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A Comparison between the Acid-Catalysed Reactions of Some Dihydroxamic Acids, Monohydroxamic Acids and Desferal

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A kinetic study on the hydrolysis of some dihydroxamic acids HOHNOC–$(CH_2)_n$–CONHOH (n = 0, oxalo, [ODHA]; n = 1 malono [MDHA]; and n = 2, succino, [SDHA] dihydroxamic acids) in aqueous mineral acids is reported. A comparison of the kinetic data with those from the hydrolysis of simple monohydroxamic acid, (acetohydroxamic acid [AHA] $CH_3CONHOH$, benzohydroxamic acid [BHA] $C_6H_5CONHOH$) and the natural trihydroxamate-based siderophore desferal (DFB) revealed that the hydrolytic stability sequence of the compounds is generally: BHA > ODHA > MDHA > DFB > AHA > SDHA. An excess acidity analysis reveals that the reaction involving a pre-equilibrium protonation was followed by a rate determining A-2 type nucleophilic attack of water molecule on the protonated substrate. An attempt has been made to study protonation equilibria.

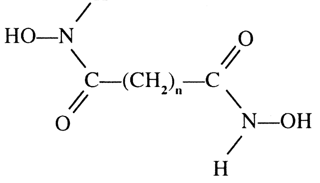
The chemistry of hydroxamic acids appears to be a never-ending wellspring of interesting problems, both fundamental and applied in nature, for scientists across the entire spectrum of chemical and biological sciences. As a result of these developments, the chemistry of hydroxamic acid is experiencing rapid, even explosive growth.[1–8] Work in our laboratories in recent years has been devoted mainly to acid-base equilibria and hydrolysis of monohydroxamic acids.[9] However, the detailed study of the hydrolysis of dihydroxamic acids has not been carried out so far. Dihydroxamic acids (–N(OH)–CO–CO–N(OH)–) are recognized as very useful and efficient absorbing agents for toxic air pollutant like SO_2[10–12] and as excellent metal complexing agents.[13–14] Recently some aliphatic dihydroxamic acids[15] have been used for organometallic derivatives, which are promising for medicinal applications. The hydrolysis of hydroxamic acid is an important first step in the quantitative analysis of hydroxamate siderophores. The hydrolysis of amide like substances is of interest because of their relationship to peptides. The present paper reports a kinetic study of some dihydroxamic acids (Scheme 1).

The hydrolysis results were compared with those obtained for other hydroxamic acids: acetohydroxamic acid (AHA), benzohydroxamic acid (BHA) and for the natural trihydroxamic siderophore desferal (DFB, desferrioxamine mesylate, Scheme 2). AHA and DFB have proved to be highly interesting substrates from a biomedical point of view, because of their well-known applications as drugs[16a] for inhibition of stone formation in the urinary tract infections[16b] and for removal of toxic amounts of iron from β-thalassemia patients[16c] respectively.

The excess acidity method[17] was used to analyse the rate data obtained. This method has been found to be very useful in obtaining mechanistic information concerning a wide variety of reactions, from the decomposition of military explosives RDX and HMX[18] to hydrolysis of acetylpyridinephenylhydrazone[19] in aqueous mineral acids. The protonation behaviors of ODHA in sulfuric and perchloric acids have also been studied.

Experimental

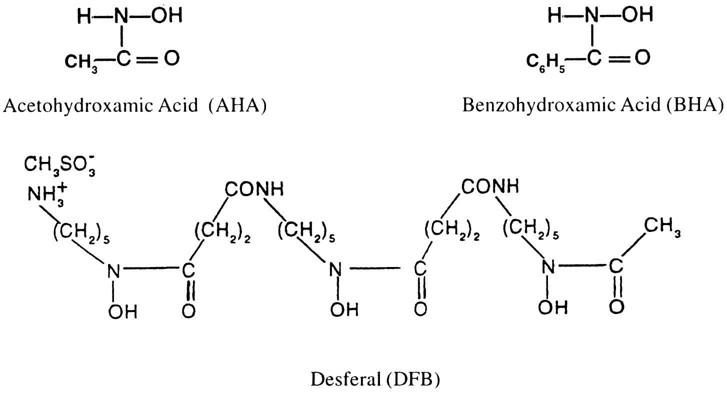
Materials. All three dihydroxamic acids (ODHA, MDHA and SDHA) were prepared[9–11] by the drop wise addition of diethyl oxalate (0.1 mol), diethyl malonate (0.1 mol) and diethyl succinate (0.1 mol) to an ammonical solution containing of hydroxylamine hydrochloride (0.2 mol) with vigorous stirring at 0 °C. The white precipitate obtained was filtered and recrystallized twice from distilled water. Desferal (DFB) was obtained as a gift from Hindustan Ciba Geigy. Acetohydroxamic acid (AHA) was pro-



n = 0, oxalodihydroxamic acid (ODHA)
n = 1, malonodihydroxamic acid (MDHA)
n = 2, succinodihydroxamic acid (SDHA)

Dihydroxamic acids

Scheme 1.



Acetohydroxamic Acid (AHA)

Benzohydroxamic Acid (BHA)

Desferal (DFB)

Scheme 2.

cured from Sigma. Benzohydroxamic acid (BHA) was prepared by standard methods.[20]

Prepared hydroxamic acids were characterized by mp (ODHA = 160 °C, MDHA = 155 °C, SDHA = 180 °C and BHA = 126 °C), elemental analysis and UV and IR spectral data. All the solvents used in spectroscopic analyses were of HPLC grade. The mineral acids (HCl, H_2SO_4, $HClO_4$) and other solvents and salts used were of analytical reagent grade.The concentrations of acids were determined by titration with standard alkali. Deuterium oxide, D_2O (isotopic purity $> 99.8\%$) and DCl (isotopic purity $> 95\%$) were procured from Bhabha Atomic Research Centre, Bombay, India. Iron (III) chloride (Qualigens) solution used in the colorimetric procedure was prepared by the standard method.[8]

Kinetic Measurements. For each kinetic run, two reaction vessels were used. One of these contained appropriate volumes of acid (catalyst) and water; the other one contained the hydroxamic acid. After thermostating for about 30 minutes the acid solution was transferred to the reaction vessel containing hydroxamic acid. After the content of the reaction vessel was shaken, an aliquot of the reaction mixture was withdrawn into a 10 mL volumetric flask containing 2 mL of Iron(III) chloride. A double purpose, quenching of the reaction and colour development, was thus served. The volume of the coloured solution was made up to 10 mL and its absorbance was measured at 500–520 nm using a reference solution containing 2 mL of the same Iron(III) chloride in 10 mL of water. The kinetic runs were studied generally up to two half-lives. For measuring absorbance, a Systronics UV-VIS Spectrophotometer type 108 was used. For protonation studies a Unicam UV2 300 spectrophotometer was used.

For a pseudo first-order reaction, a plot of log absorbance vs t will give a straight line of slope, $-k_\psi/2.303$ (where k_ψ is the pseudo first-order rate constant for the reaction). The rates of hydrolysis were determined spectrophotometrically by following the decrease in the characteristic absorption of the hydroxamic acid–ferric chloride complex. As Beer's law is applicable to all the Iron(III) hydroxamic acid complexes, the concentration of reacting species is proportional to the absorbance A. [$\log A \propto \log (a - x)$]. To obtain the rate constant k_ψ, $\log (a - x)$ was plotted against time t; from the slope of the plot, k_ψ was determined. The fact that a straight line was obtained for all the plots of ($\log a - x$) vs t measured in this investigation is, in itself, an indication that the reactions are all first-order in substrate. The initial concentration of the hydroxamic acid in reaction mixture is about 7.0×10^{-3} M. The experimental errors in the respective runs were generally less than 1.0% and the reproducibility of the rate constants was within ±1.5%.

Products. Product studies were carried out in solutions identical with those used in the kinetic measurements, except that the concentrations of the substrates employed were higher. In moderately concentrated acids, 1.5 g of the substrate was dissolved in 100 ml of acid and heated at 85 °C using a water bath. After reactions had reached at least 90% completion, aliquots were removed and chilled for product identification.

Hydrolysis products, i.e. oxalic, malonic and succinic acids and hydroxylamine hydrochloride, were identified qualitatively for dihydroxamic acids. For desferal succinic acid, acetic acid and 5-amino pentyl hydroxylamine were identified qualitatively by usual organic tests. These products were separated by fractional crystallization and purified by recrystallization. The UV spectra of isolated products were compared with those of authentic samples.

Results and Discussion

All the reactions followed pseudo first order kinetics:

$$\begin{aligned} -\frac{d}{dt}[\mathrm{HA}] &= k_2[\mathrm{HA}][\mathrm{H}^+] \\ &= k_\psi[\mathrm{HA}]. \end{aligned}$$

The observed pseudo-first-order rate constants of ODHA and MDHA for the catalytic effects of hydrochloric (0.58 to 11.4 M), sulfuric (0.58 to 13.5 M) and perchloric acids (0.58 to 11.1 M) are given in Table 1. In order to explain the differences in the catalytic efficiencies of the different acids and to illustrate that the rate-acidity profiles go through maxima, these data have been plotted in Fig. 1 against molarity (HCl). In the weakly acidic solutions, linear plots were obtained. From the intercept it could be inferred that hydroxamic acid did not react with water (in the absence of catalyst) to a measurable extent at 55 °C. Generally, hydroxamic acids are susceptible both to acid catalysis and to base catalysis, but their spontaneous hydrolysis contributes relatively little to the overall reaction rate. In higher acid regions, the dependence of hydroxamic acid is characterised by an initial rate increase with the acid concentration, passing through a maxima, followed by a rate decrease with further increasing acid concentration. This non-linearity is because the equilibrium between the reactants and the protonated species of the rate-determining step does not correspond only to a simple protonation, but also to addition of water mol-

Table 1. Observed Pseudo-First-Order Rate Constants for the Hydrolysis of Dihydroxamic Acids in Aqueous Mineral Acids Mineral Acids at 55 °C

[Acid] (M)	$k_\psi \times 10^5/\mathrm{s}^{-1}$					
	ODHA			MDHA		
	H_2SO_4	HCl	$HClO_4$	H_2SO_4	HCl	$HClO_4$
0.58	2.04	1.76	1.35	10.6	13.8	7.64
0.72	2.93	—	—	—	—	—
1.35	6.02	—	—	—	—	—
1.39	—	—	3.55	—	—	—
1.45	—	5.54	—	20.5	16.9	13.4
1.45*	—	8.53	—	—	—	—
2.25	11.2	—	—	—	—	—
2.79	—	—	7.21	—	—	—
2.90	—	10.8	—	47.1	29.6	22.4
3.15	15.7	—	—	—	—	—
4.18	—	—	11.1	64.7	53.0	28.1
4.35	—	19.2	—	—	—	—
4.50	27.2	—	—	—	—	—
5.57	—	—	13.0	—	—	—
5.80	—	21.4	—	99.5	67.9	38.9
5.85	32.0	—	—	—	—	—
6.50	—	—	—	106.3	82.8	41.9
6.96	—	—	12.8	—	—	—
7.20	32.9	—	—	—	—	—
7.25	—	30.2	—	114.9	89.1	51.3
8.00	—	—	—	113.9	86.1	51.0
8.36	—	—	14.4	—	—	—
8.70	—	28.8	—	89.9	78.6	53.3
9.00	32.0	—	—	—	—	—
9.75	—	—	14.3	—	—	—
10.2	—	25.2	—	60.2	64.6	40.9
11.1	—	—	11.6	—	—	—
11.3	23.0	—	—	—	—	—
11.4	—	23.7	—	10.8	57.3	—
13.5	5.86	—	—	—	—	—

*DCl in D_2O.

ecules. On the one hand, increased acidity raises the concentration of the reactive conjugate acid form of the substrate, but at the same time if reduces the activity of water needed to complete the hydrolysis. This is true only of A-2 hydrolyses, since in A-1 reactions water does not intervene during the rate-limiting step (see below). As water becomes progressively less available, the hydrolysis rate diminishes steadily.

The transition states with little or no carbenium ion character but with good sites for hydrogen bonding with the medium will be favored in mineral acids having anions of higher charge density (e.g. HSO_4^-, Cl^-). The position of the maximum appears to differ with respect to different hydroxamic acids. At higher acidities, reaction of the protonated substrates gives inverse acidity dependence because solvation of the protonated hydroxamic acid reactant is now weaker than that of H_3O^+.

A comparative study of the hydrolytic reactivity of hydroxamic acids (mono and tri) in aqueous hydrochloric acid has been given in Table 2. Several interesting features have been observed. Firstly, the rate of hydrolysis of aromatic hydroxamic acid, i.e. benzohydroxamic acid, is very slow in comparison with that of aliphatic hydroxamic acid (AHA). At 0.58 M HCl, the rate of hydrolysis of AHA is about 20 times faster than that of ODHA. Trihydroxamic acid (DFB) is more reactive than ODHA but less reactive than AHA. The rate constant

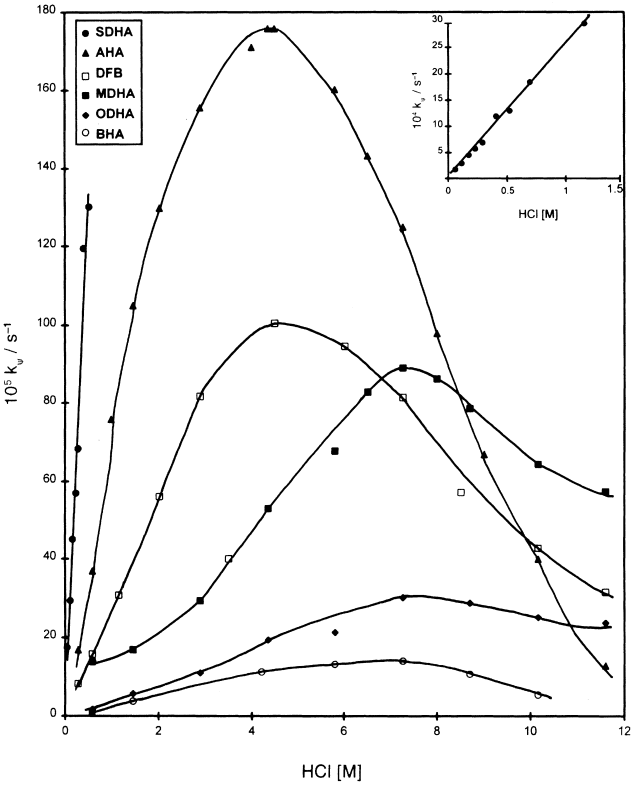


Fig. 1. Rate acidity profiles for the hydrolysis of different hydroxamic acids at 55 °C in HCl (inset: SDHA).

Table 2. Observed Pseudo-First-Order Rate Constants for the Hydrolysis of Mono and Trihydroxamic Acids in Aqueous HCl at 55 °C

[HCl] (M)	$k_\psi \times 10^5/\mathrm{s}^{-1}$		
	AHA	BHA	DFB
0.29	16.9	—	8.03
0.58	37.0	1.10	15.7
1.00	76.0	—	—
1.16	—	—	30.9
1.45	105.1	3.71	—
2.02	130.0	—	56.0
2.90	150.7	—	81.9
3.52	—	—	40.1
4.00	171.0	—	—
4.22	—	11.1	—
4.50	175.8	—	100.6
5.80	160.5	13.2	—
6.00	—	—	94.7
6.50	143.2	—	—
7.25	125.0	14.0	81.6
8.00	98.1	—	—
8.50	—	—	57.2
8.70	—	10.7	—
9.00	67.0	—	—
10.2	40.0	5.21	42.7
11.4	12.9	—	31.5

Table 3. pK_{BH^+} and pK_a Values of Hydroxamic Acids

Hydroxamic acid	pK_{BH^+}	pK_a				Rate maximum of acidity (in HCl)
		pK_1	pK_2	pK_3	pK_4	
AHA	−1.15[a)]	9.27[d)]	—	—	—	4.50
BHA	−2.06[b)]	8.80	—	—	—	7.25
ODHA	—	8.50	10.2	—	—	7.25
MDHA[c)]	—	5.10	6.50	—	—	7.25
SDHA[c)]	—	5.80	6.56	—	—	No observed maximum
DFB[d)]	—	8.30	9.00	9.46	10.84	4.50

a) Ref. 22. b) Ref. 9. c) Ref. 23. d) Ref. 14.

data indicate that the relative reactivities of the hydroxamic acids toward the hydrolysis are SDHA > AHA > DFB > MDHA > ODHA > BHA. This order of reactivities is rationalized in terms of resonance, steric hindrance, and inductive effects. Thus the least sterically crowded aliphatic hydroxamic acid, AHA, is most reactive, because less intensive forces are operating when non-bonded atoms approach each other, whereas the most bulky, BHA, is least reactive.

The pK_{BH^+} and pK_a values of some hydroxamic acids are listed in Table 3. Many of the trends in the pK_{BH^+} and pK_a values in Table 3 run counter to intuition, and several factors must be taken into account when comparing them. It is apparent from Table 3 that AHA is more basic than BHA by 0.91 pK_{BH^+} units. Part of this must be due to the higher electronegativity of the sp^2 carbons in BHA, causing electron withdrawal and making protonation more difficult. It is interesting that for the BHA, ODHA and MDHA, which show a hydrolysis rate maximum, the acidity at which this occurs is in roughly of the same order.

Hydrolysis of carboxylic acid derivatives[17] in mineral acid solutions has generally been discussed in terms of three mechanisms: i.e., A-1, A-2 and A-S$_\mathrm{E}$2 (Eqs. 1–3).

$$\mathrm{S} + \mathrm{H}^+ \underset{\text{fast}}{\overset{K_{\mathrm{SH}^+}}{\rightleftharpoons}} \mathrm{SH}^+ \xrightarrow[\text{slow}]{k_0} \text{Products} \tag{1}$$

$$\mathrm{S} + \mathrm{H}^+ \underset{\text{fast}}{\overset{K_{\mathrm{SH}^+}}{\rightleftharpoons}} \mathrm{SH}^+ + \mathrm{Nu} \xrightarrow[\text{slow}]{k_0} \text{Products} \tag{2}$$

$$\mathrm{S} + \mathrm{H}^+ \xrightarrow[\text{slow}]{k_0} \mathrm{SH}^+ \xrightarrow[\text{fast}]{} \text{Products} \tag{3}$$

The A-1 mechanism (Eq. 1) involves protonation in a fast pre-equilibrium step followed by rate-determining unimolecular reaction of the protonated substrate SH$^+$. The A-2 mechanism involves a rapid pre-equilibrium to give SH$^+$, but this is attacked by a nucleophile (water, Nu) in the rate-determining step. In the A-S$_\mathrm{E}$2 (Eq. 3) mechanism, the proton transfer is rate determining. In the systems under investigation, some of these mechanisms can be rejected or favored on experimental grounds and other considerations.

Solvent Isotope Effect. From the rate data in Table 1, solvent isotope effect ($k_\mathrm{D}/k_\mathrm{H}$) of 1.54 (1.45 M HCl) can be calculated for the hydrolysis of ODHA at 55 °C. Deuterium oxide is a weaker base than water and therefore nuecleophilic attack by D_2O in an A-2 mechanism (Eq. 2) will be less effective than one by H_2O. The substrate will be able to compete with the solvent for a deuteron in D_2O more effectively than for a proton in H_2O and thus the concentration of the protonated species will be greater in D_2O than in H_2O; consequently, the rate should be faster in the former. The above result is consistent with a reaction involving a rapid pre-equilibrium followed by a bimolecular water attack.[24]

Salt Effect. Many added salts increase the protonating power of the medium, as measured by acidity function, and therefore generally assist acid hydrolysis. Bunton et al.[21] have shown that the salt effect of perchlorates is negligible or slightly negative in A-2 acid catalyzed hydrolysis of esters.

The rate of hydrolysis of ODHA was studied in hydrochloric acid (1.45 mol dm^{-3}) using NaCl, KCl and $NaClO_4$, and in sulfuric acid (1.45 M) using $KHSO_4$ and K_2SO_4 (Table 4). Added Cl^- and HSO_4^- produce slight accelerations in rates, whereas added perchlorate (ClO_4^-) and SO_4^{2-} have rate retarding effects. Thus, the data in Table 4 suggest that the substrate is undergoing reaction by an A-2 pathway.

Activation Parameters. The temperature dependence of rate of hydrochloric acid catalyzed hydrolysis of ODHA, MDHA, and SDHA and activation parameters at different acidities are recorded in Table 5. These values are fairly typical for A-2 reactions. The large negative values of $\Delta S^{\ddagger}$ indicate ordered transition structures for the reactions of all the substrates, in accord with charge development in the transition state and the consequent electrostriction of solvent molecules.

Table 4. Effect of Salt on the Hydrolysis of ODHA at 55 °C

[Salt](M)	$10^5\, k_\psi/\mathrm{s}^{-1}$				
	HCl (1.45 M)			H_2SO_4 (1.45 M)	
	KCl	NaCl	$NaClO_4$	K_2SO_4	$KHSO_4$
Nil	5.6	5.6	5.6	6.9	6.9
0.5	6.1	5.9	5.5	4.6	7.0
1.0	—	—	—	2.9	7.1
1.5	6.2	6.3	5.3	1.8	7.3
2.0	6.4	6.7	5.2	1.3	7.8
3.0	6.3	7.8	4.7	—	7.6

Table 5. Temperature Dependance of Rate and Activation Parameters for the Acid-Catalysed Hydrolysis of Dihydroxamic Acids in HCl

Dihydroxamic acids	[HCl](M)	$10^5 k_\psi/\mathrm{s}^{-1}$			E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	$\Delta S^{\neq}$
		45 °C	55 °C	65 °C				
ODHA	1.45	1.84	5.54	13.8	90.0	87.5	105.6	−61.0
	7.25	9.89	30.2	68.1	85.9	83.8	101.2	−59.0
	10.2	8.12	25.2	61.2	90.0	87.8	101.9	−48.0
MDHA	1.45	6.82	16.9	38.9	77.8	75.1	101.6	−80.6
	7.25	36.8	89.0	170.4	68.2	65.5	97.0	−96.0
SDHA	0.058	6.94	17.4	49.7	88.2	85.3	102.3	−58.0
	0.290	28.0	68.2	171.8	81.2	78.5	97.8	−58.8
	0.522	58.8	130.1	342.4	79.0	76.0	96.5	−69.0

ΔE_a, $\Delta H^{\neq}$, $\Delta G^{\neq}$ in kJ mol^{-1} and $\Delta S^{\neq}$ in JK^{-1} mol^{-1}.

The $\Delta H^{\neq}$ decreased as the acid medium become more concentrated. The free energies of activation $\Delta G^{\neq}$ do not vary greatly at different acid concentrations.

Excess Acidity Analysis. The Cox–Yates excess acidity[17] method is a powerful tool to study the effect of medium acidity upon the rate and equilibrium of reactions in aqueous mineral acids. Three possible hydrolysis mechanisms (A-1, A-2 and A-S_E2) can be easily distinguished by this method. The excess acidity represents the difference between the actual solution acidity and the stoichiometric acid concentration.[25] Excess acidity indicates the extra acidity of the medium due to its non-ideal nature. It has the useful property of being zero in the standard state of unit acidity coefficient. They proposed the following three equations for A-1, A-S_E2 and A-2 (Eqs. 4–6) mechanisms respectively.

$$\log k_\psi - \log[\mathrm{H}^+] = \log\frac{k_0}{K_{\mathrm{BH}^+}} + m^{\ddagger}m^{*}X \tag{4}$$

$$\log k_\psi - \log[\mathrm{H}^+] = \log k_2 + m^{\ddagger}m^{*}X \tag{5}$$

$$\log k_\psi - \log[\mathrm{H}^+] - n\log a_{\mathrm{Nu}} = \log\frac{k_2}{K_{\mathrm{BH}^+}} + m^{\ddagger}m^{*}X \tag{6}$$

In these equations k_ψ are observed rate constants as a function of acidity, $[\mathrm{H}^+]$ is the molar proton concentration, X is the excess acidity of the medium, k_0 is the medium-independent rate constant, k_2 is the rate constant for the slow step and K_{BH^+} is the substrate basicity constant. Nu stands for the nucleophile (normally water) and n is the number of water molecules. The X and $a_{\mathrm{H_2O}}$ values for hydrochloric, perchloric and sulfuric acids employed in these correlations were taken from the literature.[17] The excess acidity method works by examining plots of log k_ψ − log $[\mathrm{H}^+]$ against X. In the present case, plots of log k_ψ − log $[\mathrm{H}^+]$ verses X for A-1 (Eq. 1) and A-S_E2 (Eq. 2) are curved (Fig. 2). This means that the reaction mechanism is clearly not A-1 or A-S_E2. Once a mechanism is identified as being A-2, the species reacting with the protonated substrate at the transition state (Nu) can be positively identified by plotting log k_ψ − log $[\mathrm{H}^+]$ − n log a_{Nu} against X, trying different Nu values, until linearity is achieved. Linear plots were obtained with $n = 2$ (2 log $a_{\mathrm{H_2O}}$). Some representative excess acidity plots for ODHA and MDHA are shown in Figs. 3 and 4 respectively. The two water molecules must be involved in bond breaking/making processes at the transition state, since the excess acidity method separates kinetically involved water from

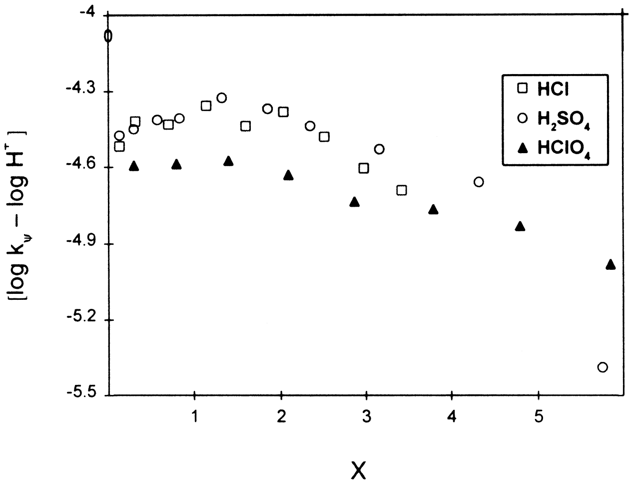


Fig. 2. Cox–Yates excess acidity plots for the hydrolysis of ODHA in mineral acids [log k_ψ − log $[\mathrm{H}^+]$ vs X].

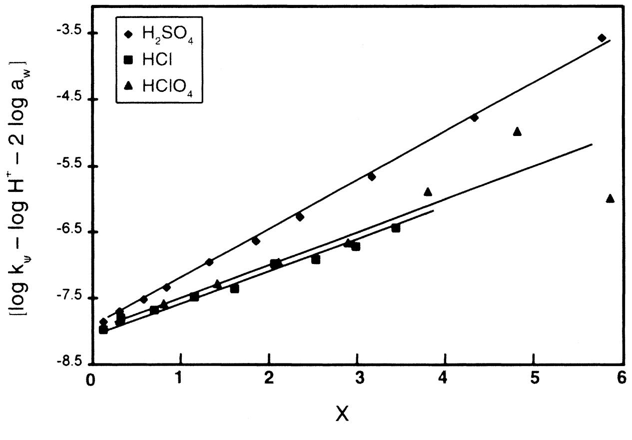


Fig. 3. Excess acidity plots for the hydrolysis of ODHA in mineral acids at 55 °C.

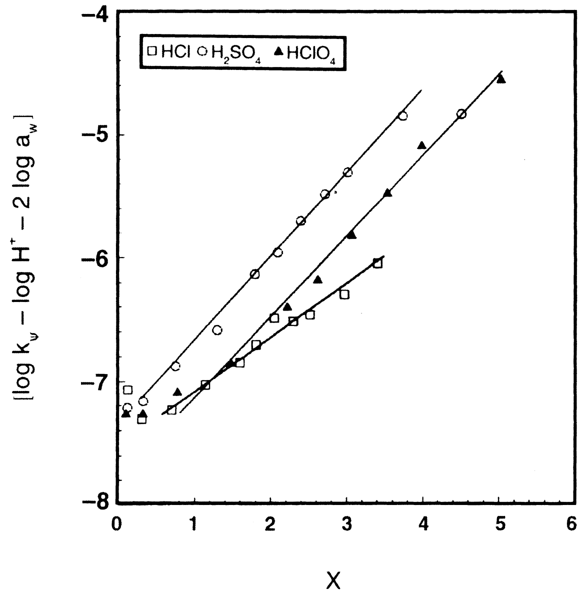


Fig. 4. Excess acidity plots for the hydrolysis of MDHA in mineral acids at 55 °C.

Table 6. Excess Acidity Correlation for the Hydrolysis of Hydroxamic Acid.

Hydroxamic acid	$m^{\neq}\ m^*$		
	HCl	H_2SO_4	$HClO_4$
ODHA	0.40	0.70	0.60
MDHA	0.36	0.61	0.57
SDHA	0.24	—	—
AHA	0.28	—	—
BHA	0.29	—	—
DFB	0.17	—	—

solvation water (which shows up in m^* or $m^{\neq}$). One water molecule is a nucleophile, attacking the carbonyl oxygen; the second is an acid/base, transferring protons between the water molecules. The slope ($m^{\neq}\ m^*$) values for all the hydroxamic acids are given in Table 6. These values are consistent with the A-2 mechanism.[26–27] The m^* for carbonyl oxygen protonation[28] is 0.6 or less and for A-2 reactions $m^{\neq} = 1$; thus an overall slope against X of 0.6 or less should result for Eq. 6.

Protonation Equilibrium. We have attempted to determine protonation constants by UV spectroscopy using mineral acids i.e. H_2SO_4 and $HClO_4$. The UV spectra of ODHA in different acid solutions of H_2SO_4 (0.0 to 7.2 M) and $HClO_4$ (0.0 to 8.0 M). No clear-cut isosbestic points have been observed. Furthermore, only minor changes are observed in the UV spectra of ODHA as acid concentration is increased from 0.5 to 8.0 M. The molar extinction coefficients at the absorption maxima were : in water, at 204 nm, $\varepsilon_{\max}$ 3.78 × 10^{-5} L mol^{-1} cm^{-1}, in 7.2 M H_2SO_4, at 208 m, $\varepsilon_{\max}$ 4.56 × 10^{-5} L mol^{-1} cm^{-1} and in 8.0 M $HClO_4$ at 208 nm, $\varepsilon_{\max}$ 4.69 × 10^{-5} L mol^{-1} cm^{-1}. The position of $\lambda_{\max}$ did not shift as the substrate become protonated, while for other monohydroxamic acids[7] there was a definite bathochromic shift in $\lambda_{\max}$. We cannot explain this small spectral change. The exact method of evaluating pK_{BH^+} was therefore dependent on the behavior of each particular substrate. The protonation constants could not be accurately determined because of the small differences between the spectra of ODHA and its conjugate acid.

Mechanism. The excess acidity plots, the solvent isotope effect, activation parameters and the salt effects support an A-2 type mechanism (Scheme 3). This is very similar to a previously proposed mechanism for monohydroxamic acids.[8] At acid concentrations in the range 0.58 to 3.5 M the catalytic effect of acids decreases in the order H_2SO_4 – HCl > $HClO_4$. At acid concentration above 3.5 M, the catalytic effectiveness of the acids decreases in the sequence H_2SO_4 > HCl > $HClO_4$. Bunton and his co-workers[21] have suggested that such an order is associated with an A-2 mechanism. A marked difference in reactivity between SDHA and other hydroxamic acids due to intramolecular hydrogen bonding operates in the protonated SDHA.

No evidence for a unimolecular pathway, such as changes in activation entropies or solvent isotope effects, was seen for the hydrolysis of dihydroxamic acid in the acidity range studied. The reactive species could in theory be the monoprotonated or the diprotonated or even the triprotonated species involving O– and N–. Reaction from a diprotonated or triprotonated species is unlikely on the following grounds. (i) Normal monohydroxamic acid hydrolysis proceeds by way of a pre-equilibrium oxygen protonation and one might reasonably assume that the dihydroxamic acid would hydrolyze in a similar way. The question concerning the actual site of protonation has long been debated. Recently Caro et al.[28] presented experimental and theoretical studies of the protonation processes in acetohydroxamic acid in the gas phase using ab initio methodology. Protonation on the carbonyl oxygen is favored on energetic grounds by 37 kJ mol^{-1}. Moreover a two- or three-proton mechanism would demand rates of reaction that would increase throughout the entire range of acidity studied; this is contrary to the kinetic results, which actually show a downturn in k_ψ (Fig. 1) in the higher acid concentration range. Having applied several mechanistic criteria in relation to the present study, we can predict the A-2 mechanism. This would involve 2 molecules of water, as indicated by the Cox–Yates excess acidity method (Figs. 2–3). The requirement for two water molecules stems from the need for one to act as nucleophile and the other to provide solvation as the nucleophilic water acquires a positive charge. This tetrahedral intermediate deprotonates and gives neutral species. This intermediate can protonate in three places. By far the most probable is protonation at N to give unstable species. Protonated oxalodihydroxylamine gives oxalic acid and protonated hydroxylamine. In case of dihydroxamic acids the reaction intermediates are more stable; therefore they form products more easily than mono hydroxamic acids.

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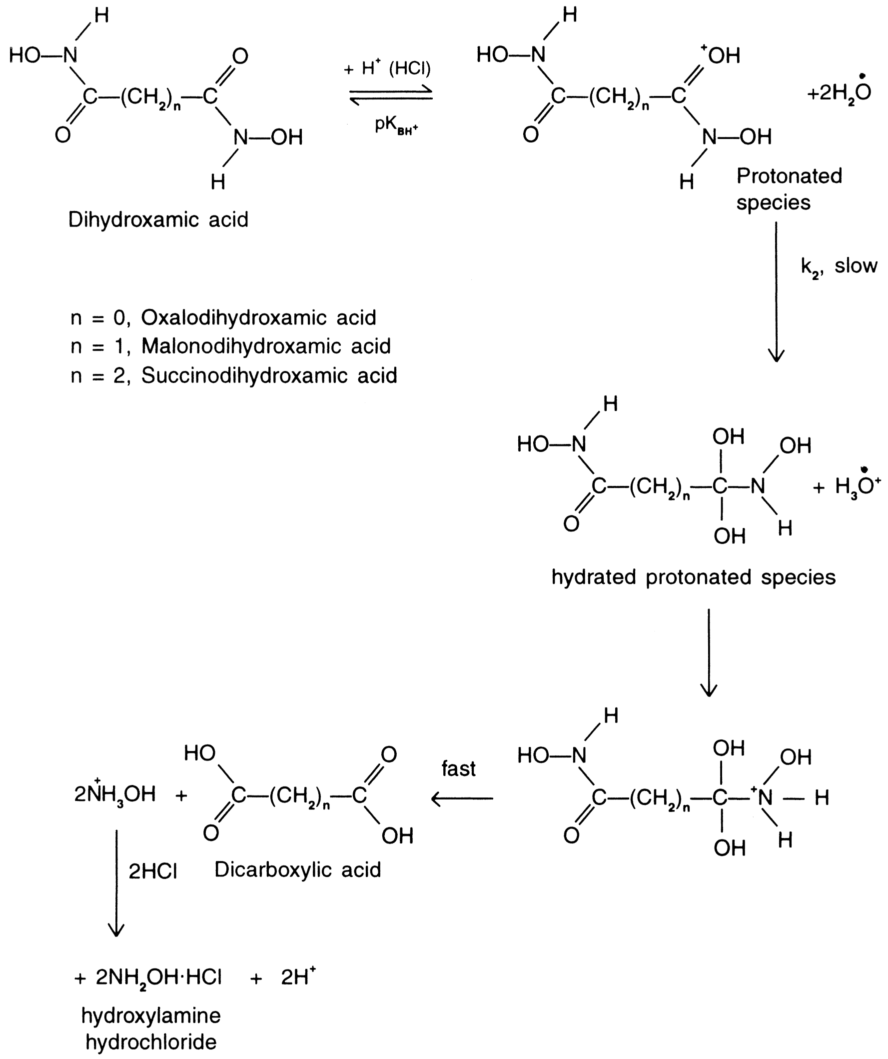

Scheme 3.

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