Kinetics of Proton Transfer Reactions in Aqueous Solution. III. Rates of Internally Hydrogen-Bonded Systems

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Abstract: Relaxation measurements by the temperature-jump technique have been carried out in a number of indicator systems: alizarin yellow R (I), alizarin yellow G (II), tropaeolin O (III), Clayton yellow (IV), quinizarin-2-sulfonic acid (V), phenolphthalein (VI), and *p*-xylenol blue (VII). Observed relaxation times ranged from 5 μsec to 0.3 msec and were interpreted in most cases on the basis of the hydrolysis reaction $OH^- + HIn^z \rightleftharpoons In^{z-1} + H_2O$. The smallest bimolecular rate constant (k_f) measured was 2.9×10^4 (for IV); the largest 3.0×10^9 (for VII). These values, in many instances several orders of magnitude lower than diffusion controlled, are interpretable on the basis of a finite chemical activation barrier resulting usually from internal hydrogen bonding. On a Brønsted plot of log k *vs.* pK_a the data correlated well with other measurements in such systems. Several parallel curves were observed depending on the type of bonding present. The Brønsted coefficient was found to be 1.0 in each case, indicating that the transition state is very similar to the products. The present data also support the generalization that the O–H···N hydrogen bond is stronger than that in O–H···O.

Eigen and his coworkers[2-4] have shown that the rates of all "normal" acid–base reactions in aqueous media are diffusion controlled; that is, reaction occurs as soon as the partners have approached to within a critical separation. At that distance the proton transfer is accomplished by the proton jumping across one or more intervening solvent molecules hydrogen bonded to the reacting partners. Rate constants for the diffusion-controlled reaction of the hydrogen ion with an acid anion are on the order of 10^{11} M^{-1} sec^{-1}; for the reaction of hydroxyl ion with an acid molecule rate constants are about 3×10^{10} M^{-1} sec^{-1}. The difference reflects primarily the higher mobility of the hydrogen ion.

A requirement for diffusion control is the presence of hydrogen-bonded solvent molecules between the partners such that the proton jumping across the solvent molecules can proceed unhindered with virtually no energy barrier. This requirement is not fulfilled (a) if intramolecular electronic rearrangement must occur (as in pseudo acids), (b) where strong intramolecular hydrogen bonds in one reactant are present, or (c) where steric factors reduce the angle acceptable for successful encounter.[2-4] Such reactions may no longer be diffusion controlled, and in some instances will be quite slow.

We report here an investigation of proton transfer reactions involving high pK_a indicator systems. The work was carried out because first, many high pK_a systems are internally hydrogen bonded. A study of the kinetics of hydrolysis in such systems can provide correlations between the rates and strength of hydrogen bonding. Second, fast reaction measurements in colorless systems usually involve coupling to a rapid indicator in order to allow the detection to be carried out in the visible region of the spectrum. From a practical standpoint, it is necessary to characterize the indicator preequilibrium rates, particularly when they are substantially slower than diffusion controlled.

The indicators studied in this investigation were alizarin yellow R (I), alizarin yellow G (II), tropaeolin O (III), Clayton yellow (IV), quinizarin-2-sulfonic acid (V), phenolphthalein (VI), and *p*-xylenol blue (VII).

Experimental Section

Materials. Stock solutions of each indicator[5] (10^{-3} M) were made up in degassed distilled water. Aliquots were diluted to the desired concentrations using sufficient KNO_3 to maintain an ionic strength of 0.1.

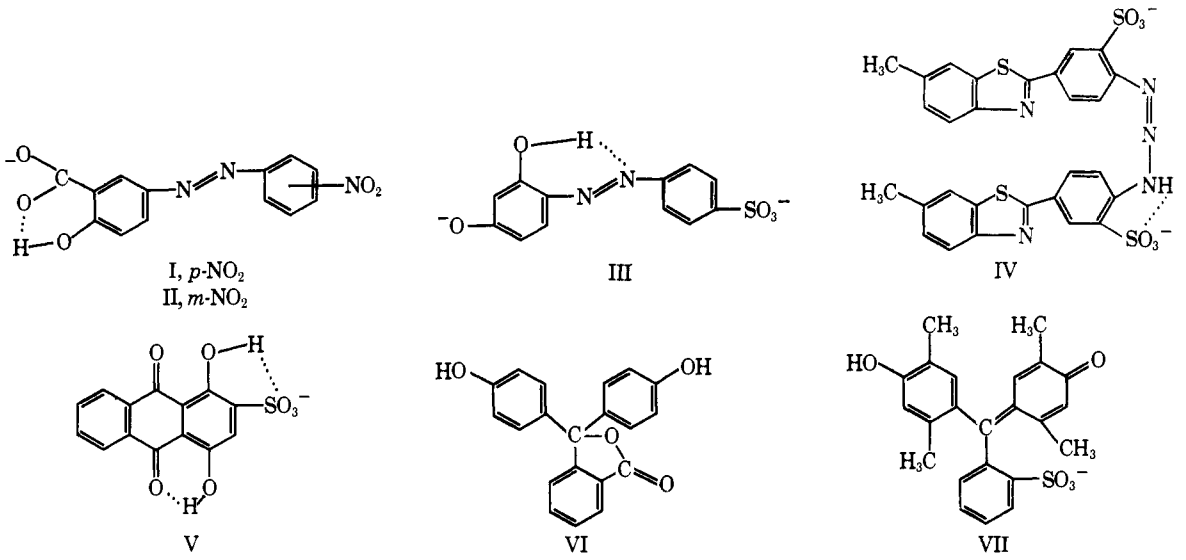
Instrumentation. pH measurements were made on a Beckman Expandomatic meter standardized with Fisher Certified buffers. The pH in the temperature-jump cell was measured before and after *each* temperature-jump experiment. Visible spectra of the indicators were measured on a Bausch and Lomb 505 spectrophotometer in order to locate the optimum wavelengths for maximum changes in transmittance. For each pH range studied, the pK_a of each indicator, at the same temperature and ionic strength as the kinetic study, was determined optically[6] on a Beckman DU spectrometer modified with the Gilford Direct Reading Absorbance Indicator Unit. All kinetic runs were carried out on a temperature-jump relaxation spectrometer[7] obtained from Messanlagen Studiengesellschaft.[8] The cell was thermostated with the Lauda Ultra Kyromat TK-30D such that the temperature following the jump was $25 \pm 1°$ (except for Vb and VI where $T = 15 \pm 1°$). The resultant relaxation curves were photographed with a Polaroid camera system. Relaxation times were evaluated directly from the photograph or from an enlarged copy.

Results

The conditions and measured relaxation times are given in Table I. A single relaxation time in each pH region studied was observed for most systems. The exceptions were quinizarin-2-sulfonic acid and Clayton yellow which are discussed below. All the measurements can be interpreted on the basis of the hydrolysis reaction

$$OH^- + HIn^z \underset{k_r}{\overset{k_f}{\rightleftharpoons}} In^{z-1} + H_2O \qquad \text{(a)}$$

(1) To whom all correspondence should be addressed.
(2) M. Eigen, *Angew. Chem.*, 75, 489 (1963); *Angew. Chem. Intern. Ed. Engl.*, 3, 1 (1964).
(3) M. Eigen and L. DeMaeyer, "Technique of Organic Chemistry," Vol. VIII, Part II, L. Friess and A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1963, Chapter XVIII.
(4) M. Eigen, W. Kruse, G. Maass, and L. DeMaeyer, *Progr. Reaction Kinetics*, 2, 287 (1964).
(5) Sources: I and III sodium salts, Eastman Kodak; II sodium salt, Matheson Coleman and Bell; IV, Fisher Scientific; V, Aldrich; VI, Mallinckrodt; VII sodium salt, Aldrich.
(6) M. G. Mellon, "Analytical Absorption Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1950, pp 128–133.
(7) G. Czerlinski and M. Eigen, *Z. Elektrochem.*, 62, 652 (1959); see also ref 3.
(8) Göttingen, W. Germany.



I, p-NO_2
II, m-NO_2

III

IV

V

VI

VII

where z is the charge on the protonated indicator in the pH region studied and k_f and k_r are the forward and reverse hydrolysis rate constants. The relaxation time for a is given by (charges omitted)

$$\tau^{-1} = k_f(\bar{C}_{OH} + \bar{C}_{HIn}) + k_r \qquad (1)$$

where the bar refers to equilibrium concentrations. The rate constants k_f and k_r were obtained as the slope and intercept, respectively, of a graph of τ^{-1} *vs.* the

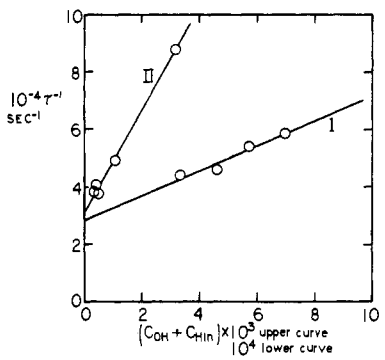
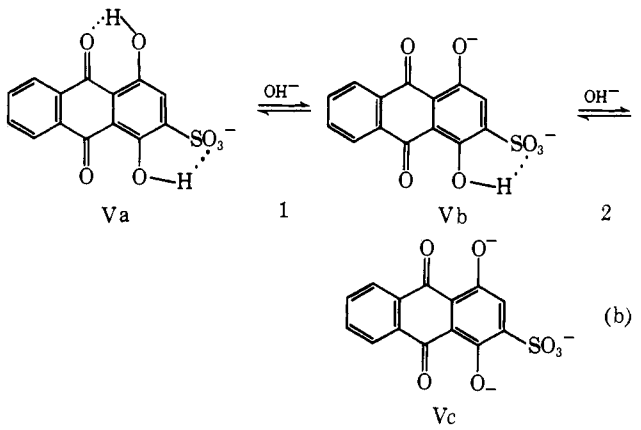


Figure 1. Concentration dependence of the relaxation time in alizarin yellow R (I) and G (II).

sum of the two concentrations (Figure 1). The second-order rate constants varied over the range 2.9×10^4 to 3.0×10^9 M^{-1} sec^{-1}. The last column of Table I compares the ratio of rate constants with the spectrophotometrically determined equilibrium constant; in general the agreement is excellent.

Two relaxation times (τ_a and τ_b of Table I) were found for quinizarin-2-sulfonic acid. Both were interpreted in terms of reaction a. The former was observed over the pH range 8–10, the latter over the pH range 11–13. The lower pK (and τ_a) is associated with step 1, the higher pK_a (and τ_b) with step 2 of the two hydrolyses represented by mechanism b. The basis for this assignment is twofold: (1) the polarity of the S^{2+}–O^- bond and the charge on the sulfonate group increases the stability of the internal hydrogen bond to the sulfonate oxygen, and (2) doubly bonded oxygen has less s character and thus is less electronegative than singly bonded oxygen.[9] This assignment is also supported by the kinetic data since $k_{Va} \gg k_{Vb}$.



Va 1 Vb 2

Vc (b)

For Clayton yellow two relaxation times were observed for each solution. The first (faster) of these could be associated unambiguously with mechanism a and eq 1. The slower time appeared to get longer with increasing [OH], but could not be quantitatively associated with a specific mechanism. It is likely that this slower time is associated with the transfer of a proton to and from the sulfur in structure IV.

Discussion

A detailed mechanism for the hydrolysis may be represented by[2]

$$\underset{1}{OH^-} + HIn^z \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \underset{2}{HO^- \cdots HIn^z} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \underset{3}{In^{z-1}} + H_2O \qquad (c)$$

where the state $HO \cdots HIn$ represents an "encounter complex" in which the partners are bridged by the minimum number of water molecules (presumably two) prior to proton transfer. The rate constants k_{12}, k_{21} are diffusion-controlled values and k_{23}, k_{32} refer to the chemical transformation. If the intermediate is present in vanishingly small concentrations, then stationary-state treatment yields[2,4] a single relaxation time, eq 1, where $k_f = k_{12}k_{23}/(k_{21} + k_{23})$ and $k_r = k_{32}k_{21}/(k_{21} + k_{23})$. For "normal" proton transfer $k_{23} \gg k_{21}$ and the frequency

(9) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, Chapter 3.

Table I. Thermodynamic and Kinetic Results[a]

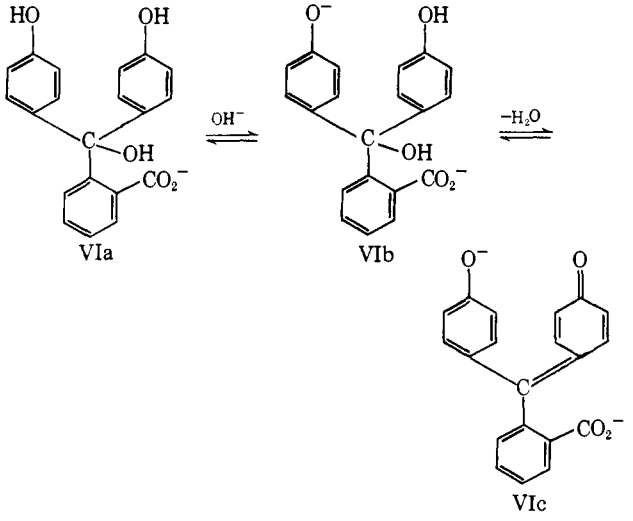
Indicator concn, M	pH[b]	$\tau^{-1} \times 10^{-4}$, sec^{-1}	k_f, M^{-1} sec^{-1}	k_r, sec^{-1}	$K^c = k_r/k_f$
		I, Alizarin Yellow R			
9.8×10^{-5}	10.30	4.37	4.0×10^{7}	3.2×10^{4}	8.1×10^{-4}
	10.49	4.62			(8.9×10^{-4})
	10.60	5.41			
	10.70	5.81			
		II, Alizarin Yellow G			
1.9×10^{-4}	10.03	3.40	1.7×10^{7}	3.2×10^{4}	1.7×10^{-3}
	10.11	3.85			(1.6×10^{-3})
	10.39	4.32			
	10.44	3.80			
	10.88	4.93			
	11.40	8.77			
		III, Tropaeolin O			
7.9×10^{-5}	11.00	1.49	9.0×10^{5}	1.3×10^{4}	1.4×10^{-2}
	11.04	1.32			(1.3×10^{-2})
	11.20	1.97			
	11.30	1.71			
	11.40	1.92			
	11.50	1.80			
	11.60	1.92			
	11.71	1.44			
	11.80	1.98			
	11.90	2.15			
		IV, Clayton Yellow[e]			
2.9×10^{-4}	11.20	0.36	2.9×10^{4}	$\sim 3 \times 10^{3}$	
	11.48	0.40			(1.0×10^{-1})
	11.59	0.35			
	11.92	0.39			
	12.12	0.34			
	12.25	0.35			
	12.32	0.50			
	12.71	0.53			
		Va, Quinizarin-2-sulfonic Acid (τ_a)			
7.74×10^{-5}	9.08	0.92	1.0×10^{8}	2.6×10^{3}	2.6×10^{-5}
1.04×10^{-4}	9.49	1.21			(2.5×10^{-5})
1.50×10^{-4}	8.09	1.73			
	8.72	1.36			
1.79×10^{-4}	9.12	1.39			
	9.73	1.47			
		Vb, Quinizarin-2-sulfonic Acid[d] (τ_b)			
1.59×10^{-4}	12.00	4.47	2.7×10^{6}	9×10^{3}	3.3×10^{-3}
	12.05	5.60			(3.6×10^{-3})
	11.90	4.40			
5.9×10^{-5}	11.98	4.00			
	12.30	5.60			
	12.40	8.60			
	11.91	3.76			
		VI, Phenolphthalein[d]			
1.38×10^{-5}	8.57	11.6	1.7×10^{9}	4.7×10^{4}	2.7×10^{-5}
	8.92	10.5			(2.3×10^{-5})
	9.10	7.4			
	9.90	21.7			
2.78×10^{-5}	9.60	16.5			
6.91×10^{-5}	8.83	15.4			
	9.31	17.3			
		VII, *p*-Xylenol Blue			
1.77×10^{-5}	8.20	8.7	3.0×10^{9}	3.2×10^{4}	1.1×10^{-5}
6.47×10^{-5}	8.70	17.4			(1.2×10^{-5})
6.08×10^{-5}	9.08	13.9			

[a] All results at $I = 0.1$ and 25° unless otherwise specified; $pK_w = 13.80$. [b] Hydroxyl ion concentrations calculated by dividing the measured activity by γ_{OH} ($\cong 0.80$). [c] Ratio of rate constants given first; spectrophotometrically determined equilibrium constant given in parentheses. [d] Temperature 15°; $pK_w = 14.14$ at $I = 0.1$. [e] A slower relaxation time was also observed (see text).

of encounter is rate determining. The requirements for this are that the lone pair of electrons on the hydroxide ion have free access to the proton reaction site on the indicator *via* hydrogen bonding to the solvent and that the reactants be in a suitable configuration so that the reaction occurs before the partners separate. As a result $k_f = k_{12}$ and $k_r = k_{32}k_{21}/k_{23}$. In principle, of course, the step 2–3 has a finite energy barrier. Usually it is sufficiently low that diffusion is rate determining. As the chemical activation energy increases,

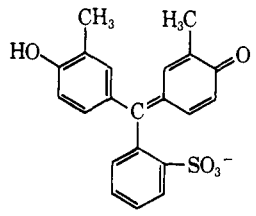
however, eventually the chemical transformation becomes rate determining ($k_{23} \ll k_{21}$). The rate constants for such proton transfers become then $k_f = K_{12}k_{23}$ and $k_r = k_{32}$, where $K_{12} = k_{12}/k_{21}$. The existence of a chemical activation barrier has been invoked in cases where the reactant is internally hydrogen bonded, or where intramolecular electronic rearrangement must take place before proton transfer can occur (*e.g.*, pseudo acids).[2,4]

Nonhydrogen-Bonded Systems. For two of the compounds investigated, the rate constants are substantially less than diffusion controlled, yet the systems apparently are not internally hydrogen bonded. The two compounds and their forward rate constants are phenolphthalein (VI), $k_f = 1.7 \times 10^9$, and *p*-xylenol blue (VII), $k_f = 3.0 \times 10^9$. The value of k_f found for phenolphthalein differs by about a factor of five from an approximate value reported earlier[4] ($\sim 1 \times 10^{10}$). The present work gave clear concentration dependence of the relaxation time with the ratio of slope to intercept in good agreement with the experimental equilibrium constant (Table I). For phenolphthalein, the observed relaxation time is associated with mechanism d,[10] in which VIb is present in only infinitesimal



concentrations. If a stationary-state approximation is made for VIb there results (*cf.* mechanism c) $k_f = k_{ab} \cdot k_{bc}/(k_{ba} + k_{bc})$ and $k_r = k_{ba}k_{cb}/(k_{ba} + k_{bc})$. Since the conversion a → b is probably diffusion controlled, then $k_f = K_{ab}k_{bc}$ and $k_r = k_{cb}$. As a result k_f will be less than that for a diffusion-controlled process.

For *p*-xylenol blue, which does not have electronic rearrangement occurring before or during proton transfer, the source of chemical activation energy must be elsewhere. An activation barrier may result from the presence of electron-releasing groups in the compound which strengthens the X–H bond. This would lower the ground state relative to the parent compound, and thus increase the activation barrier.[11] We suggest in fact that this is the explanation for the sulfonphthaleins *p*-xylenol blue (VII) and cresol red (VIII). The forward rate constants are VIII,[12] 6×10^9; and VII, 3.0



VIII

$\times 10^9$. Since these compounds differ only by substituents, and are presumably not internally hydrogen bonded,[13] it is difficult to see why they are not diffusion controlled. The explanation may be that the electron-donating ability of the methyl groups strengthens the O–H bond, raises the activation barrier, and lowers the rate. Since k_f for VII is less than that for VIII, the inductive effect of four, compared to two, methyl groups apparently strengthens the O–H bond such that k_f decreases. The decrease probably cannot be explained on the basis of a steric factor alone. Since k_f for the reaction of H^+ with the chlorophenol red anion[4] (a sulfonphthalein with the same basic structure as VII and VIII) is 2.3×10^{10}, the steric factor would have to be about 10 for the hydrolysis of VII.

Hydrogen-Bonded Systems. Several factors are known to influence the strength of intramolecular hydrogen bonds:[14] electronegativity of the proton-acceptor group, charge on the reactants, steric effects, and resonance stabilization of the ring formed by the internal hydrogen bond. Much evidence indicates that the order of decreasing hydrogen-bond strengths is: O–H···N > O–H···O ≅ N–H···O.[15] A recent kinetic study[16] supports this order.

Examination of the values in Table I shows that the results of this kinetic study also support this hypothesis. The smaller rate constant of III relative to I and II is presumably due to its stronger internal hydrogen bond, which results in an increase in the energy of activation for hydrolysis.[17] As compounds I and II differ only by position of a nitro group, the larger rate constant for the *para* compound I most likely results from an increase in its resonance energy, which effectively reduces the resonance stabilization of the ring formed by the intramolecular hydrogen bond. Thus the strength of bonds is O–H···N > O–H···O where the acceptor is a carboxylate oxygen. For compounds IV and Vb, $k_{f(IV)} < k_{f(Vb)}$, indicating that N–H···O > O–H···O where the acceptor is a sulfonate oxygen. Since, however, the donor atom presumably has a stronger role in determining hydrogen-bonding strengths than the acceptor atom, it is not rigorously valid to compare N–H···O and O–H···O bonds unless the molecules have the same type of internally hydrogen-bonded structures. In IV the donor nitrogen is one of three linear nitrogens able to participate in resonance; in Vb the donor is a phenolic oxygen. One may, however, compare I and II with Va and Vb and tentatively conclude that where the hydrogen is bonded to a phenolic oxy-

(10) This is very similar to, but not identical with, the mechanism proposed by I. M. Kolthoff and C. Rosenblum, "Acid–Base Indicators," The Macmillan Company, New York, N. Y., 1937, p 222.

(11) An activation barrier could also be increased by the presence of bulky substituent groups that, by forcing a molecule slightly out of a planar configuration, would change the ground state of the molecule, thereby affecting the resonance possibilities.

(12) M. H. Miles, E. M. Eyring, W. W. Epstein, and M. T. Anderson, *J. Phys. Chem.*, 70, 3490 (1966).

(13) Stick and space-filling models indicate that an internal H-bond distance could be no less than about 10 Å.

(14) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," H. C. Freeman and Co., San Francisco, Calif., 1960.

(15) H. H. Freedman, *J. Am. Chem. Soc.*, 83, 2900 (1961).

(16) J. L. Haslam and E. M. Eyring, *J. Phys. Chem.*, 71, 4470 (1967).

(17) Our results for III are within the error limits of the measurements reported by Haslam and Eyring, ref 16, for the same system.

gen, the order of intramolecular hydrogen-bond strengths is sulfonate oxygen > carboxylate oxygen > carbonyl oxygen. This order might be expected as this is the order of decreasing s character for the acceptor oxygens and thus of decreasing electronegativity.

Brønsted Correlation. A linear free energy relationship (LFE), based on intersecting Morse curves and subsequent substitution for ΔH° and $\Delta H^\pm$, can be derived for a series of closely related compounds[18,19] (eq 2). If the

$$\delta \log k_f = -\alpha\delta pK_a + (\alpha\delta\Delta S^\circ + \delta\Delta S^\pm)/2.303R \quad (2)$$

assumption is made that $(\alpha\delta\Delta S^\circ + \delta\Delta S^\pm) = 0$, *i.e.*, that ΔS° and $\Delta S^\pm$ remain constant for a series of similar reactants, eq 2 reduces to the Brønsted equation (3).

$$\delta \log k_f = -\alpha\delta pK_a \quad (3)$$

When hydrolysis reactions approach the diffusion-controlled limit ($\log k_f \rightarrow 10.5$) the rate constant becomes independent of k_a ($\alpha = 0$). A physical meaning of α is obtained by comparing the equilibrium constant and the rate constant according to transition-state theory (eq 4). As a result, $\delta\Delta H^\pm = \alpha\delta\Delta H^\circ$: that is,

$$\delta \log k_f/\delta pK_a = -\delta\Delta H^\pm/\delta\Delta H^\circ = -\alpha \quad (4)$$

α represents the fraction of the change in ΔH° that appears as a change in the activation energy. If $\alpha = 1$ ($\delta\Delta H^\pm = \delta\Delta H^\circ$), the activated complex is thought to closely resemble the products,[20] *i.e.*, the proton is associated more with H_2O than with In^{z-1} in the transition state and may have an arrangement very much like HO··H····In.

The results of this study, together with data from other sources, are shown graphically in Figure 2. Some 20 internally hydrogen-bonded acids are shown,[21] including salicylates (I, II, XII), *o*-azo compounds (III, X, XI), dicarboxylates (XIX, XX), and zwitterions (XV–XVII). All points do not fall on a common curve. However, the salicylates, *o*-azo compounds, and phthaleins all fall on a common curve (the upper). The slope of this line as accurately as can be determined is −1, and the same appears to be true for curve b. When lines with the same slope are drawn through the other points, the zwitterions (XV–XVII), thiosalicylate (XIV), and quinizarin-2-sulfonic acid (Va) fall on the middle curve (b), and the dicarboxylates (XIX, XX) and the enol form of a pseudo acid (XVIII) fall on either side of the lower curve (c).

In a recent paper Eyring and coworkers[22] reported a study of five additional internally hydrogen-bonded *o*-azo compounds. If these are graphed as in Figure 2 all but one fall on curve a. The constancy of the slope for *o*-azo and dicarboxylate compounds implies that for a series of these compounds the shape of the Morse-energy curves remains similar. One may then predict that other compounds with these types of intramolecular hydrogen bonds should fall on curve a. Those compounds which fall on curves b and c have dissimilar types of bonding and perhaps are too limited in number to be able to make such a prediction. A series of substituted malonic acids studied by Eyring and coworkers[12] appears to fall on a curve intermediate between b and c. Examination of Figure 2 shows that if one considered only the data prior to this investigation, he might conclude that the data (open circles) scatter very badly around a single curve of slope −0.5 and that log $k_f = 9.8$ (VIII) was scattering from the diffusion-controlled rate. Our data (closed circles) clearly indicate that not one, but several curves are needed for the hydrolysis of internally hydrogen-bonded acids. We believe this is the closest experimental representation of the idealized theoretical curves proposed by Eigen[4] (*i.e.*, a very narrow region of curvature as $\alpha = 1 \rightarrow \alpha = 0$).

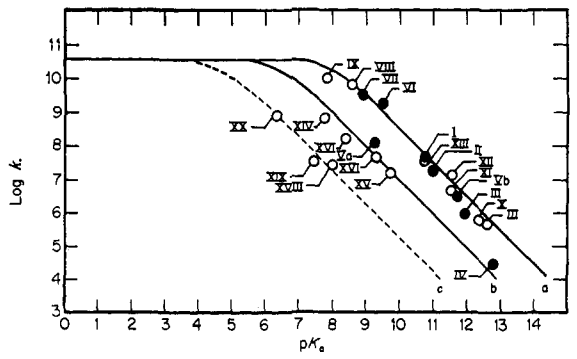


Figure 2. Brønsted plots for hydrolysis of internally hydrogen-bonded acids: ●, present measurements; O, from ref 4 and 16; VIII, cresol red; IX, *o*-nitrophenol; X, 2,4-dihydroxyazonitrobenzene; XI, orange II; XII, alizarin S; XIII, $HEDTA^{3-}$; XIV, thiosalicylate; XV, nitrilotriacetic acid; XVI, N,N-dimethylanthranilate; XVII (the lower XVI in the figure), N-methyl-N-ethylanthranilate; XVIII, acetylacetone (enol); XIX, di-*n*-propylmalonate; XX, maleate. pK values were adjusted, where necessary, to $I = 0.1$.

It is probably not valid to compare dissimilar types of internally hydrogen-bonded systems to determine hydrogen-bonding strengths if their pK's differ, for the value of k_f will depend not only on structure, but also on the value of pK_a. Nonetheless, a comparison of k_f for different types of internal hydrogen bonds represented in Figure 2 indicates that the order of strengths, O–H···N > O–H···O ~ N–H···N > N–H···O, is apparently true when the proton acceptor for an O–H···O bond is a carboxylate, dicarboxylate, or sulfonate oxygen. If a nitro oxygen is the proton acceptor, the O–H···O bond is weaker than N–H···O. Thiosalicylate (XIV) is the only example of a S–H···O bond given; this bond appears to be weaker than a salicylate-type bond in an azo compound. It is interesting that compounds such as the sulfonphthaleins, which are unlikely to form hydrogen bonds, also fall upon the LFE curves. The explanation probably lies in the fact that the increase in pK_a is reflected completely in the higher chemical activation energy.

Acknowledgment. This investigation was supported by the Division of General Medical Sciences, Public Health Services, in the form of Research Grant No. GM 13116.

(18) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 169.

(19) The negative sign results from the fact that K_h refers to the hydrolysis equilibrium constant, which is reciprocally related to K_a.

(20) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, p 156 ff.

(21) Data and structures are from ref 4 and 16.

(22) W. H. Inskeep, D. L. Jones, W. T. Silfvast, and E. M. Eyring, *Proc. Natl. Acad. Sci. U. S.*, **59**, 1027 (1967).