Acid-Catalyzed Hydrolysis of *N*-Phenyl-4-substituted-benzohydroxamic Acids[†]

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Acidity rate profiles have been established for the hydrolysis of some *N*-phenyl-4-substituted-benzohydroxamic acids 4-$XC_6H_4(C{=}O)N(OH)C_6H_5$ (X = H, CH_3, OCH_3, NO_2, Cl, F) in sulfuric acid solutions in 20/80 (v/v) dioxane–water medium. Analysis of the data by the Cox–Yates excess acidity method and substitutent, temperature, and solvent isotope effects are all compatible with a changeover from an A-2 mechanism at low acidities to a predominantly A-1 mechanism at high acidities.

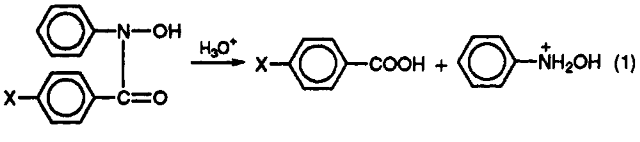
N-Substituted hydroxamic acids have acquired phenomenal importance because of their current use in nuclear fuel reprocessing,[1] pharmaceuticals,[2] solvent extraction,[3] and spectrophotometric determination of metals particularly using concentrated acid solutions.[4] Particular attention has been devoted to the biological and chemical aspects of hydroxamic acids[5] as well as to their potential clinical use as novel therapeutic agents.[6–7] Recently[8] the chemistry of hydroxamic acids and the relationship of the chemistry to their carcinogenicity have been investigated. The chemical kinetics data of the hydrolysis reaction provides a judicious and rational basis for the search for new analytical reagents. We recently have initiated a study of the acid-catalyzed hydrolysis of certain hydroxamic acids[9–13] and analyzed the data in terms of existing criteria of mechanism. Some hydroxamic acids hydrolyze by an A-2 mechanism in all concentrations of acid, while some switched to an A-1 pathway at high acidity. In order to determine the mechanistic crossover point for the hydrolysis of hydroxamic acids we have examined the hydrolysis of some *N*-phenyl-4-substituted-benzohydroxamic acids in a wide range of sulfuric acid concentrations. Substituent effects, kinetic solvent isotope effects, and the Cox–Yates excess acidity approach have been employed to elucidate mechanisms.

Table 1. Pseudo-First-Order Rate Constants of 4-X-C_6H_4-(C=O)N(OH)C_6H_5 in Aqueous Dioxane Medium at 55 °C

H_2SO_4 (M)	$k_\psi 10^5$ s^{-1}					
	X = H	X = OCH_3	X = CH_3	X = NO_2	X = Cl	X = F
0.75	2.40	2.28	1.75	1.90	1.80	2.01
1.45	4.90	3.42	5.09	2.05	4.51	5.10
2.90	10.4	7.19	9.78	5.46	11.4	10.7
3.25	11.1	8.95	10.2	7.32	16.2	–
3.50	12.9	9.30	11.9	8.80	17.2	15.0
4.25	15.7	10.7	14.5	10.6	19.0	–
4.50	15.9	11.5	16.9	19.5	19.9	18.6
5.00	17.1	–	–	18.9	–	–
5.50	21.9	–	–	25.8	–	19.9
5.80	17.5	9.33	12.1	13.6	16.1	–
6.50	13.6	8.77	10.4	17.6	15.8	16.9
7.54	9.10	7.34	6.96	13.9	14.3	12.3
8.00	7.56	9.34	8.31	15.6	12.5	10.0
8.50	9.55	10.7	9.06	21.7	14.4	–
9.00	11.1	19.8	14.6	14.5	15.6	11.2
10.4	42.9	59.4	65.4	40.2	26.1	20.6
12.0	208.2	395.7	417.9	113.7	–	–

Results and Discussion

N-Phenyl-4-substituted-benzohydroxamic acids (I) undergo hydrolysis in sulfuric acid solutions to give the corresponding carboxylic acids and *N*-phenylhydroxylamine (eq 1).



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Because hydroxamic acids are not soluble in water, a 20/80 (v/v) dioxane–water medium was used. Dioxane was inert under our experimental conditions and permitted rate measurement for long periods of time.

The reactions showed a first-order dependence on substrate, and pseudo-first-order rate constants were obtained at several sulfuric acid concentrations. These are summarized in Table 1 and illustrated in Figure 1. For all the compounds studied, rates increase initially with increasing acidity and reach a maximum, followed by a rate decrease, and then a final steep increase occurs at very high acidities. The maxima are a consequence of opposing effects of increasing protonation and decreasing water activity. At low acidity, increasing acid concentration increased hydrolysis rate by raising the concentration of protonated substrates. But as the acidity becomes sufficient to convert a large fraction of substrate

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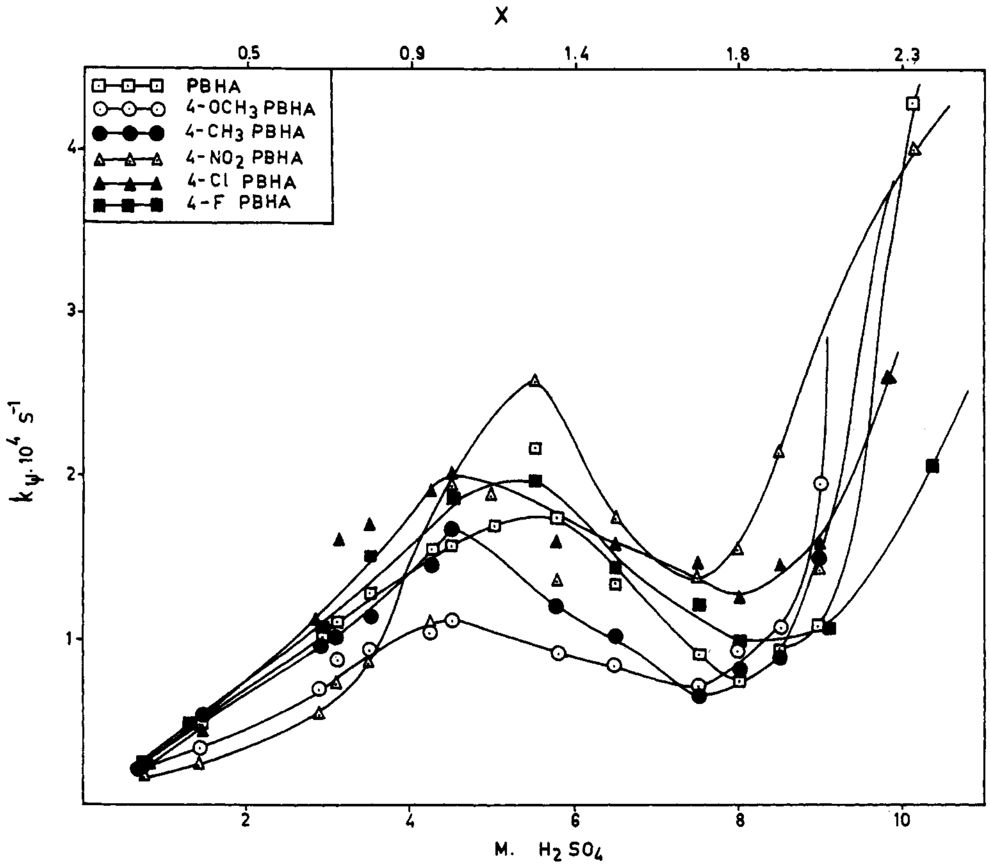

Figure 1. Rate acidity profiles for the hydrolysis of 4-X-$C_6H_4(C{=}O)N(OH)C_6H_5$ in H_2SO_4.

into its protonated form, increasing acid concentration has little effect on the rate of hydrolysis. A new factor now becomes important: decrease in the activity of water with increasing acidity. As water becomes progressively less available, the hydrolysis rate diminishes steadily. The rate–acidity profile closely resembles the profiles for the hydrolysis of esters, studied by Edward and Wong,[14] and by analogy hydrolysis occurs by two distinct mechanisms: (i) in acid concentrations up to 8.0 M by an A-2 mechanism; and (ii) in acid concentrations above 8.0 M by an A-1 mechanism. This dichotomy of mechanism is supported by various lines of evidence reported below. In 0.75 M sulfuric acid the observed kinetic constants show the following reactivity order H > 4-OCH_3 > 4-F > 4-NO_2 > 4-Cl > 4-CH_3 and in 10.4 M sulfuric acid the order is 4-CH_3 > 4-OCH_3 > H > 4-NO_2 > 4-Cl > 4-F.

Activation Parameters. The temperature dependence of the rate constants of the hydrolysis reaction was analyzed by a least squares procedure using a computer program (Eyring equation) which produces values for ΔH^*, ΔS^*, and ΔG^* together with their standard deviations. The values at different acidities are shown in Table 2. Acid-catalyzed hydrolyses of esters and amides[15] proceeding by an A-1 mechanism have ΔS^* of about 0 to −41.8 J K^{-1} mol^{-1}, while those proceeding by an A-2 mechanism have ΔS^* of −62.8 to −125.5 J K^{-1} mol^{-1}. The large change in ΔS^* at very high acid concentrations is consistent with a change to an A-1 mechanism. Although ΔS^* values are based on pseudo-first-order rate constants which are dependent on acidity, the observed medium dependence of ΔS^* (Table 2) is not expected to lead to such a drastic change, unless a change in mechanism is involved. The trends in ΔH^* and ΔG^* in Table 2 are in accord with expectation with some exceptions. The enthalpies of activation ΔH^* become more positive with increasing acidity as expected for a change over to a unimolecular mechanism. The ΔG^* values do not vary greatly with acid concentration. The change in ΔS^* implies that a change from a more- to a less-restricted transition state is occurring as the acidity is increased (or as a_{H_2O} is decreased).

Kinetic Solvent Isotope Effects. The kinetic solvent isotope effects (k_H/k_D) observed for the hydrolysis of hydroxamic acids are shown in Table 3. It has been found that all reactions proceed up to 8 M, more readily in D_2SO_4–D_2O than in H_2SO_4–H_2O. H_2O is about twice as basic[16] or nucleophilic as D_2O. Thus, the substrate will be able to compete with the solvent for the deutron in D_2O more effectively than the proton in H_2O. Since the concentration of the conjugate acid of the substrate will then be higher in D_2O, the rate of the reaction should also be higher in D_2O than in H_2O. When the preequilibrium is significant, at lower acidities, k_H/k_D is less than 1. When protonation is substantially complete, k_H/k_D is greater than 1. At higher acidities the hydroxamic acid is largely in the form of the conjugate acid in either solvent. The displacement on the conjugate acid would be expected to be slower for D_2O than for H_2O since the former is the weaker base, and thus the isotope effect is reversed under these conditions. Solvent isotope effects are not particularly well understood[17] for strongly acidic media.

Substituent Effects. The effect of substitution has been assessed by the use of the Hammett equation[18] using para σ values.[19] The reaction constants, ρ, are shown in Table 4. The change in mechanism is also supported by

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Table 2. Activation Parameters for the Hydrolysis of 4-X-$C_6H_4(C{=}O)N(OH)C_6H_5$

substituent X	H_2SO_4, M	temp range	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ J mol^{-1} K^{-1}	$\Delta G^{\ddagger}$ kJ mol^{-1}	correl coeff
H	0.75	45–65	70.0 ± 0.50	−121 ± 1.54	105.9 ± 0.38	0.999
	4.5	45–65	72.7 ± 0.66	−97 ± 2.01	101.5 ± 0.50	0.999
	7.5	45–65	87.8 ± 1.77	−56 ± 5.39	104.2 ± 1.35	0.999
	10.4	35–55	105.3 ± 0.83	+10 ± 2.61	102.1 ± 0.64	0.999
OCH_3	0.75	45–65	85.8 ± 1.50	−74 ± 4.59	107.6 ± 1.15	0.999
	4.5	45–65	81.1 ± 1.96	−74 ± 5.98	103.0 ± 1.49	0.999
	7.5	45–65	101.7 ± 4.34	−14 ± 3.31	105.9 ± 3.31	0.998
	10.4	35–55	109.2 ± 3.99	+34 ± 12.6	100.7 ± 3.09	0.998
CH_3	0.75	45–65	81.5 ± 3.82	−88 ± 11.6	107.6 ± 2.91	0.997
	4.5	45–65	77.5 ± 7.73	−84 ± 23.6	102.2 ± 5.90	0.989
	7.5	45–65	91.1 ± 1.85	−48 ± 5.66	105.2 ± 1.42	0.999
	10.4	35–55	103.7 ± 1.15	+9 ± 3.61	100.9 ± 0.89	0.999
NO_2	0.75	45–65	91.3 ± 0.90	−58 ± 2.76	108.5 ± 0.69	0.999
	4.5	45–65	89.7 ± 2.52	−44 ± 7.70	102.7 ± 1.93	0.999
	7.5	45–65	90.9 ± 1.78	−43 ± 5.44	103.5 ± 1.36	0.999
	10.4	35–55	107.7 ± 0.58	+17 ± 1.82	102.5 ± 0.45	0.999
Cl	0.75	45–65	75.1 ± 3.78	−108 ± 11.6	106.9 ± 2.88	0.997
	4.5	45–65	79.9 ± 1.03	−73 ± 3.14	101.6 ± 0.78	0.999
	8.0	45–65	82.9 ± 4.67	−67 ± 14.3	102.8 ± 3.58	0.997
	9.0	45–65	90.6 ± 1.91	−43 ± 5.82	103.2 ± 1.46	0.999
F	0.75	45–65	73.1 ± 0.33	−113 ± 0.99	106.7 ± 0.25	0.999
	4.5	45–65	75.8 ± 1.17	−86 ± 3.58	101.4 ± 0.89	0.999
	7.5	45–65	79.3 ± 1.29	−79 ± 3.93	102.7 ± 0.98	0.999
	10.4	35–55	105.0 ± 0.78	+3 ± 2.48	103.9 ± 0.61	0.999

Table 3. Kinetic Solvent Isotope k_H/k_D Effect in the Hydrolysis of 4-X-$C_6H_4(C{=}O)N(OH)C_6H_5$

X	$k_\psi 10^5$ s^{-1} with 2.9 M			$k_\psi 10^5$ s^{-1} with 10.4 M		
substituent	H_2SO_4	D_2SO_4	k_H/k_D	H_2SO_4	D_2SO_4	k_H/k_D
H	10.4	17.5	0.59	42.9	40.4	1.06
OCH_3	7.19	8.95	0.80	59.4	53.6	1.11
CH_3	9.78	15.1	0.65	65.4	-	-
NO_2	5.46	7.96	0.68	40.2	34.2	1.17
Cl	11.4	12.4	0.93	26.1	25.2	1.03
F	10.7	14.0	0.76	20.6	19.6	1.05

Table 4. Values of ρ at Different Acid Concentrations

H_2SO_4 (M)	ρ	correlation coefficient	standard deviation
2.9	0.043 ± 0.02	0.867	0.014
4.5	0.219 ± 0.09	0.916	0.060
7.5	0.258 ± 0.02	0.996	0.017
9.0	−0.906 ± 0.16	0.984	0.031
12.0	−0.547 ± 0.07	0.992	0.025

these values. The rates of A-2 hydrolyses follow σ and have small ρ values, because of the opposing effects of substituents on the preequilibrium protonation and on the subsequent rate-determining attack of water. For the change from A-2 to A-1 mechanism when hydrolysis is carried out in 12 M sulfuric acid, ρ has changed from +0.043 to −0.547. The negative sign of ρ is expected for an A-1 reaction. The effect of substituents on the hydrolysis rates are dependent on acidity and invert on going from dilute to concentrated sulfuric acid. Thus, the electron-donating substituents produce the lowest rate at low acidity, but the highest rate at high acidity. Generally in the proposed mechanism (A-2), electron-donating substituents accelerate the protonation step, and electron-withdrawing substituents facilitate the attack of water molecules on the protonated species. When the A-2 mechanism is operative, electron-withdrawing substituents facilitate the reaction as shown in Table 1; the attack by the water molecule is rate-determining. Similar trends have been observed for acid-catalyzed hydrolysis of *N*-methyl-*N*-nitrobenzamide.[20]

Excess Acidity Method. This method[21] provides detailed insight into the various mechanisms of hydrolysis and a good quantitative formulation regarding the rate-determining step for each. To date it has been applied to acid-catalyzed hydrolysis of esters,[22] , amides,[23] hydrazines,[24] acylals,[25] and azo compounds[26] and pyridines.[27] Recently[9–11] we have applied this method to unsubstituted hydroxamic acids.

From the activation parameters, the Hammett equation and the solvent isotope effect it is clear that two mechanisms are operative over the range of acidity studied. The A-2 mechanism (Scheme 1) involves again a rapid preequilibrium to give SH^+, but this is attacked by water in the rate-limiting step. The A-1 mechanism (Scheme 2) involves equilibrium protonation of the substrate S to give protonated species SH^+, which decomposes unimolecularly in the rate-limiting step to give an intermediate X^+; this intermediate reacts rapidly with water to give the products. The excess acidity method can readily be applied to distinguish between A-2 and A-1 mechanisms. On the basis of reasonable reaction mechanisms (Scheme 1 and 2), eqs 2 (A-1) and 3 (A-2) can be derived.

$$\log k_\psi - \log C_{H^+} = \log (k_1/K_{SH^+}) + m_1^{\ddagger} m^* X \qquad (2)$$

$$\log k_\psi - \log C_{H^+} - r \log a_{H_2O} = \log (k_1/K_{SH^+}) + m_2^{\ddagger} m^* X \qquad (3)$$

Where m^* is obtained from protonation studies, $m^{\ddagger}$ is characteristic of the type of reaction, and $r \log a_{H_2O}$ for the A-2 reaction represents nucleophilic activity, where r is

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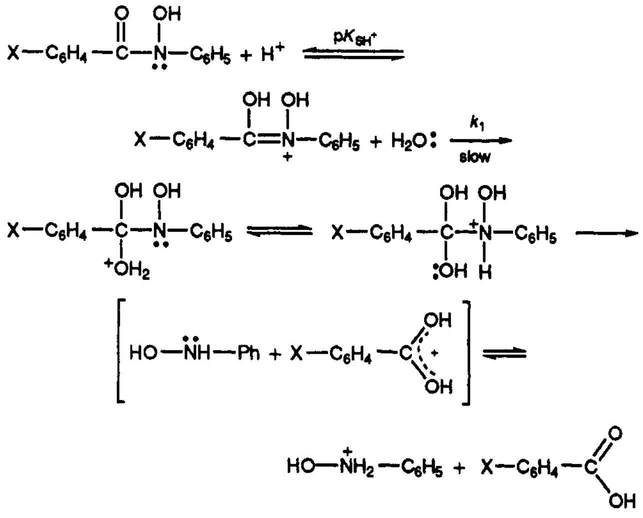
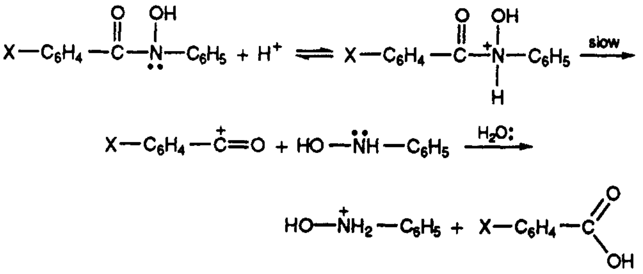
Scheme 1



Scheme 2



the number of water molecules involved in forming the transition state. This has been found[13] in the case of *N*-phenylbenzohydroxamic acid (I) hydrolysis to be 2. The excess acidity function[28] being defined as $X = \log(\gamma_{B^*}\gamma_{H^+}/\gamma_{B^*H^+})$, where B* is the nitroaniline taken as reference, the activity coefficient term for another base B will be linearly related to X according to eq 4. For A-1 processes

$$\log(\gamma_B\gamma_{H^+}/\gamma_{BH^+}) = m^* \log(\gamma_{B^*}\gamma_{H^+}/\gamma_{BH^+}) \quad (4)$$

$m_1^‡ > 1$, probably about 2-3,[21b] and m^* for nitrogen protonation is 1,[27] so an overall slope of 2-3 should be obtained for the plot of left hand side of eq 2 vs X. For A-2 reactions, $m_2^‡ > 1$ and m^* for carbonyl oxygen protonation is 0.6 or less, thus an overall slope of 0.6 or less should result[21b,22] for the plot of the left hand side of eq 3 against X. A good illustration of this can be found in the work of Cox and Yates,[24] who studied the hydrolysis of acyl- and benzoylhydrazines. They found that the substrate hydrolyzed by an A-2 process in dilute acidities and switched to an A-1 process at higher acidities, with the position of mechanism change being very substrate-dependent.

The kinetic data of Table 1 have been analyzed first by the Cox–Yates excess acidity eq 3. A straight line immediately results (Figure 2) with 2 log a_{H_2O} showing that two water molecules are reacting with the protonated substrate in the slow step. Points above ≃7.5 M sulfuric acid plots are curved. This is exactly what one would expect, i.e. a change in mechanism. At about 7.5–12.0 M sulfuric acid another mechanism takes over, with log k_ψ − log C_{H^+} again linear against X (Figure 4) in this region. The change in mechanism is clearly indicated. The slope and intercept values for all the substrates are given in Table 5. Scheme 1 was followed by all the compounds examined (results in Table 1) involving two water molecules. The requirement for two water molecules stems from the need for one to act as a nucleophile and the second to assist in dispersing the positive charge developing on oxygen in the transition state as progress is made toward the neutral tetrahedral intermediate. The second water molecule is then in a position to accept a proton in the formation of the intermediate. An A-1 mechanism (Scheme 2) is found at high acidities, as confirmed by excess acidity plots and the $\Delta S^‡$ values. The X values ($-H_A + \log C_{H^+}$) and log a_{H_2O} values employed in the excess acidity correlation are for 25 °C, while the reactions were conducted at 55 °C. The magnitudes of the slopes and intercepts may therefore be somewhat affected.

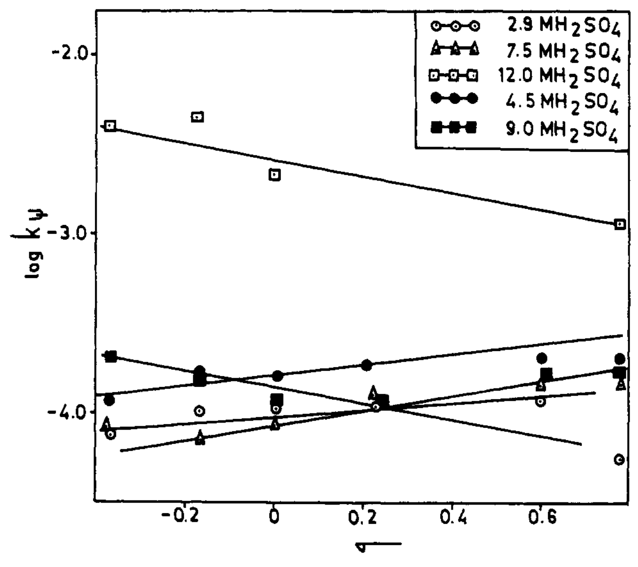
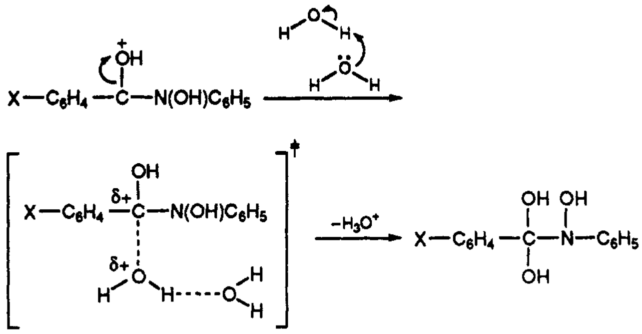


Figure 2. Hammett plots for the hydrolysis of 4-X-C_6H_4-(C=O)N(OH)C_6H_5 in H_2SO_4.



A central issue in hydroxamic acid hydrolysis is whether the actual hydrolyses proceeds via the N- or O-protonated conjugate acid. Protonation of hydroxamic acids usually causes modest but significant changes in their UV and NMR spectra. We have determined[29] the UV spectra of hydroxamic acids. The pK_{SH^+} values obtained were between −2 to −3. As solutions of hydroxamic acid cation are made still more acidic the spectra continue to undergo changes (λ_{max} and ϵ_{max} both increase). We found that the spectra in sulfuric acid suffer form medium effects and the spectral changes thus produced cannot be separated from those due to protonation in any simple way. We concluded that the UV method generally is an inadequate technique for the determination of protonation param-

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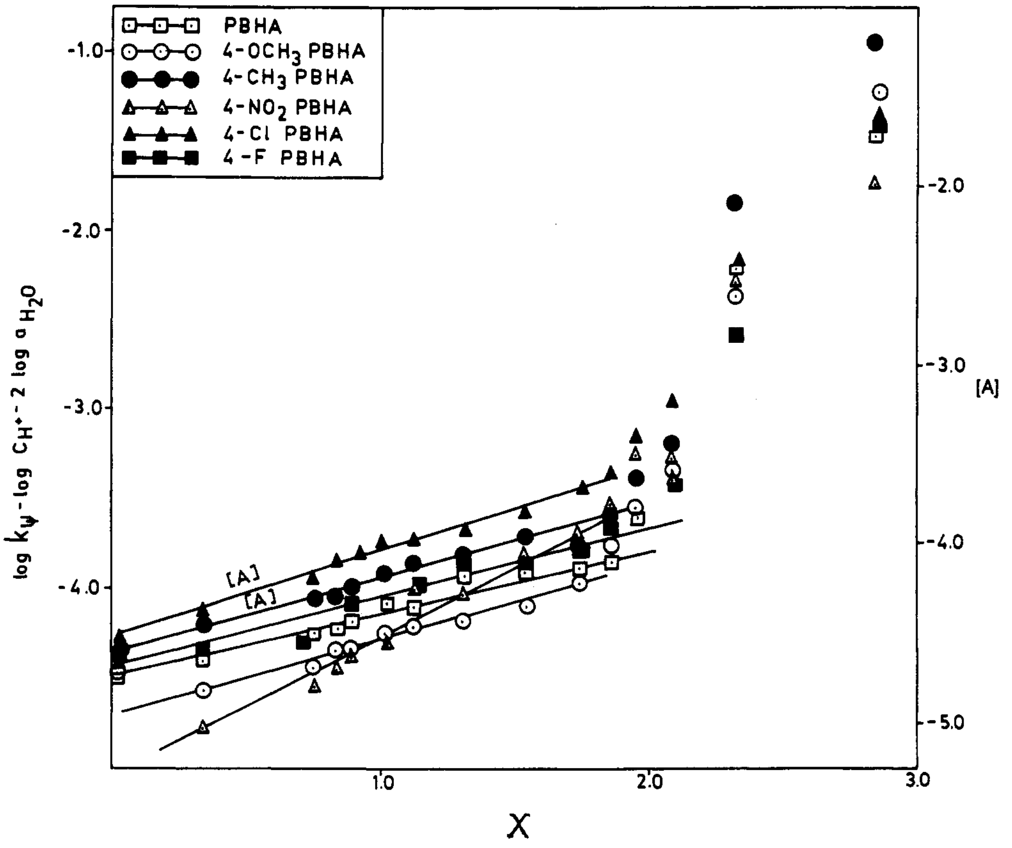

Figure 3. Cox–Yates excess acidity plot for the hydrolysis of 4-X-C$_6$H$_4$(C=O)N(OH)C$_6$H$_5$ [log k_ψ − log C_{H^+} − 2 log a_{H_2O} vs X].

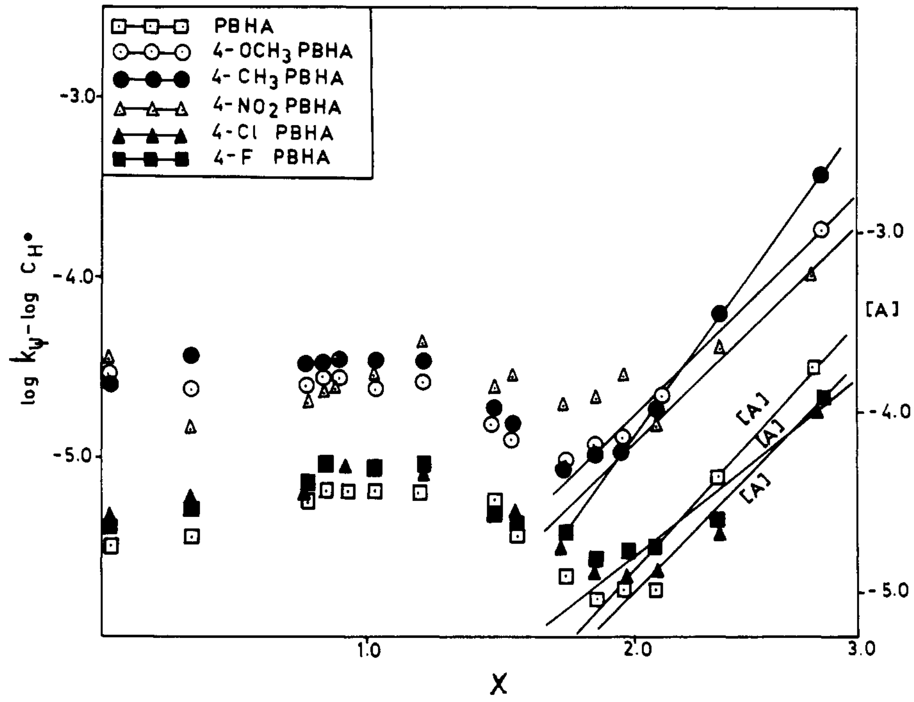

Figure 4. Cox–Yates excess acidity plot for the hydrolysis of 4-X-C$_6$H$_4$(C=O)N(OH)C$_6$H$_5$ [log k_ψ − log C_{H^+} vs X].

eters. NMR signals of aromatic protons generally do not provide good data for the determination of pK_{SH^+}. Liler[30,31] also interpreted these changes as a medium effect. But the alternative explanation, and one that is generally accepted, is that the observed medium effect is not on the equilibrium but on the spectra of the O-protonated forms. Recently Bagno[32] et al. determined the protonation sites of many polyfunctional acids and bases based on the changes in NMR longitudinal relaxation time of all the nuclei potentially involved. The results of the application of this method (by means of ^{14}N, ^{15}N, and ^{17}O NMR spectroscopy), as well as of theoretical calculations confirm O-protonation.[33] The activity coefficient behavior and

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Table 5. Slope Value of Eqs 2 (A-1) and 3 (A-2) for the Hydrolysis of 4-X-$C_6H_4(C{=}O)N(OH)C_6H_5$ in Sulfuric Acid at 55 °C

	A-2 reaction				A-1 reaction			
X substituent	acid range	slope $m_2^{\ddagger}m^*$	intercept	correl coeff	acid range	slope $m_2^{\ddagger}m^*$	intercept	correl coeff
H	1.45–8	0.389 ± 0.02	–4.55 ± 0.02	0.989	8–12	1.279 ± 0.04	–7.418 ± 0.09	0.999
OCH_3	1.45–7.5	0.409 ± 0.02	–4.715 ± 0.02	0.992	7.5–12	1.391 ± 0.06	–7.494 ± 0.15	0.996
CH_3	1.45–8	0.353 ± 0.04	–4.544 ± 0.05	0.947	8–12	1.603 ± 0.09	–8.040 ± 0.40	0.995
NO_2	1.45–7.5	0.761 ± 0.02	–5.063 ± 0.02	0.999	7.5–12	1.282 ± 0.03	–7.452 ± 0.07	0.999
Cl	1.45–8	0.503 ± 0.04	–4.577 ± 0.04	0.981	8.5–10	1.060 ± 0.24	–7.016 ± 0.59	0.975
F	0.75–8	0.449 ± 0.02	–4.535 ± 0.02	0.996	8.5–10	1.325 ± 0.27	–7.758 ± 0.67	0.979

p*K* measurements in strongly acidic solutions indicate protonation at the carbonyl oxygen like in amides,[34] but it has been claimed that protonation takes place at nitrogen.[35] Novak et al.[36] suggested that for the acid-catalyzed hydrolysis of *N*-hydroxyacetanilides, the protonation of the carbonyl oxygen is favored over the hydroxyl oxygen by about 7 orders of magnitude. One cannot, however, exclude the possibility of nitrogen protonation. More kinetic and thermodynamic studies are necessary to establish the protonation behavior of hydroxamic acids. An effort to do this is in progress.

Experimental Section

The hydroxamic acids were prepared by the standard method.[37] The sulfuric acid used was of analytical reagent grade. Dioxane (BDH, LR) was used without further purification. The ferric chloride solution used in the colorimetric procedure was prepared by dissolution of 44.0 g of anhydrous ferric chloride (SM, LR) in 1 L of distilled water containing 10 mL of concentrated hydrochloric acid. Deuterium oxide (D_2O, isotopic purity > 99.8%) and D_2SO_4 (isotopic purity > 95%) were procured from Bhabha Atomic Research Centre, Bombay. Kinetic measurements were made by use of the spectrophotometric method reported previously[12] using an EC 5700A digital spectrophotometer and systronics UV-VIS 108 set at 520 nm. Least squares analyses were carried out on a WIPRO 386 computer under MS-DOS.

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