.

It might be expected that these changes in bond length of hydrogen bonds would lead to changes in α with increasing strength of the acid and in β with increasing strength of the base. Such changes could be described by negative values of the direct-interaction coefficients p_x and p_y[31] that are defined by eq 9 and 10 (τ is a cross-interaction coefficient that describes the effects

$$p_x = \frac{\partial \alpha}{\partial \mathrm{p}K_{\mathrm{aAH}}} \tag{9}$$

$$p_y = \frac{\partial \beta}{-\partial \mathrm{p}K_{\mathrm{BH}}} \tag{10}$$

of changing acid strength on β and base strength on α). These changes are analogous to "anti-Hammond" effects on rate constants that correspond to movement of the transition state perpendicular to the reaction coordinate, toward the position of lower energy, when the energy on one side of a potential well is changed.[32]

Most of the available evidence indicates that such effects are small or absent for hydrogen-bond formation. The Brønsted plots of Figures 8 and 9 show no evidence of upward curvature corresponding to a significant p_x or p_y coefficient. This is not surprising, because K_{AB} describes the *exchange* of hydrogen bonds rather than net hydrogen-bond formation. Since the curvature described by $p_x = \partial\alpha/\partial pK_{AH}$ is constant by definition, regardless of the pK_a of the base, it will be present in the hydrogen bonds with B and with water so that it will not ordinarily be detectable in aqueous solution. The same cancellation will occur in transition states, so that perpendicular effects involving hydrogen bonds to acids and bases may not give rise to detectable p_x or p_y coefficients in structure–reactivity correlations for general acid–base-catalyzed reactions.

Correlations of log K or $-\Delta H$ for hydrogen-bond formation against σ or σ^* are also linear in nonaqueous solvents and in the gas phase when a closely related series of compounds is compared. For example, the strength of the interaction of a series of substituted alcohols with fluoride ion in the gas phase is linear over a range of >30 kcal mol^{-1} in proton affinity.[33] The infrared stretching frequency of an acidic proton decreases as the bond length increases when an acid forms a hydrogen bond to a base, and the magnitude of this change, $\Delta\nu$, becomes larger as the strength of the acid increases.[28,34] This means that the value of α is not necessarily an absolute measure of bond length or of changes in bond length or bond order when different acids in a series are compared, since the structure–reactivity correlations show that α is constant in these series. Instead, α is a proportionality constant that measures the extent to which the proton transfer in a hydrogen bond or a transition state resembles the products of complete proton transfer in the reference ionization reactions for a series of compounds of different acidity. An increase in α for a particular compound or series of compounds means that a hydrogen bond or transition state more closely resembles the product from complete proton transfer, with an increase in the AH bond length and a decrease in bond order for each acid in the series.

On the other hand, there is abundant evidence for an increase in the sensitivity of hydrogen-bond strength to the acidity of HA with increasing basicity of B and for an increase in sensitivity to the basicity of B with increasing acidity of HA, i.e., a positive value of τ, for the net formation of hydrogen bonds in nonhydroxylic solvents.[29]

Other Properties of the Hydrogen-Bonding Interaction. The difference spectra of the hydrogen-bonded complexes of the anions of *p*-hydroxyacetophenone (Figure 3, inset) and phenol (not shown) with acids of similar pK_a are similar to those of the parent anions in water but are shifted 3–4 nm toward shorter wavelengths. This result is consistent with a double-minimum potential well for the hydrogen-bonded complex,[35] in which partial proton

(25) Hydrogen bonding to the carboxylate group of these compounds is unlikely to be significant because the carboxylate ion is much less basic than the phenolate ion and little or no hydrogen bonding could be detected between ethylenediamine dication and benzoate ion (Table II); in any case, it would not be expected to increase the observed concentration of phenolate anion significantly. The positive deviations cannot be explained by the formation of a chelate ring with protons on the two nitrogen atoms of ethylenediamine dication because *N,N,N*-trimethylethylenediamine dication shows a similar statistically corrected value of K_{buff} (Table II, footnote *d*).

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transfer from the acid shifts the position of the absorption maximum toward that of the phenol. This shift arises from stabilization of the complex and an increase in proton transfer to the base in the hydrogen-bonded complex.[14,36] An upper limit of $\leq 10^{14}$ s^{-1} can be assigned to the rate constant for proton transfer within the complex as there is no evidence for large distortions in the ultraviolet spectra of the substituted phenolate ions due to signal-averaging effects.[37] The spectrophotometric observation of hydrogen-bonded complexes with acids of pK_a up to 4 units below that of the phenolate ion and the linear Brønsted plot of Figure 8 suggest that the double-minimum energy well may be maintained, with a significant barrier for proton transfer, even when the proton transfer is strongly favorable.

The small amount of available data for intermolecular hydrogen bonding of oxygen acids in water suggests that the value of τ for oxygen acids is not very different from that for the amine cations described here. The value of $\tau = 0.013$ gives values of $K_{AB} = 0.12$ and 0.14 M^{-1} for formic acid–formate and acetic acid–acetate complexes, respectively. The value for formate is somewhat smaller than a value of $K_{AB} = 0.25$ M^{-1} that was obtained from the downward curvature of plots of log k against buffer concentration for catalysis of several reactions by formate buffers.[4] However, no such curvature was observed in similar experiments with acetate buffers, which suggests either that the calculated value of K_{AB} is too large or that the hydrogen-bonded complex is active as a catalyst for these reactions.[4] The calculated value of K_{AB} for the acetic acid–phenolate complex is 0.39 M^{-1}. An attempt to measure this association constant gave a small increase in phenolate absorbance that is consistent with a value of $K_{AB} \leq 0.4$ M^{-1}.[38] The satisfactory fit of water to the Brønsted line in Figure 8 also suggests that oxygen acids do not behave very differently from protonated amines.

The difference between the value of $K_{AB} = 0.09$ M^{-1} for the self-association of dihydrogen phosphate, calculated from $\tau = 0.013$, and the value of 0.6 M^{-1} measured spectroscopically[10] may represent additional stabilization from bifunctional hydrogen bonding in this complex. The calculated value of $K_{AB} = 0.06$ M^{-1} for the complex of phenol and acetate ion is much smaller than a reported value of 0.47 M^{-1}, based on changes in the absorbance of phenol in the presence of acetate ion.[7,39] Strong hydrogen bonding would not be expected for an acid of pK 9.9 and a base of pK 4.7 in water, and the change in phenol absorbance might be accounted for by a medium effect on the spectrum,[15,16] as described in Results (Figure 4).

The thiolate anion of 2-mercaptoethanol shows no detectable hydrogen bonding to the dication of ethylenediamine (Table II); the upper limit of log K_{AB} falls well below the line for substituted phenolate ions of comparable pK_a on the Brønsted correlation of Figure 9. The dianion of mercaptoacetic acid has a value of K_{buff} similar to that for phenolate ion (Table II), but also falls below the Brønsted line of Figure 9 after correction for the electrostatic advantage from a dianion–dication interaction. This is consistent with the known weak hydrogen-bonding ability of sulfur compounds.[28,40] However, compared with oxygen anions of similar pK, thiol anions cause larger shifts in the stretching frequency of hydrogen-bonded acids in nonaqueous solvents[28] and larger solvent isotope effects through interaction with the solvent in aqueous solution.[41] This is consistent with a larger contribution of covalent interaction to hydrogen bonds of sulfur compared with oxygen anions.[28] Since K_{AB} is a measure of the *difference* in hydrogen-bonding ability to two acids, not the absolute strength of hydrogen bonding, the value of τ may be smaller for thiol than for oxygen anions because of the relatively small density of negative charge on the large sulfur atom.

The values of K_{AB} for *p*-nitrophenolate anion and 5-nitrosalicylate dianion are considerably smaller than the values of K_{AB} for the other monoanions and dianions that are shown in Figure 9. The decrease in hydrogen bonding appears to be an effect of the *p*-nitro substituent; the point for *m*-nitrophenolate anion falls close to the line. This suggests that the negative deviations are a consequence of the large resonance delocalization of negative charge that is provided by the *p*-nitro substituent. There is evidence that the delocalization of electron density into the *p*-nitro substituent of nitrophenolate ions is sufficient to bring about solvation of the nitro group by water molecules.[42]

These negative deviations show that there is an *imbalance* between the effects on the basicity and on the hydrogen-bonding ability of *p*-nitrophenolate ion that arises from electron delocalization into the *p*-nitro substituent; the decrease in hydrogen-bonding ability is larger than expected from the change in pK_a and the Brønsted β value. Similar imbalances between effects on transition states and on ground states are well-known for resonance delocalization into the nitro group and other substituents in structure–reactivity correlations.[43] They have been identified with the "principle of imperfect synchronization" (PIS).[44] We prefer the term "imbalance" because it is simpler and because synchronization is not appropriate for a system at equilibrium, such as a hydrogen-bonded complex.[45]

The imbalance means that, for a given decrease in pK_a, a substituent that delocalizes negative charge by resonance causes a larger decrease in hydrogen-bonding ability than a substituent that decreases charge density by a simple polar effect. The polar substituent produces a dipole that offsets the negative charge on the proton acceptor and decreases hydrogen-bonding ability and basicity proportionately, as defined by β. However, hydrogen bonding can still occur at the negative end of the dipole. With resonance delocalization, on the other hand, a certain fraction of the negative charge is entirely removed to another part of the molecule, where it is not available for either hydrogen bonding or protonation. In the limit of complete delocalization of charge, protonation will cause loss of the resonance stabilization and relocalization of the electron density on oxygen. However, significant hydrogen bonding will not be observed because the relatively small favorable energy of hydrogen bonding would not be sufficient to overcome the loss of resonance stabilization and bring about return of the electron density to oxygen. If the same argument can be applied to partial delocalization of charge, the larger effect of delocalization on hydrogen bonding than on protonation will give a negative deviation from a Brønsted correlation.

The imbalance arises because the free energy change from resonance delocalization is a constant for a given substituent, while the effects of polar substituents on the energies for protonation

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(38) This approximate value was obtained as follows: Increasing the concentration of an acetate buffer (95% base) from 0.1 to 0.9 M resulted in an increase in phenolate ion absorbance from 0.065 to 0.072 at 300 nm in solutions containing 0.4 M phenol, at 25 °C and ionic strength maintained at 0.9 M with trifluoroacetate ion. The measured pH increased by 0.05 unit over this range of buffer concentration. The absorbance change was corrected for the observed change in pH because little effect on the liquid-junction potential was expected upon exchanging acetate anion for trifluoroacetate anion. This expectation is supported by the results of another experiment in which trifluoroacetate ion was used to maintain ionic strength, and an increase in *p*-nitrophenolate absorbance was observed that nearly accounted for the apparent change in the observed pH of solutions containing *p*-nitrophenol and various concentrations of acetate buffer, 50% anion. The value of K_{AB} was calculated from the value of K_{buff} by using the pH-corrected absorbance and the fraction of acetic acid in the buffer.

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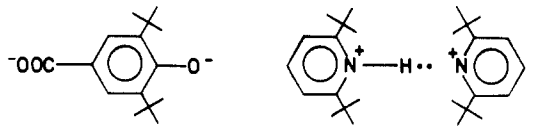
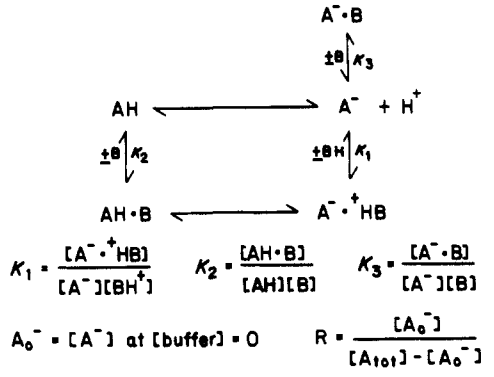
Chart I



1 2

Scheme III



and for hydrogen-bond formation are very different. The same kind of imbalance can arise in structure–reactivity correlations for nucleophilic reactions from a requirement for desolvation of a basic site before reaction, when substituent effects on the rate constants are smaller than on the reference ionization reaction.[46] In general, imbalance of this kind will occur when a process, such as desolvation or resonance delocalization, involves a certain change in Gibbs energy and the two different reactions being compared have different sensitivities to substituent effects so that the perturbation introduced by the process is a constant and does not influence the two reactions proportionately.

The value of K_{AB} for the hindered phenolate ion 3,5-di-*tert*-butyl-4-hydroxybenzoate (**1**) shows a *positive* deviation above the Brønsted line for hydrogen bonding of ethylenediamine dication with other phenolate ions in Figure 9. This result is consistent with a favorable electrostatic effect from its two negative charges. However, it was initially surprising because *o-tert*-butyl groups cause large decreases in the equilibrium constants for formation of hydrogen-bonded complexes in nonhydroxylic solvents.[47,48] The normal value of K_{AB} in water must, again, reflect the fact that an exchange reaction rather than net hydrogen-bond formation is being measured; there must be a cancellation of similar unfavorable steric effects for the solvation by water and by a protonated amine. Examination of space-filling molecular models suggests that both water and ethylenediamine dication can form hydrogen bonds to the dianion of **1** (Chart I) without severe steric hindrance, but with only a limited number of possible orientations. The unfavorable equilibrium constants for the net formation of such hydrogen-bonded complexes arise from an unfavorable entropy term that is caused in large part by hindrance to free rotation of the two *tert*-butyl groups; the values of ΔH are almost normal.[47,48] Furthermore, ΔH for the formation of the hindered hydrogen-bonded complex **2** in the gas phase is similar to that for the unsubstituted pyridine–pyridinium ion complex.[48]

Acknowledgment. We are grateful to Ana-Maria Garcia for carrying out preliminary experiments on this problem.

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Appendix

Derivation of an equation describing the hydrogen-bonding interactions (Scheme III) of a dicationic buffer with a substituted phenol, AH, and phenolate anion, A^- is as follows:

$$[A^-_{obsd}] = [A^-] + [A^-\cdot B] + [A^-\cdot {}^+HB] \quad (11)$$

$$[A_{tot}] = [AH] + [AH\cdot B] + [A^-_{obsd}] \quad (12)$$

Substituting equilibrium expressions into eq 12 gives

$$[A_{tot}] = [AH](1 + K_2[B]) + [A^-_{obsd}]$$

$[AH] = [A^-]/R$, and substituting for $[A^-]$ from eq 11 gives

$$[A_{tot}] = \frac{[A^-_{obsd}](1 + K_2[B])}{R(1 + K_1[BH^+] + K_3[B])} + [A^-_{obsd}]$$

Expanding and rearranging gives

$$K_1[BH^+] + K_3[B] = \frac{[A^-_{obsd}] - [A^-_{obsd}]K_2[B] - ([A_{tot}] - [A^-_{obsd}])R}{R([A_{tot}] - [A^-_{obsd}])}$$

$[B] = f_B[\text{buffer}]$, where f_B = fraction buffer base, and $[BH^+] = f_A[\text{buffer}]$, where f_A = fraction buffer acid; thus

$$K_1f_A + K_3f_B = \frac{[A^-_{obsd}] - [A^-_{obsd}]K_2[\text{buffer}]f_B - R([A_{tot}] - [A^-_{obsd}])}{[\text{buffer}]R([A_{tot}] - [A^-_{obsd}])}$$

Expanding the expression for R and splitting the right side into two terms give

$$K_1f_A + K_3f_B = \frac{[A^-_{obsd}][A_{tot}] - [A_0^-][A^-_{obsd}] - [A_{tot}][A_0^-] + [A^-_{obsd}][A_0^-]}{[\text{buffer}][A_0^-]([A_{tot}] - [A^-_{obsd}])} + \frac{[A^-_{obsd}]f_BK_2}{R([A_{tot}] - [A^-_{obsd}])}$$

Simplifying and dividing by $[A_{tot}]$ gives eq 13. When $[A_{tot}] \gg [A_0^-] + [A^-_{obsd}]$, this equation simplifies to eq 2. The left side of this equation is equal to K_{buff}, which is identical with K_{AB} at $f_B = 0$.

$$f_AK_1 + f_BK_3 - \frac{[A^-_{obsd}]([A_{tot}] - [A_0^-])K_2f_B}{[A_0^-]([A_{tot}] - [A^-_{obsd}])} = \frac{[A^-_{obsd}] - [A_0^-]}{[\text{buffer}][A_0^-]\left(1 - \frac{[A^-_{obsd}]}{[A_{tot}]}\right)} \quad (13)$$

$$f_AK_1 + f_BK_3 - \frac{[A^-_{obsd}]}{[A_0^-]}K_2f_B = \frac{[A^-_{obsd}] - [A_0^-]}{[A_0^-][\text{buffer}]}$$

Registry No. $HOCH_2CH_2NH_3^+$, 22852-66-0; $^+H_3NCH_2CH_2CH_2NH_3^+$, 61696-59-1; $^+H_3NCH_2CH(OH)CH_2NH_3^+$, 102283-80-7; $^+H_2N(Et)CH_2C{\equiv}CCH_2(Et)NH_2^+$, 102283-81-8; $^+H_3NCH_2CH_2NH_3^+$, 22534-20-9; $^+H_3NCH_2CH(CH_3)NH_3^+$, 62063-19-8; $(Me)_3N^+CH_2CH_2NH_3^+$, 102283-82-9; $(Me)_2NH^+CH_2CH_2NH_3^+$, 38685-42-6; $(Me)_2NH^+CH_2CH_2N(Me)_2H^+$, 38685-37-9; ^+H_3NOH, 20712-83-8; 1,2-cyclohexanediamine conjugate diacid, 102283-83-0; 2-chloro-4-nitrophenolate, 30388-46-6; piperazine conjugate diacid, 21006-07-5; 3,5-di-*tert*-butyl-4-hydroxybenzoate dianion, 102283-84-1; *p*-methoxyphenolate, 29368-59-0; phenolate, 3229-70-7; *m*-hydroxybenzoate dianion, 16887-56-2; 5-nitrosalicylate, 102283-85-2; *p*-chlorophenolate, 24573-38-4; *p*-hydroxybenzoate dianion, 16885-71-5; *m*-nitrophenolate, 16554-54-4; *p*-hydroxyacetophenone anion, 18983-84-1; *p*-nitrophenolate, 14609-74-6; mercaptoacetate dianion, 16561-17-4; 2-mercaptoethanol anion, 102283-86-3; benzoate, 766-76-7.