In addition, heterocondensed rings such as thiazole, oxazole, thiophene, pyrrole, and pyridine, and substituents such as F, Cl, OMe, OPh, SMe, and SPh are fully consistent with such a trend. Another relevant challenge was the investigation of the synthetic potential of this new kind of reactivity. We think that the aim has been fully reached since a number of general methods for the syntheses of aromatic alkyl compounds containing different nitrogen functional groups (NO_2, NO, or NH_2) or a chlorine group have been devised. The synthetic utility of these reactions is also evidenced by specific methods involving the synthesis of unknown, 1,1-dialkyl-1,2-dihydronaphthalene-2-nitronic acids or difficulty available 10,10-dialkylanthracen-9-ones from commercial 1-methoxy-2-nitronaphthalene and 9-nitroanthracene, respectively.

It is a pleasure to acknowledge the contribution of Prof. G. Rosini and Drs. M. Bosco, G. Baccolini, and R. Dal Pozzo to this research. Thanks are also due to Prof. P. E. Todesco for encouragement and stimulating discussions. Financial support from CNR, Roma, "Progetto Finalizzato Chimica Fine e Secondaria", is also acknowledged.

Proton Transfer from Intramolecularly Hydrogen Bonded Acids

FRANK HIBBERT

Department of Chemistry, King's College London, Strand, London WC2R 2LS, England

Received February 1, 1983 (Revised Manuscript Received August 1, 1983)

Proton transfers are important because of their widespread occurrence as elementary steps in many reactions. In acid- and base-catalyzed and enzyme-catalyzed reactions, proton transfer between oxygen and nitrogen atoms in the catalyst and substrate is often a key step in the mechanism.

In enzymic reactions, in particular, proton transfer often occurs between groups that are involved in intramolecular hydrogen bonds. For example, in the charge relay mechanism of action of serine proteases a proton is delivered from serine to aspartate through an intervening histidine residue that is held in position by intramolecular hydrogen bonds.[1] Protons are transferred simultaneously from serine to histidine and from histidine to aspartate along these intramolecular hydrogen bonds.

Mechanistic proposals such as this are more complicated than any mechanisms that have been found for proton transfer in chemical systems. If these processes are to be understood, it is important to provide information from studies of more simple model systems.

Fortunately the kinetics of proton transfer between most oxygen and nitrogen acids is particularly straightforward since the reactions are usually diffusion controlled.[2] In one direction the rate coefficient has the diffusion limited value (10^9–10^{10} dm^3 mol^{-1} s^{-1}) and in the other direction the rate coefficient therefore differs from the diffusion-controlled limit by a factor equal to the value of the equilibrium constant of the reaction.

However, when the acidic proton in an oxygen or nitrogen acid is involved in an intramolecular hydrogen bond, as in many of the examples in enzymic reactions, the situation is more complicated. The rate of proton removal by external base is much reduced and the kinetic behavior varies considerably from one system to another. Until recently,[3] no definite information was available to explain these results and there was some controversy[4] about the mechanism of proton removal from acids of this type.

Two possible mechanisms had been suggested.[2,5] One possibility[2] is a two-step process involving a rapid equilibrium between hydrogen-bonded and non-hydrogen-bonded forms of the acid with proton transfer occurring from the more reactive open form present in low concentration. An alternative mechanism[5] consists of a single-step attack by base on the hydrogen-bonded proton through a transition state in which the hydrogen bond is partially broken. The difference between these mechanisms is quite subtle.

Some of our work in recent years has been directed toward understanding the reasons for slow proton removal from intramolecular hydrogen bonds. Significant progess has been made. Firm mechanistic conclusions have been reached and quite dramatic and unexpected effects have been observed in some cases. For example, an aromatic amine has been found that binds a proton so tightly that the amine is protonated even in 1 mol dm^{-3} aqueous sodium hydroxide. Under extremely basic conditions when proton removal is favorable, deprotonation occurs very slowly and a conventional spectrophotometer can be used to follow the reaction, in sharp contrast to the diffusion-controlled rates ob-

Frank Hibbert was born in Royton, England, and graduated from London University (King's College) in 1968. After postdoctoral research as a Fulbright Scholar with F. A. Long at Cornell University, he returned to London to lectureships at Queen Elizabeth College and later at Birkbeck College. He took up his present staff position at King's College in 1980.

(1) D. M. Blow, *Acc. Chem. Res.*, *9*, 145 (1976).
(2) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, *3*, 1 (1964); M. Eigen, W. Kruse, G. Maass, and L. de Maeyer, *Prog. React. Kinet.*, *2*, 285 (1964).
(3) F. Hibbert and A. Awwal, *J. Chem. Soc., Chem. Commun.*, 995 (1976); F. Hibbert and A. Awwal, *J. Chem. Soc., Perkin Trans. 2*, 939 (1978); F. Hibbert, *ibid.*, 1304 (1981).
(4) A. J. Kresge, *Chem. Soc. Rev.*, *2*, 475 (1973).
(5) M. H. Miles, E. M. Eyring, W. W. Epstein, and R. E. Ostlund, *J. Phys. Chem.*, *69*, 467 (1965).

0001-4842/84/0117-0115$01.50/0

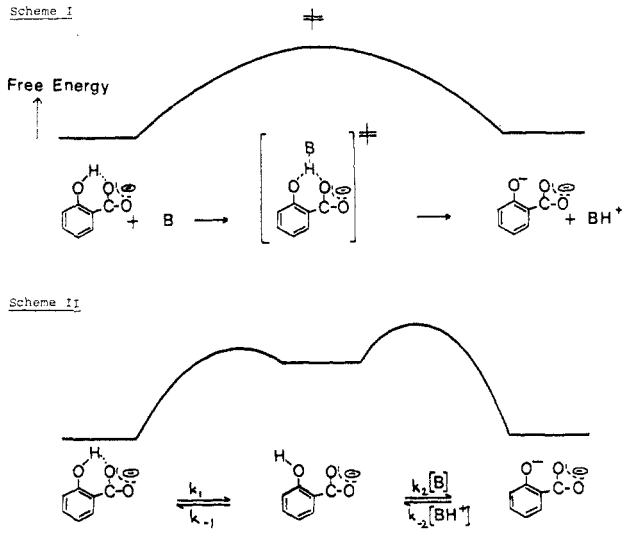


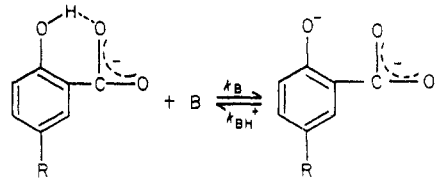
Figure 1. Free energy profile for proton removal from salicylate ion.

served for other nitrogen acids.

Proton Transfer from Salicylate Ion

The two mechanisms that were originally suggested[2,5] for proton removal from a hydrogen-bonded acid are shown for salicylate ion in Figure 1. Scheme I involves synchronous breakage of the intramolecular hydrogen bond and proton transfer to base, whereas in Scheme II these processes occur stepwise through an intermediate open form of the acid that is externally hydrogen bonded to water. For a number of hydrogen-bonded acids, mechanistic tests such as solvent effects,[6] isotope effects,[7] and substituent changes in the acid[8] failed[4] to provide positive evidence for one of these mechanisms over the other and the problem remained unsolved for several years.

We were able to reach definite conclusions[3] from studies of general-base-catalyzed proton removal from 4-[(3-nitrophenyl)azo]salicylate ion (eq 1). The phe-



(1)

R = 3-nitrophenylazo

nolic group in 4-[(3-nitrophenyl)azo]salicylate ion is weakly acidic (pK = 12.13). With hydroxide ion as the base (B) in eq 1, reaction in the forward direction is thermodynamically favorable and the rate constant, k_{OH^-} = 2.4 × 10^7 dm^3 mol^{-1} s^{-1}, was obtained.[3] This value is fairly typical of the results obtained for intramolecularly hydrogen bonded acids. Although these reactions are slower than would be observed for oxygen or nitrogen acids without an internal hydrogen bond, one must usually use fast reaction techniques to follow the reactions. Equilibrium 1 was studied by the temperature–jump method and relaxation times around 10 μs were measured. General-base catalysis of reaction 1 was studied with use of aliphatic amines as bases that were chosen so that the salicylate ion (ROH) and the conjugate acid (BH^+) of the base catalyst were of similar acidity, ΔpK = pK(ROH) − pK(BH^+) = ca. 0. For proton transfer from an oxygen or nitrogen acid without an internal hydrogen bond, the values of the forward and reverse rate coefficients (k_B and k_{BH^+}) vary with the base strength of B according to the dashed line in Figure 2.

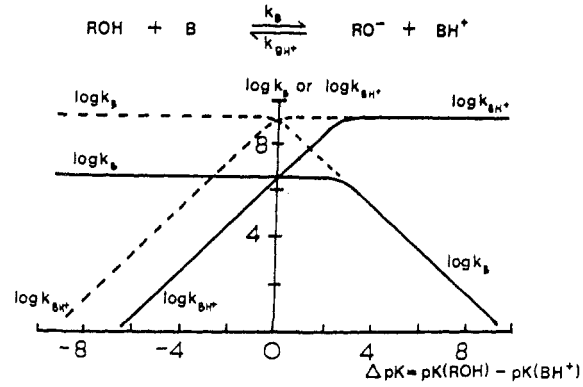


Figure 2. Base-catalyzed proton removal from oxygen and nitrogen acids.

For a hydrogen-bonded salicylate ion that deprotonates by Scheme I or II, different results are predicted.[3] For the mechanism in Scheme II, on the assumptions that the non-hydrogen-bonded intermediate is present in low concentration and that the rate at which the hydrogen bond closes is greater than the rate of proton removal from the intermediate, the rate coefficients are given by eq 2 in which K^* is the equi-

$$k_B = k_2K^* \text{ and } k_{BH^+} = k_{-2} \quad (2)$$

librium constant between hydrogen-bonded and open forms of the salicylate ion and k_2 and k_{-2} are the forward and reverse rate coefficients for proton transfer between the open form and base B. If the second step in Scheme II behaves as a normal proton transfer, the rate coefficient in the forward direction will have a value, k_2 ca. 2 × 10^{10} dm^3 mol^{-1} s^{-1}, with B = OH^-. Since the result, k_{OH^-} = 2.4 × 10^7 dm^3 mol^{-1} s^{-1}, was obtained, the model of Scheme II (cf. eq 2) calls for the equilibrium constant for opening of the intramolecular hydrogen bond to have the value, K^* = ca. 1 × 10^{-3}. It then follows that the second step in Scheme II should be thermodynamically favorable in the forward direction for reaction with amine bases, even though for the overall reaction ΔpK = ca. 0. In that case, k_2 and therefore k_B will be independent of the base strength of B around ΔpK = 0.

The predictions of this analysis are shown as the solid lines in Figure 2, which is constructed for an intramolecularly hydrogen bonded acid for which K^* = 1 × 10^{-3} and k_2 = 2 × 10^9 dm^3 mol^{-1} s^{-1} for reaction with amines. The region of bending, where the plots of log k_B and log k_{BH^+} against ΔpK depart from zero and unity, is predicted to occur at ΔpK = −logK^* = 3 for this intramolecularly hydrogen bonded acid as opposed to around ΔpK = 0 for an acid without an internal hydrogen bond. For an acid with a stronger hydrogen bond, the value of K^* will be smaller and this will have the effect of lowering the constant value of k_B found at

(6) R. P. Jensen, E. M. Eyring, and W. M. Walsh, *J. Phys.* Chem., *70*, 2264 (1966).
(7) J. L. Haslam and E. M. Eyring, *J. Phys. Chem.*, *71*, 4470 (1967).
(8) M. H. Miles, E. M. Eyring, W. W. Epstein, and M. T. Anderson, *J. Phys. Chem.*, *70*, 3490 (1966); M. C. Rose and J. E. Stuehr, *J. Am. Chem. Soc.*, *94*, 5532 (1972); T. Fueno, O. Kajimoto, Y. Nishigaki, and T. Yashioka, *J. Chem. Soc., Perkin Trans. 2*, 738 (1973).

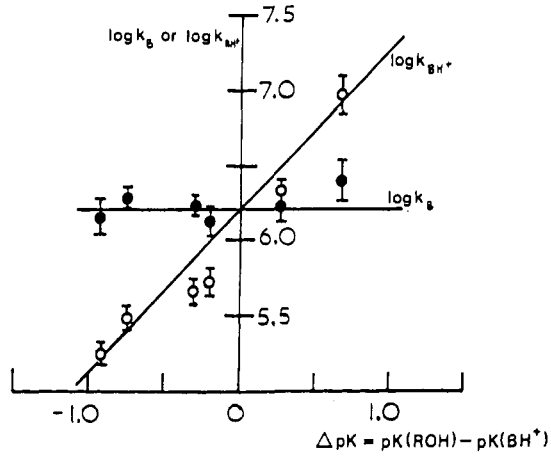


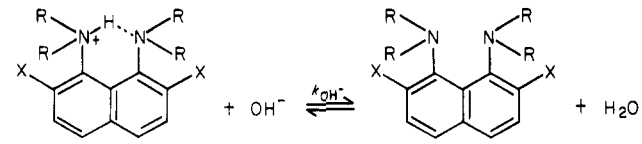
Figure 3. Amine-catalyzed proton removal from 4-[(3-nitrophenyl)azo]salicylate ion. The filled-circle data points are log k_B for reactions of amines with the salicylate ion, and the open-circle points are log k_{BH^+} for reactions of ammonium ions with the salicylate dianion.

$\Delta pK = 0$ and of shifting the region of curvature in the plots of log k_B and log k_{BH^+} toward higher ΔpK.

The predictions of Figure 2 are nicely confirmed by the results shown in Figure 3. The plots of log k_B and log k_{BH^+} against ΔpK have slopes of 0.0 ± 0.1 and 1.0 ± 0.1, respectively, and these results were taken as evidence for the operation of Scheme II. It was argued[3] that, if proton transfer were occurring by the mechanism in Scheme I, it would be expected that, when the salicylate ion and BH^+ have similar acidities (ΔpK = 0), the proton in the transition state would be roughly half-transferred and plots of log k_B and log k_{BH^+} against ΔpK would have slopes around 0.5. Since the data in Figure 3 are not compatible with this prediction, Scheme I was ruled out.

It is interesting that the two-step mechanism for proton transfer is kinetically more favorable. Presumably the one-step reaction is unfavorable because the base must attack the proton directly with no intervening solvent molecule and because the groups between which the proton is transferred cannot take up the most favorable in-line orientation in the transition state. In the two-step process the actual proton transfer from the open form of the acid may well occur at diffusion-controlled rate, as for a normal acid, and the overall reaction rate is reduced because the process occurs through a low-concentration intermediate. Since the overall reaction is first order in base, the rate at which the open form reverts back to the hydrogen-bonded species must be greater than the rate of proton removal from the open form by base. Hence a value of $k_{-1} \geq$ ca. 6×10^7 s^{-1} can be estimated for this step in Scheme II, and from the value $K^* = 1.0 \times 10^{-3}$, it follows that $k_1 \geq 6 \times 10^4$ s^{-1}. It is clear from Figure 2 that a rate of proton removal from an intramolecularly hydrogen-bonded acid reduced with respect to a normal acid will be observed only for reactions that are thermodynamically favorable or weakly unfavorable and that for thermodynamically unfavorable proton transfer to weak bases (for which $\Delta pK > 3$) normal diffusion-controlled rates of reaction will be osberved, with a rate coefficient in the reverse direction of ca. 10^{10} dm^3 mol^{-1} s^{-1}.

Table I
Kinetic and Equilibrium Data for Reaction of Protonated Naphthalenediamines with Hydroxide Ion



K = [naphthalenediamine]/[protonated naphthalenediamine] [OH^-]

R, X	K/dm^3 mol^{-1}	k_{OH^-}/dm^3 mol^{-1} s^{-1}	solvent (v/v)	pK
R = Me, X = H	52	1.9×10^5	aqueous	12.1
R = Me, X = H	2800	6.1×10^5	30% Me_2SO-H_2O	12.1
R = Et, X = H	380	1.6×10^4	30% Me_2SO-H_2O	13.0
R = Me, X = OMe	250	4.4×10^2	60% Me_2SO-H_2O	16.1
R = Et, X = OMe	116	3.3	60% Me_2SO-H_2O	16.3

Acid-Base Properties of Naphthalenediamines

Over the past 10 years[9-12] we have discovered some intriguing acid–base behavior of 1,8-naphthalenediamines. In the protonated amines the proton sits in a strong intramolecular hydrogen bond and this is partly responsible for the unique behavior. 1,8-Bis(dimethylamino)naphthalene (R = Me, X = H in Table I) is half-protonated[9,13] in aqueous solution in the presence of 0.02 mol dm^{-3} sodium hydroxide and this corresponds to a pK value of 12.1. This is an exceptionally high value for an aromatic amine. As a result, the molecule is often referred to as proton sponge. 1,8-Bis(diethylamino)-2,7-dimethoxynapthalene is even more basic; it remains fully protonated in 1 mol dm^{-3} aqueous sodium hydroxide. To study the acid–base equilibrium of this amine it was necessary to use extremely basic Me_2SO–H_2O mixtures containing hydroxide ion and to estimate the aqueous pK values given in Table I by using a stepwise procedure.[9,11]

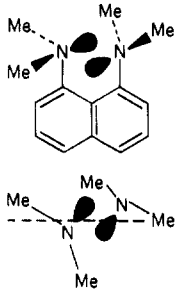
The amines in Table I also show very unusual kinetic behavior. As the amines become stronger bases, the rate coefficients (k_{OH^-}) are reduced increasingly further below the diffusion-limited value. In the case of 1,8-bis(diethylamino)-2,7-dimethoxynaphthalene,[11] when sodium hydroxide is introduced into a solution of the protonated amine in 60% (v/v) Me_2SO–H_2O, the increase in absorbance at 350 nm accompanying formation of the free amine can be followed by using a conventional spectrophotometer since the reaction occurs with a half-life in the range of seconds. When these observations were first made, we found it difficult to accept that such a simple amine should depart so dra-

(9) F. Hibbert, *J. Chem. Soc., Perkin Trans. 2*, 1862 (1974); A. Awwal and F. Hibbert, *ibid.*, 1589 (1977).
(10) F. Hibbert, *J. Chem. Soc., Chem. Commun.*, 463 (1973); F. Hibbert and A. Awwal, *J. Chem. Soc., Perkin Trans. 2*, 152 (1977); F. Hibbert and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 141 (1980); F. Hibbert and K. P. P. Hunte, *J. Chem. Soc., Perkin Trans. 2*, 1562 (1981).
(11) R. W. Alder, N. C. Goode, N. Miller, F. Hibbert, K. P. P. Hunte, and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 89 (1978); F. Hibbert and K. P. P. Hunte, *J. Chem. Soc., Perkin Trans. 2*, 1895 (1983).
(12) F. Hibbert and H. J. Robbins, *J. Am. Chem. Soc., 100*, 8239 (1978).
(13) R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).

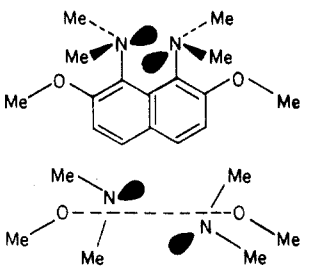
matically from the behavior observed for other amines.

One of the factors that is responsible for the high basicities of these amines, and the low rates, is the presence of a strong intramolecular hydrogen bond in the protonated amine. The acidic protons are seen at δ 19.5 in the NMR spectrum of the protonated amines, typical of protons strongly deshielded by hydrogen bonding. Hydrogen isotope effects on the chemical shift indicate that the proton is located in a double minimum potential well[14] and the ESCA spectrum shows that the hydrogen bond is unsymmetrical.[15]

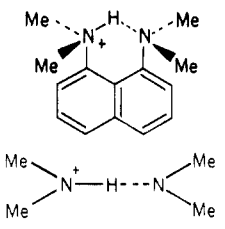
It is unlikely that the hydrogen bond alone could lead to the enhanced basicities that are observed. Destabilization of the amines by steric interactions between the nitrogen lone pairs and between the alkyl substituents may also contribute. The structures[16] of 1,8-bis(dimethylamino)naphthalene (1) and 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene (2) show how the amines are able to avoid these unfavorable interactions to some extent, but only by loss of the planarity of the naphthalene ring and of the dimethylamino groups with the naphthalene ring. For both amines relief of strain occurs on protonation because the proton can be accommodated with less strain in the intramolecularly hydrogen-bonded ammonium ions.[17]



1



2



3

We now turn to the factors that are responsible for the low rates of proton transfer to and from the amino groups in these compounds. We again consider two possible mechanisms for the reaction. To distinguish between single-step and two-step removal of the hydrogen-bonded proton, we studied the reaction of 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene in 70% (v/v) Me_2SO–H_2O in the presence of various buffers by means of the temperature–jump technique.[12] Studies were also made with 1,8-bis(diethylamino)-2,7-dimethoxynaphthalene under similar conditions with use of the stopped-flow technique or a conventional spectrophotometer to follow these slower reactions.[18]

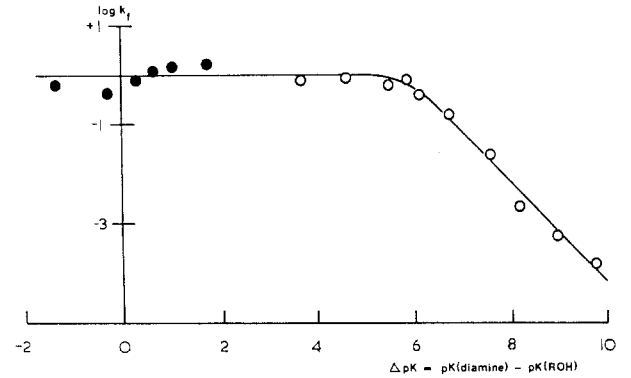
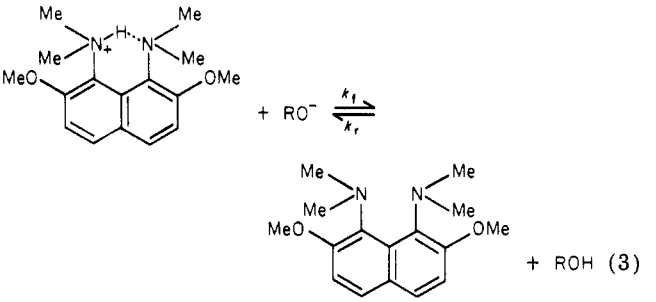


Figure 4. Proton transfer for 1,8-Bis(dimethylamino)-2,7-dimethoxynaphthalene.

The data for reaction 3 are shown as the solid points



+ ROH (3)

in Figure 4 and, as can be seen, the rate coefficient for proton removal (k_f) is largely unaffected by a change in catalyst basicity of 3 pK units.[12,18]

These observations are best explained by the two-step mechanism for proton removal as described for salicylate ion (Scheme II). It therefore appears that the same mechanism operates for these different hydrogen bonds. Using an isotope tracer technique, Kresge[19] has extended the data for 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene to weaker base catalysts; his results are shown as the open circles in Figure 4. Actually these latter results refer to aqueous solution, and in order to show both sets of data on the same plot, the values of the rate coefficients in 70% (v/v) Me_2SO–H_2O were reduced by a factor of 200. The solid line in Figure 4 is calculated on assumption of the two-step mechanism with values of $K^* = 1.0 \times 10^{-6}$ and $k_2 = 1.0 \times 10^6$ $dm^3\ mol^{-1}\ s^{-1}$ in eq 2.

Thus it is concluded that the overall rate of proton removal from protonated 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene is low because the intermediate open form is present in extremely low concentration ($K^* = 1.0 \times 10^{-6}$) and because proton removal from the open form occurs at a rate that is 3 orders of magnitude below the diffusion limit. This latter is probably the result of a steric effect.

Studies of Hydrogen-Bonded (Phenylazo)resorcinol Monoanions

Interesting behavior has recently been found for removal of phenolic protons that are intramolecularly hydrogen-bonded to azo groups. Although there are a number of unresolved problems, some important con-

(14) L. J. Altman, D. Laungani, G. Gunnarsson, H. Wennerstrom, and S. Forsen, *J. Am. Chem. Soc.*, *100*, 8264 (1978).
(15) E. Haselbach, A. Henriksson, F. Jachimowicz, and J. Wirz, *Helv. Chim. Acta*, *55*, 1757 (1972).
(16) H. Einspahr, J.-B. Robert, R. E. Marsh, and J. D. Roberts, *Acta Crystallogr., Sect. B 29B*, 1611 (1973).
(17) M. R. Truter and B. L. Vickery, *J. Chem. Soc., Dalton Trans.*, 395 (1972).
(18) F. Hibbert, *J. Am. Chem. Soc.*, in press.
(19) A. J. Kresge and M. F. Powell, *J. Am. Chem. Soc.*, *103*, 972 (1981).

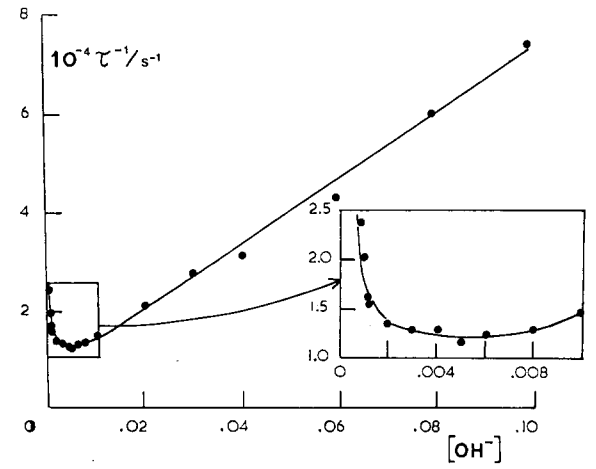
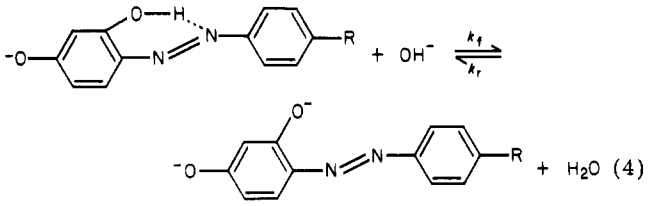


Figure 5. Hydroxide ion catalyzed ionization of 4-[(4-sulfonatophenyl)azo]resorcinol.

clusions are beginning to emerge. Kinetic results for reaction 4, involving 4-(phenylazo)resorcinol monoan-



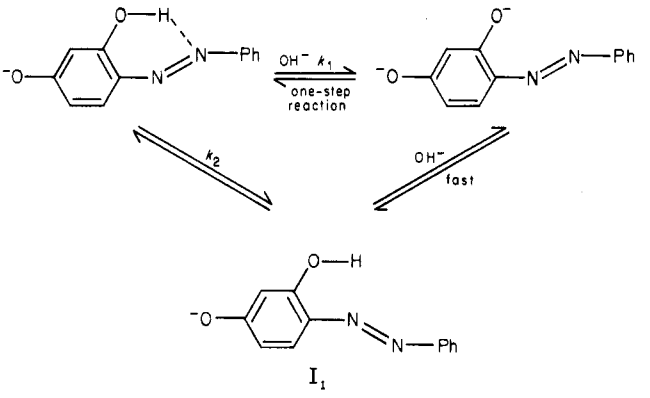
ions with different substituents R, have been known for some time. Results for this reaction obtained in different laboratories[20] appeared to show that the reciprocal relaxation time for equilibration between the hydrogen-bonded monoanion and the dianion in the presence of excess or buffered hydroxide ion was linearly related to the hydroxide ion concentration (eq 5),

$$\tau^{-1} = k_f[OH^-] + k_r \quad (5)$$

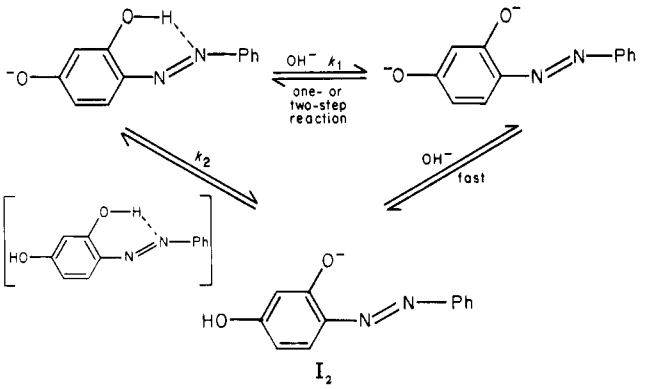
as expected. However closer examination[21,22] of the results has revealed that in some cases the reciprocal relaxation time actually goes through a minimum value as $[OH^-]$ is varied. This fascinating observation means that at low hydroxide ion concentrations the rate of approach to equilibrium decreases as the hydroxide ion concentration is increased. The data are therefore not compatible with eq 5. In some cases the minimum in τ^{-1} is indistinct, occurring at low $[OH^-]$; this is the reason that minima were not detected in the earlier work.

A minimum in τ^{-1} was first observed for proton transfer from 4-[(4-sulfonatophenyl)azo]resorcinol (R = SO_3^- in eq 4). Data for this reaction determined[23] in our laboratory by the temperature-jump technique and which confirm the original results[21] are given in Figure 5. Two different mechanistic explanations have been proposed to account for the results when a minimum in τ^{-1} is observed. These are shown in Schemes III and IV for 4-(phenylazo)resorcinol monoanion. In Scheme III[21] reaction from the monoanion to the dianion occurs by two routes. The upper route consists of direct attack

Scheme III



Scheme IV



by hydroxide ion on the hydrogen-bonded proton, while the lower route consists of opening of the hydrogen bond to give a low concentration intermediate from which proton transfer occurs.

These paths are precisely the two possible mechanisms that we have considered for proton removal from other hydrogen-bonded acids. Therefore studies of the (phenylazo)resorcinol monoanions are of great interest because, if it can be shown that proton removal follows Scheme III, it will mean that both one-step and two-step proton transfer can occur for these hydrogen-bonded acids.

Equation 6, which predicts a minimum in τ^{-1} at $[OH^-]$

$$\tau^{-1} = (k_2 + k_1[OH^-])(1 + 1/K[OH^-]) \quad (6)$$

$= (k_2/Kk_1)^{1/2}$, is derived from Scheme III by assuming that the proton-transfer equilibrium between the open form and the dianion occurs rapidly. In equation 6, K is the overall equilibrium constant between the monoanion and dianion. An alternative explanation for the minimum in τ^{-1} is shown in Scheme IV.[22] Two routes from the monoanion to dianion are again involved. In the upper route proton removal from the monoanion occurs either by direct attack or by two-step reaction through an open form; the precise mechanism is not specified. The dependence of τ^{-1} on $[OH^-]$ predicted for Scheme IV is identical with that for Scheme III as given in eq 6, although k_1 and k_2 refer to different reaction steps in each case.[24]

We addressed ourselves to the problem of devising an experiment that would permit a choice between Schemes III and IV. An interesting experiment[25] that

(20) M. Eigen and W. Kruse, *Z. Naturforsch. B, 18*, 857 (1963); W. H. Inskeep, D. L. Jones, W. T. Silfvast, and E. M. Eyring, *Proc. Natl. Acad. Sci., 59*, 1027 (1968); M. C. Rose and J. E. Stuehr, *J. Am. Chem. Soc., 93*, 4350 (1971).

(21) B. Perlmutter-Hayman and R. Shinar, *Int. J. Chem. Kinet., 7*, 453 (1975); B. Perlmutter-Hayman, R. Sarfaty, and R. Shinar, *ibid., 8*, 741 (1976).

(22) N. Yoshida and M. Fujimoto, *Chem. Lett.*, 1301 (1977).

(23) F. Hibbert and G. R. Simpson, unpublished results.

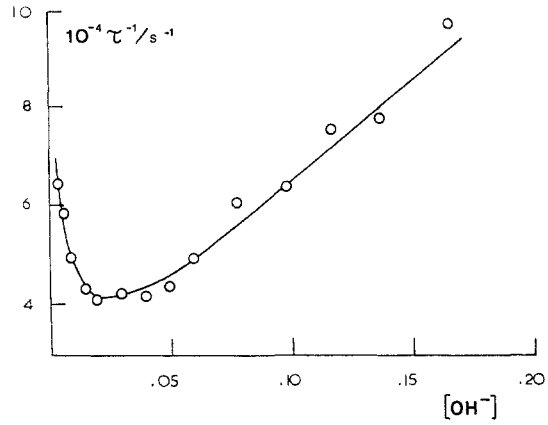
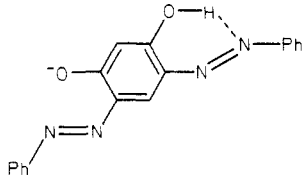
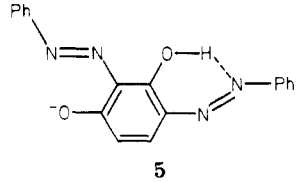


Figure 6. Hydroxide ion catalyzed ionization of 2,4-bis(phenylazo)resorcinol monoanion.

provides some further information involves the bis(phenylazo)resorcinol monoanions **4** and **5**. In the



4



5

deprotonation of mono(phenylazo)resorcinol monoanions, the intermediates I_1 and I_2 in Schemes III and IV differ in the location of a proton. If these schemes are considered for the deprotonation of **4**, however, it is seen that the intermediates I_1 and I_2 become identical. This arises because in **4** a proton cannot be relocated to a position where it is unable to participate in an intramolecular hydrogen bond. Similar conclusions are reached for **5**.

It is therefore of interest to compare **4** and **5** with the mono(phenylazo)resorcinols for which a minimum in τ^{-1} has been observed. It turns out that for **5** a clear minimum in τ^{-1} is observed as shown in Figure 6, and for **4** the data are compatible with a minimum in τ^{-1} just outside the experimentally accessible range of hydroxide ion concentrations. Hence the conclusion is reached that for the bis(phenylazo)resorcinols, as for mono(phenylazo)resorcinols, two routes from the monoanion to the dianion are operating. However for **4** and **5** it can further be deduced that one route involves direct attack by hydroxide ion on the intramolecularly hydrogen-bonded proton and the other route involves an open non-hydrogen-bonded form that arises either by unimolecular (or solvent assisted) opening of the hydrogen bond or through a protonation–deprotonation sequence as in the lower route of Scheme IV. Thus the results lend support to the claim[21] that direct attack by base on a hydrogen-bonded proton can occur.

It is our view, however, that this process will not be found generally for hydrogen-bonded acids. In fitting eq 6 to the experimental results for 4-[(4-sulfonatophenyl)azo]resorcinol and for **5**, values for the rate coefficients for opening of the intramolecular hydrogen bond of 2.0×10^3 and 7.4×10^3 s^{-1}, respectively, are found. These values seem very low and perhaps indicate that the hydrogen bonds in (phenylazo)resorcinols are unusual. If the value of the rate coefficient for opening of the intramolecular hydrogen bond is larger, as seems probable for the majority of hydrogen-bonded acids, the two-step deprotonation through the open form will predominate.

Concluding Remarks

When the proton in an acid is involved in an intramolecular hydrogen bond, dramatic effects on the proton acidity and on the rate of proton removal are manifested. Examples are now known where a hydrogen bond in combination with other factors increases the half-life for thermodynamically favorable ionization of a proton from nitrogen into the seconds range, although the typical effect of a hydrogen bond is usually not as large as this. The mechanism for most of these reactions involves rapid preequilibrium formation of a low concentration of a non-hydrogen-bonded open form of the acid from which the proton is removed, although in some cases the possibility of direct attack by base on the hydrogen-bonded proton has not been ruled out.

Given this progress in our understanding of proton transfer from intramolecular hydrogen bonds to an external base, future work will be directed toward the complex part that this and related processes play in enzymic reactions.

(24) Yet another possibility that was not specifically considered previously involves the keto–imino tautomer of 4-(phenylazo)resorcinol monoanion as a low-concentration intermediate. This is an interesting possibility for future work.

(25) F. Hibbert and G. R. Simpson, *J. Am. Chem. Soc.*, *105*, 1063 (1983).