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Review

Kinetic and mechanistic aspects of acid-catalysed hydrolysis of hydroxamic acids

Kallol K Ghosh
School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur 492 001, India

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The available experimental observations for the acid-catalyed hydrolysis of hydroxamic acids have been presented. For *N*-substituted hydroamic acid both A-2 and A-1 path are recognied. For primary hydroxamic acid no evidence for A-1 pathway is oberved. If *N*-versus *O*-protonation controversy is ignored, it is found that protonation involves specific acid protonation of the hydroxamic acid to activate it towards attack by water. That atack is assisted by a second water molecule to directly yield the neutral tetrahedral intermediate T_0 and H_3O^+, which avoids the formation of a highly unstable. *O*-protonated tetrahedral intermediate. The breakdown of T_0, in all cases involves protonation by H_3O^+ to yield T_N^+, which then undergoes C–N cleavage. That process is assisted by simultaneous proton removal from OH in T_N^+ by solvent water, so that the immediately formed products are hydroxylamine, carboxylic acid and H_3O^+. The result of the hydrolysis could be useful for analytical reactions. A knowledge of mechanism of reactions of this group of compounds can be of great assistance in planning their use as analytical reagents and also in explaining their role in biological reactions.

Introduction

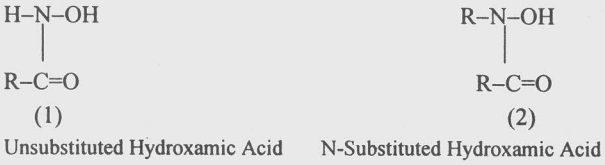
Over a century[1] the chemistry of hydroxamic acids has been the subject of extensive chemical research. Several aspects such as their synthesis[2-15], photochemical formation[16], physical and chemical properties[17-23], ionization and structure[24-29], analytical[30-36] and therapeutic[37,38] applications have been reviewed from time to time. Hydroxamic acids are weak proton donors which have numerous applications in such diverse fields as enyme inhibitors[39], siderophores[40-45], nuclear fuel processing[46], soil enchancers[47], fungicides[48], mutagens[49], carcinogens[50] and DNA cleavage[51,52]. The increasing interest in hydroxamic acids has been attributed, in part, to work on artificial metallonucleases[51,52], drug delivery systems[53,54], biological[55] and malaria research[56]. Hydroxamic acid metal complexes would be the promising DNA cleaving agents. A complete review on the biochemical, medicinal studies and analytical applications of hydroxamic acids is beyond the scope of this work. The hydrolysis mechanism, structure, acid-base equilibria and overall stability of hydroxamic acids are known to have an important bearing of their general usefulness in many of these applications.

Several hydroxamic acids have been found to be excellent spectrophotometric reagents for the determination of metal ions from concentrated acid solutions. However, due to hydrolysis of hydroxamic acids into the parent carboxylic acids and hydroxylamines, severe problems are faced in achieving the desired objectives. Hence, hydrolytic stabilities have been examined. This novel approach, based on chemical kinetics data, provides a judicious and rational basis to the search of new analytical reagents. A voluminous literature concerns the kinetic and mechanism of hydrolysis of esters, amides, anilides and other carboxylic acid derivatives. Strangely enough, the hydrolysis behaviour of hydroxamic acids have been generally ignored for a long time. Moreover, no comprehensive treatment of the mechanism of acidic hydrolysis has appeared. The main purpose of this review is to provide the reader with an overview of the literature of the kinetics and mechanism of the acidic hydrolysis and protonation behaviour of hydroxamic acids and to highlight the recent developments in this field.

Systems

Chemically, hydroxamic acids are regarded as N-acyl derivatives of hydroxylamine. The work hitherto reported on the acidic hydrolysis of

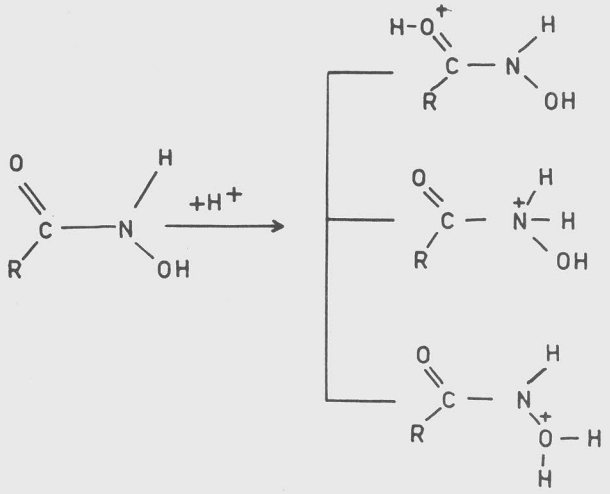
hydroxamic acids can be classified under the two broad categories of **1** and **2**.



(1) Unsubstituted Hydroxamic Acid

(2) N-Substituted Hydroxamic Acid

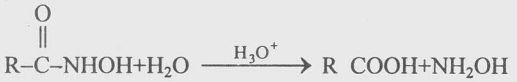
Hydroxamic acids have more than one site for addition of a proton (Scheme I), and determining which of these is the principal locus of the reaction is not always straightforward. The question concerning actual site of protonation has been long debated.



Scheme I

Kinetics

Whatever work that has been done on the kinetics of hydrolysis reaction, deals primarily with unsubstituted hydroxamic acids[57-74] and in dilute acid media. Only a few studies have been reported on the hydrolysis of N-substituted acids[75-84] under non-dilute acidic conditions. The acid-catalysed hydrolysis of hydroxamic acids affords carboxylic acids and hydroxylamine according to equation (1).

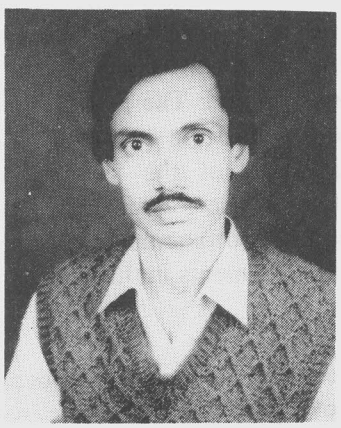


... (1)

The acidic hydrolyses of unsubstituted and N-substituted hydroxamic acids studied so far are given in Tables I and II.

Unsubstituted Hydroxamic Acids

The most widely known compound of this series is benzohydroxamic acid (BHA) ($C_6H_5CONHOH$). The kinetics of acid-catalysed hydrolysis of BHA in aqueous solution was studied for the first time by Berndt and Fuller[65]. In this pioneering work rates of hydrolysis were determined spectrophotometrically by following the decrease in the characteristic absorption of the hydroxamic acid-ferric chloride complex. This study, however, only covered the low acidity range (0.1-0.58 *M*) in which extensive protonation is unlikely to occur. Tillett *et al.*[66] have carried out a careful study of protonation behaviour and the acid-catalysed hydrolysis of a number of *para*-substituted benzohydroxamic acids, *p*–*X*–$C_6H_4CONHOH$ (X=H, –CH_3O–CH_3, –NO_2, –Cl and –OH). At low acidity the rate increases linearly with acid concentration, in accord with the earlier observations of Berndt and Fuller[65]. At higher concentrations of acid, however, the rate rises to a maximum and then starts decreasing. It seems reasonable to suppose that in this region of acidity, complete conversion



Dr Kallol Kumar Ghosh is presently a Senior lecturer of Chemistry at Pt. Ravishankar Shukla University Raipur. Born in 1960, he received his M.Sc. (Physical Chemistry) in 1981 and Ph.D. in 1986 from Pt. Ravishankar Shukla University. Prof. S G Tandon introduced him to hydroxamic acid chemistry. He has published extensively in the field of physical organic chemistry with special bias on mechanism and kinetics. His current research interests include micellar catalysis, acid-base equilibria of polyfunctional acids and bases, metal complexation and DNA cleavage.

Table I—Acid-catalysed hydrolysis of unsubstituted hydroxamic acids ($R-\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{/}{\underset{\backslash}{N}}}-H$)

R	Mol. formula	Temp. °C	Catalyst	Medium	Ref.
CH_3	$C_2H_5NO_2$	40.0	HCl (1-7M)	Aqueous	57
		40.0	H_2SO_4 (1-7M)		
		40.0	$HClO_4$ (1-7M)		
		50.5	*p*-Toluenesulphonic acid (0.249*N*)	Aqueous	58
$Cl-CH_2$	$C_2H_4ClNO_2$	90.1	$HClO_4$ (Proton activity a_{H^+} 0.0634-0.4528)	50% (w/w) Ethanol	59
CH_3-CH_2	$C_3H_7NO_2$	25	H_2SO_4 (9.5-74% w/v)	Aqueous	60
		25-35	H_2SO_4 (9.5-57.2%)	Aqueous	61
		25.0	HNO_3 (12-22.4%)		
		50.2	*p*-Toluenesulphonic acid (0.124-0.494 *M*)	Aqueous	58
$(CH_3)_3C$	$C_5H_{11}NO_2$	50.5	*p*-Toluenesulphonic acid (0.249*M*)	Aqueous	58
$CH_3(CH_2)_4$	$C_6H_{13}NO_2$	40.0	HCl (1-8 *M*)	Aqueous	64
		40.0	H_2SO_4 (1-8 *M*)		
		40.0	$HClO_4$ (1-8 *M*)		
C_6H_5	$C_7H_7NO_2$	78.6-88.6	HCl (0.109-0.577 *M*)	Aqueous	65
		74.9	HCl (1-5 *M*)		
		74.9	$HClO_4$ (1-6 *M*)	Aqueous	66
		74.9	HBr (1-5 *M*)		
		70-80	$HClO_4$ (4.9-59.2%)	Aqueous	67
		90.2	$HClO_4$ (Proton activity a_{H^+} 0.0324-1.081	Ethanol	59
		55.0	H_2SO_4 (1.45-8.0 M)	10% (v/v) Dioxane	68
		55.0	HCl (0.75-10.4 *M*)	10% (v/v) DMSO	69
			H_2SO_4 (0.75-10.4 *M*)		
			$HClO_4$ (0.75-7.5 *M*)		
$2\text{-}OH\cdot C_6H_4$	$C_7H_7NO_3$	55.0	HCl (1.45-10.1 *M*)	10% (v/v) Dioxane	74
			H_2SO_4 (1.45-7.54 *M*)		
			$HClO_4$ (1.5-10.1 *M*)		
$4\text{-}OCH_3\cdot C_6H_4$	$C_8H_9NO_3$	55.0	HCl (0.75-9.5 *M*)	10% (v/v) Dioxane	74
			H_2SO_4 (1.45-7.54 *M*)		
			$HClO_4$ (1.5-10.1 *M*)		
$4\text{-}OCH_3\cdot C_6H_4$	$C_8H_9NO_3$	55.0	HCl (0.75-9.5 *M*)	10% (v/v) DMSO	71
			H_2O_4 (0.75-8.5 *M*)		
			$HClO_4$ (0.75-7.5 *M*)		
$2\text{-}X\cdot C_6H_4$	—	90.0	HCl (0.605 *M*)	Aqueous	70
(X=OC_2H_5, OCH_3, CH_3, Cl, Br)					
$3\text{-}Br\cdot C_6H_4$	$C_7H_6BrNO_2$	80.0	$HClO_4$ (10.1-59.2%)	Aqueou	67
$3\text{-}Cl\cdot C_6H_4$	$C_7H_6ClNO_2$	80.0	$HClO_4$ (10.1-59.2%)	Aqueous	67
		55.0	HCl (0.75-10.4 *M*)	10% (v/v) DMSO	72
			H_2SO_4 (0.75-10.4 *M*)		
			$HClO_4$ (0.75-7.5 *M*)		
$3\text{-}NO_2\cdot C_6H_4$	$C_7H_6N_2O_4$	70-80	$HClO_4$ (4.9-59.2%)	Aqueous	67
$3\text{-}CH_3\cdot C_6H_4$	$C_8H_9NO_2$	80.0	$HClO_4$ (10.1-59.2%)	Aqueous	67
$4\text{-}OH\cdot C_6H_4$	$C_7H_7NO_3$	50.3	$HClO_4$ (1-5 *M*)	Aqueous	66
$4\text{-}Cl\cdot C_5H_4$	$C_7H_6ClNO_2$	50.3	$HClO_4$ (1-5 *M*)	Aqueous	66
		80.0	$HClO_4$ (10.1-59.2%)	Aqueous	67

(*Contd*)

Table I—Acid-catalysed hydrolysis of unsubstituted hydroxamic acids (R–C(=O)–N(OH)–H) (*Contd*)

4-Br·C_6H_4	$C_7H_6BrNO_2$	80.0	$HClO_4$ (10.1-59.2%)	Aqueous	67
4-CH_3·C_6H_4	$C_8H_9NO_2$	50.3	HCl (1-6 *M*)	Aqueous	67
		50.3	$HClO_4$ (0.5-6 *M*)	Aqueous	67
		50.3	HBr (1-4 *M*)	Aqueous	67
		50.3	H_2SO_4 (1-4 *M*)	Aqueous	66
4-OCH_3·C_6H_4	$C_8H_9NO_3$	50.3	HCl (1-2 *M*)	Aqueous	66
		50.3	H_2SO_4 (1-2 *M*)		
		50.3	$HClO_4$ (1-5 *M*)		
		80.0	$HClO_4$ (10.1-59.2%)	Aqueous	67
$C_6H_5CH_2$	$C_8H_9NO_2$	49.8	H_2SO_4 (1-7 *M*)	Aqueous	63
		50.3	*p*-Toluenesulphonic acid (0.249 *M*)	Aqueous	58
		70.3	HCl (0.0479 *N*, 0.240 *N*)	Sulfolane	73
		50.5			
Picolinohydroxamic Acid		90.1	$HClO_4$ (Proton Activity a_{H^+} 0.1430-0.6325)	50% (w/w) Ethanol	59
Nicotinohydroxamic Acid		90.1	$HClO_4$ (a_{H^+} 0.1173-0.4128)	50% (w/w) Ethanol	59
Iso-nicotinohydroxamic Acid		90.1	$HClO_4$ (a_{H^+} 0.1430-0.5995)	50% (w/w) Ethanol	59

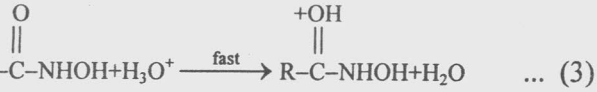
Table II—Acid-catalysed hydrolysis of *N*-substituted hydroxamic acids (R_1–C(=O)–N(OH)–R_2)

R_1	R_2	Mol. formula	Temp. °C	Catalyst	Medium	Ref.
CH_3	C_6H_5	$C_8H_{11}NO_2$	50.0	H_2SO_4 (0.1-9.0 *M*)	50% (v/v) CH_3CN	75
$CH_3(CH_2)_2$	C_6H_5	$C_{10}H_{13}NO_2$	40.2	HCl (0.1-1.2 *M*)		
			35-40.2	HCl (1-5 *M*)	Aqueous	76
			35	$HClO_4$ (1-5 *M*)		
2-X·C_6H_4 (X=Cl, Br, I, NO_2, CH_3, OCH_3)	CH_3	—	90.0	HCl (0.764 *M*)	Aqueous	77
2-CH_3·C_6H_4	CH_3	$C_9H_{11}NO_2$	90.0	HCl (0.149-0.751 *M*)	Aqueous	78
			70-80	HCl (0.751 *M*)		
			61.1			
4-CH_3·C_6H_4	CH_3	$C_9H_{11}NO_2$	71.7	HCl (0.225 *M*)		78
			84.0			
C_6H_5	CH_5	$C_8H_{11}NO_2$	55.0	HCl (0.75-9.00 *M*)	20% (v/v) Dioxane	84
				H_2SO_4 (0.75-6.5 *M*)		
				$HClO_4$ (0.88-8.5 *M*)		
C_6H_5	C_6H_5	$C_{13}H_{11}NO_2$	55	HCl (1.45-8.22 *M*)	10% (v/v) Dioxane	79
			45-65	H_2SO_4 (0.72-14.0 *M*)	10% (v/v) Dioxane	79
			45-65	$HClO_4$ (0.72-10.0 *M*)		
4-X·C_6H_4	C_6H_5	—	90.1	$HClO_4$ (a_{H^+} 0.1429-0.4848)	50% by wt Ethanol	159
4-X·C_6H_4 (X=OCH_3, CH_3, NO_2, Cl, F)	C_6H_5	—	55.0	H_2SO_4 (0.75-12.0 *M*)	20% (v/v) Dioxane	80
C_6H_5	$C_6H_5CH_2$	$C_{14}H_{13}NO_2$	55	HCl (1.16-10.4 *M*)		
			55	H_2SO_4 (0.72-10.0 *M*)	10% (v/v) Dioxane	82
			55	$HClO_4$ (1.16-10.1 *M*)		
X·C_6H_4 4-X=CH_2, NO_2, F)	$C_6H_5CH_2$	—	55	HCl (0.75-10.4 *M*)	10% (v/v) Dioxane	83

of the substrate into conjugate acid is occurring. The values of activation parameters are in the range normally associated with a bimolecular mechanism ($\Delta H^{\ddagger}$ =68 to 90 kJ mol^{-1} $\Delta S^{\ddagger}$ = –64 to –87 JK^{-1} mol^{-1} and $\Delta G^{\ddagger}$ =101–105 kJ mol^{-1}). Substituent effects on the hydrolysis of BHA follow the Hammett equation with ρ=+0.64. Electron-withdrawing substituents accelerate the hydrolysis and electron-donating substituent retard it.

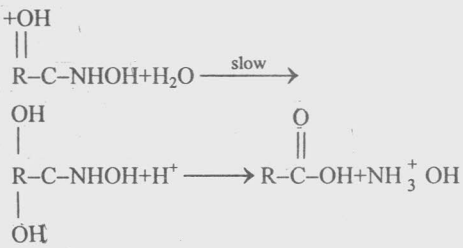
Ahmad *et al.*[67] have extended the investigation of Tillett[66] of the hydrolysis of BHA, in particular by making measurements in $HClO_4$ (4.9-59.2%) solutions at 70-80°C. It has been observed that polar effects of substituents are insignificant in acid medium, however they are marked in media where the substrates are fully protonated. The reaction constant (ρ=0.85) found is almost the same as that found by Tillett *et al.*[66] Berndt and Sharp[58] measured hydrolysis rates of propionohydroxamic acid and a series of aliphatic hydroxamic acids in aqueous *p*-toluenesulfonic acid at 50.2°C. Their results show that polar and steric effects are of comparable magnitude in the acid-catalysed hydrolysis of hydroxamic acids. In the case of aliphatic hydroxamic acids the rate constants correlate according to Taft equation[85], whereas in the case of the aromatic *ortho*-substituted derivatives[70] they correlate with the Pavelich-Taft equation[86]. Berndt and Ward[70] studied the acid-catalysed hydrolysis of a series of *ortho*-substituted benzohydroxamic acids in 0.605 *M* HCl at 90°C. A good correlation was obtained by application of Pavelich-Taft equation.

The dependence of hydrolysis rate constants of benohydroxamic acid and of some other unsubstituted hydroxamic acids on the proton activity and dielectric constant of the medium has been studied by Mollin and Kucerova[59]. In neutral region this reaction is slower than in acid medium by several orders of magnitude. Hence, the non-catalysed addition of water is kinetically insignificant. The reaction sequence started with a rapid pre-equilibrium proton transfer (Eq. 3).



... (3)

The carbon atom of the carbonyl group is then attacked by water (nucleophile) resulting in a tetrahedral intermediate is formed, and the carbonyl group is again created by the loss of a leaving group (Eq. 4).



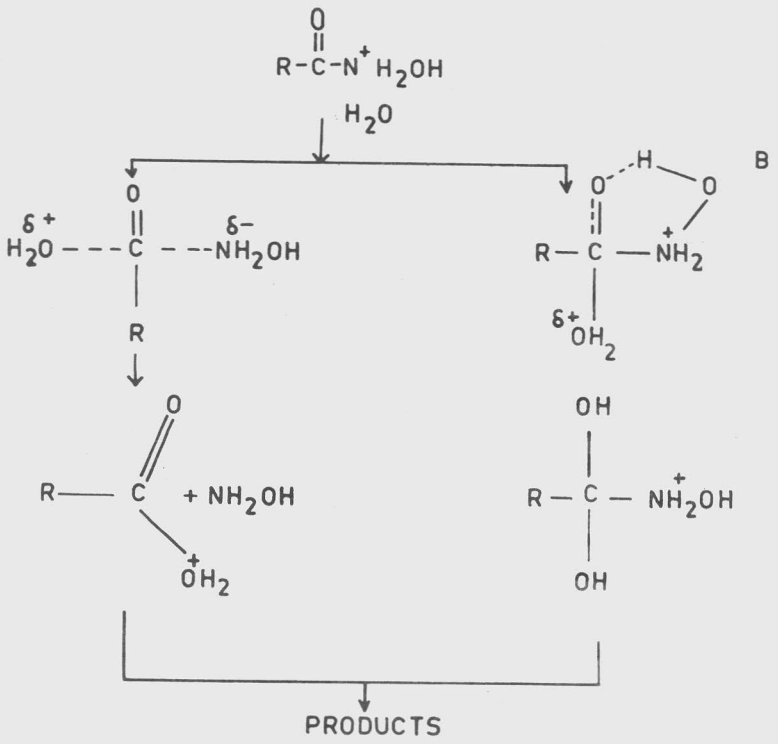
... (4)

This pattern, which was built up from a wide variety of evidence, remains the framework of our understanding. Theoretical chemists are making increasing contribution to mechanistic studies with recent advances in computational methods. It is possible to optimize reaction coordinates or to compare different paths. Most calculations refer to gas phase, but comments on the differences expected for solution reactions are often made.

The hydrolysis of some aliphatic hydroxamic acids[57,62,64] such as methyl, isobutyl and hexylhydroxamic acids has been studied in perchloric, hydrochloric and sulfuric acids.

Detailed kinetic study using concepts such as the ionic strength effect, solvent isotope effect, activation parameters and rate acidity correlation supports this mechanism. In an elegant investigation, Modena *et al.*[60] supplied more direct evidence on this matter. They have examined the hydrolytic behaviour of a model substrate, propanhydroxamic acid in aqueous sulfuric acid (9.5 to 74% w/v). The extent of the exchange of ^{18}O-labelled at the carbonyl carbon of benzohydroxamic acid with the solvent at different acidities of the medium was also studied. It has been suggested that the mechanism involves the rate determining attack of water on the *N*-protonated conjugate acid of the substrate assumed to be present as minor partner in the equilibrium protonation of hydroxamic acids together with the O-protonated form (major partner). The ^{18}O exchange experiments indicate that no significant carbonyl oxygen exchange takes place in the hydrolytic reaction. Therefore, either a tetrahedral intermediate is not formed, or it does not survive long enough to obtain equilibration with the solvent. They[60] favour a mechanism as shown in Scheme II.

Two alternative pathways may be considered.



Scheme II

Path-A amounts to S_N2 like displacement of hydroxylamine by water. Actualy this kind of reaction path at sp^2 hybridised carbon is intrinsically rather difficult and it requires a large carbonium ion character with an extended bond breaking at the transition state. This requirement cannot be met in the present case as hydroxylamine should be a rather poor leaving group. Path-B requires a rate determining attack of water to the carbonyl carbon. It formally gives raise to a zwitterionic species which should have very high energy. However, it may be envisaged that concurrent proton transfer from and to the solvent, most likely helped by the internal hydrogen bonding between the hydroxylamine hydrogen and the carbonyl oxygen, allows to avoid this heavily charged structure and to reach directly the *N*-protonated tetrahedral intermediate. This mechanism requires a transition state with a high character of oxonium ion. The *N*-protonated tetrahedral intermediate will then yield irreversibly the products.

Modena *et al.*[61] also investigated hydrolysis of propanhydroxamic in sulphuric and nitric acids. The two acids exert an identical catalytic effect. The rates pass through a maximum. The bell-shaped profile observed might suggest that a water molecule is involved in the rate determining step.

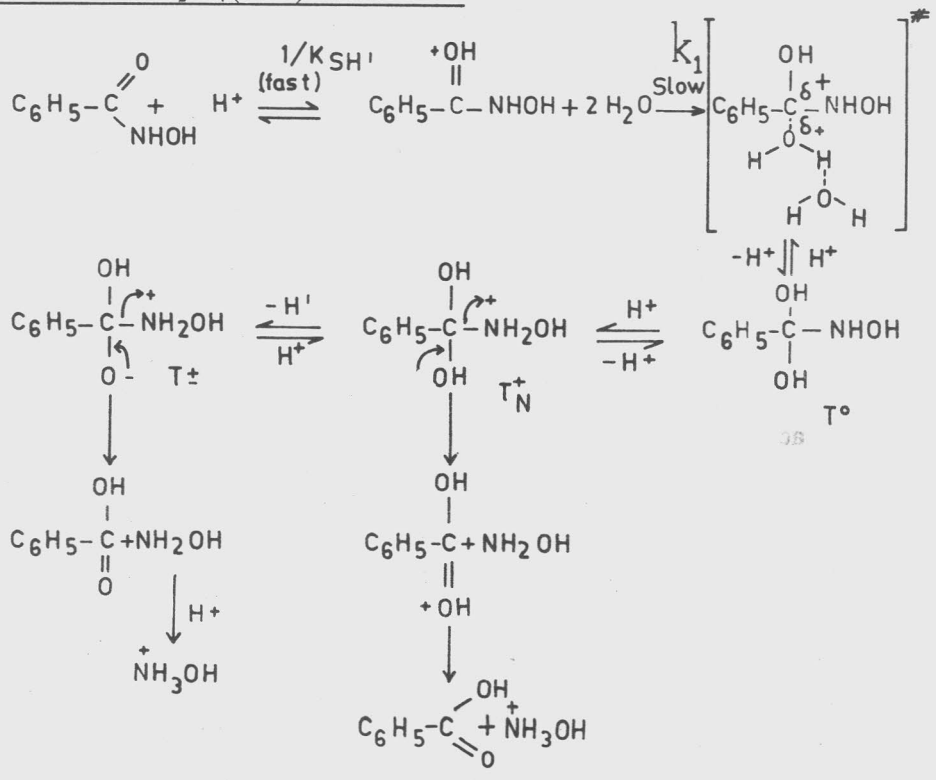
Buglass and Juffkins[63] offer an explanation for rate maximum in their work on the hydrolysis of 2,2-dimethylacetohydroxamic and phenylacetohydroxamic acids in aqueous sulphuric acid at 49.8°C. They proposed that the rate maxima occur because the acid-base pre-equilibrium steps and transition state formation step are governed by different acidity functions[87]. In particular the acidity function controlling the transition state formation increases less rapidly than the acidity function governing the acid-base equilibrium, with increasing acid concentration. It appears that the experimental findings are in agreement with an A-2 mechanism. Among other facts the A-2 mechanism was compatible with the common observation of (i) specific acid catalysis, (ii) values of activation parameters, (iii) solvent isotope effects $k_D/k_H>1$ (Table III) and (iv) Hammett equation, electron withdrawing substituents accelerate the hydrolysis and electron-donating groups retard it. The magnitude of solvent isotope effect at a given acidity reflects the extent of protonation on the

Table III—Solvent deuterium isotope effect on acid-catalysed hydrolysis of hydroxamic acids, $R_1CO{\cdot}N(OH)R_2$

R_1	R_2	Temp. °C	Acid	k_D/k_H	Ref.
CH_3	H	40	HCl (1 *M*)	1.58	
			HCl (6 *M*)	1.42	
$(CH_3)_2CH$	H	40	HCl (1 *M*)	1.70	57
			HCl (6 *M*)	1.14	
$CH_3(CH_2)_4$	H	40	HCl (1 *M*)	1.80	
			HCl (6 *M*)	1.60	
C_6H_5	H	74.9	$HClO_4$ (1 *M*)	1.58	66
C_6H_5	H	55	D_2SO_4 (1.4 *M*)	1.68	
			D_2SO_4 (5.0 *M*)	1.21	68
			D_2SO_4 (8.0 *M*)	0.795	
p-$CH_3{\cdot}C_6H_4$	H	50.3	$HClO_4$ (1 *M*)	1.67	66
m-$Cl{\cdot}C_6H_4$	H	55	D_2SO_4 (2.9 *M*)	1.68	72
			D_2SO_4 (7.5 *M*)	1.02	
3-$OH{\cdot}C_6H_4$	H	55	DCl (2.9 *M*)	1.05	74
			D_2SO_4 (2.9 *M*)	1.04	
$CH_3(CH_2)_2$	C_6H_5	40	HCl (0.6 *M*)	1.70	76
			DCl (2.9 *M*)	1.51	
C_6H_5	CH_3	55	D_2SO_4 (2.9 *M*)	1.61	84
C_6H_5	C_6H_5	55	DCl (2.32 *M*)	1.52	68
			DCl (8.22 *M*)	1.22	
			D_2SO_4 (1.45 *M*)	1.60	
			D_2SO_4 (5.8 *M*)	1.25	
			D_2SO_4 (7.5 *M*)	0.95	
$C_6H_5CH_2$	C_6H_5	55	DCl (2.9 *M*)	1.57	82
			DCl (8.0 *M*)	1.20	
			D_2SO_4 (1.45 *M*)	1.61	
			D_2SO_4 (5.8 *M*)	1.01	
			D_2SO_4 (8.5 *M*)	0.63	

hydrolytic *N*-acyl bond cleavage steps. At low acid concentration, the initial equilibrium controls, the isotope effect and the reaction are more rapid in D_2O than in H_2O. At higher acid concentrations (D_2SO_4, 8.0 *M*), the substrate is largely in the form of the conjugate acid in either solvent. The displacement on the conjugate acid would be expected to be slow for D_2O than for H_2O, since the former is a weaker base. Thus, the isotope effect is reversed ($k_D/k_H<1$) under these conditions.

In the author's own laboratory, an improved analysis of experimental data for the acidic hydrolysis of benzohydroxamic[69] acid and its derivatives[71,72] and salicylhydroxamic acid[74] has been investigated. The Yates-McClelland[88] and Bunnett-Olsen LFER methods[89] have been used to correlate rate with acidity function. Recently, the Cox-Yates excess acidity[90] method has proved to be of considerable value in determining the details of the mechanisms of reactions in strongly acidic media. The results of rate-acidity correlations are summarised in Table IV. Using Bunnett, Bunnett-Olsen, and excess acidity criteria we have confirmed the A-2 mechanism as shown in Scheme III. Although there has been no revolutionary change in viewpoint, a more detailed understanding and



Scheme III

Table IV—Summary of rate-acidity correlations in the acid-catalysed hydrolysis of hydroxamic acids, $R_1CO{\cdot}N(OH)R_2$

R_1	R_2	Acid	Bunnett ω	Bunnett Olsen φ	Yates-McClellan 'r' φ	Bunnett-Olsen LFER	Cox-Yates exxcess acidity '$m_2^{\dagger}$' m^*	Ref.
CH_3	H	HCl	6.2	1.25	—	—	—	57
$(CH_3)_2CH$	H	HCl	6.6	1.25	—	—	—	57
$CH_3(CH_2)_4$	H	HCl	6.7	1.30	3.10	—	—	57
C_6H_5	H	HCl	—	—	1.90	0.74	0.26	69
		H_2SO_4	—	—	2.13	0.83	0.37	—
		$HClO_4$	—	—	2.30	0.98	0.12	—
m-Cl·C_6H_4	H	HCl	4.0	1.06	—	—	0.42	72
		H_2SO_4	3.2	1.13	—	—	0.52	—
		$HClO_4$	3.7	1.29	—	—	0.35	—
p-OCH_3·C_6H_4	H	HCl	—	—	2.23	0.47	0.13	71
		H_2SO_4	—	—	1.72	0.41	0.51	—
		$HClO_4$	—	—	2.27	0.75	0.18	—
m-OH·C_6H_4	H	HCl	—	—	—	—	0.30	74
		H_2SO_4	—	—	—	—	0.28	—
		$HClO_4$	—	—	—	—	0.23	—
C_3H_7	C_6H_5	HCl	6.1	1.0	1.85	—	—	76
		$HClO_4$	8.9	1.3	—	—	—	—
C_6H_5	C_6H_5	HCl	4.90	1.03	1.90	0.80	0.55	79, 81
		H_2SO_4 (up to 8.0 *M*)	4.67	1.10	1.92	0.80	0.39	—
		H_2SO_4 (>8.0 *M*)	—	—	1.40	–0.60	1.28	80
		$HClO_4$ (up to 7.5 *M*)	7.17	1.19	1.98	0.92	—	—
		$HClO_4$ (>7.5 *M*)	—	—	–0.26	–0.18	—	—
C_6H_5	$C_6H_5{\cdot}CH_2$	HCl	4.4	1.14	—	—	0.53	73, 82
		H_2SO_4	3.9	1.24	—	—	—	—
		$HClO_4$	4.1	1.56	—	—	—	—

refinement of mechanisms have been made. It seems clear from our studies that the reaction rate depends on substrate acidity and water activity. No extensive study exists for solvent effects on the acidic hydrolysis of hydroxamic acids. However, Berndt[91] has studied the acid-catalysed hydrolysis of phenylacetohydroxamic acid in various water-sulfolane mixtures. The rate of hydrolysis of BHA has been measured in dioxane, DMSO, DMF, acetone, methanol, ethanol and isopropanol. The plots of log *k* against 1/D are fairly linear with positive slope over a wide range of mixtures[92].

N-Substituted Hydroxamic Acids

In comparison to primary hydroxamic acids, very limited studies have been reported so far on *N*-substituted hydroxamic acids. These acids have been strangely neglected so far as detailed studies of mechanism are concerned. The first comprehensive report on hydrolysis of *N*-substituted hydroxamic acid was published by our laboratory. Tandon and Rao[76] initiated the investigation on hydrolysis by examining the hydrolysis of *N*-phenyl-*n*-butyrohydroxamic acid in mineral acids. Thereafter, a paper appeared dealing with acidic and alkaline hydrolyses of *ortho*-substituted *N*-methylbenohydroxamic acids[78]. The reaction is clearly pseudo first order in the presence of excess hydrochloric acid (Eq 5).

$$Ar{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{CH_3}{|}}{N}{-}OH + H_3O^+ \rightarrow ArCOOH + H_2N^+(CH_3)OH \quad \ldots (5)$$

These results are consistent with the acid-catalysed bimolecular mechanism reported earlier for the unhindered RCONHOH compounds[65].

Berndt and Ward[77] studied rates of acidic

hydrolyses of a series of *ortho*-substituted *N*-methylbenohydroxamic acids at 90°C in 0.764 *M* hydrochloric acid. The data were correlated by Tafft's *ortho* polar and steric substituent constants. The results provide support for this method of correlation of quantitative data as well as support for the qualitative picture of *ortho*-substituent effects as described by McCoy and Riecke[93].

As a part of a broad programme on the synthesis and hydrolysis reaction of hydroxamic acids, Ghosh *et al.*[79-81,83,84] conducted hydrolysis of *N*-arylhydroxamic acids, *N*-benyl-substituted, *N*-methyl-substituted and several other derivatives of hydroxamic acids, in mineral acids over a wide range of acidity. The rate acidity profiles have been established. Three types of cases were observed:

(i) The rate of hydrolysis increases gradually with increasing concentration of catalysing acid. No rate maximum is observed.

(ii) The rate of hydrolysis increases steeply with increasing acid concentration, showing a rate maximum and then falls off gradually.

(iii) The rate of hydrolysis increases steeply with increasing concentration of catalysing acid, showing first a rate maximum and then a minimum and thereafter the rate increases steeply.

We first[79] observed that if an *N*-substituted hydroxamic acid, i.e. PBHA, which hydrolyses via A–AC^2 mechanism in dilute acid is studied using more concentrated acid solutions, a change in mechanism is ultimately observed.

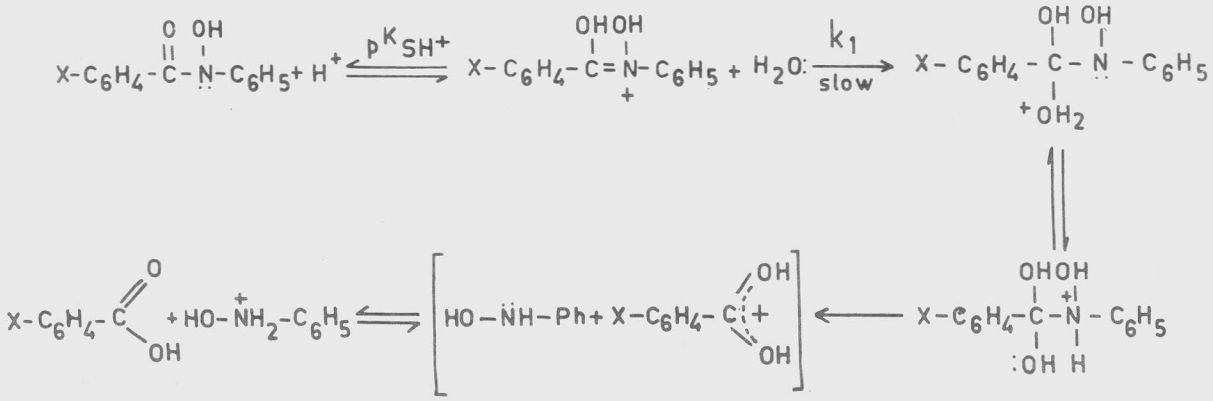
As the acid concentration is increased the concentration of free water falls (a_{H_2O}) but the protonating power of the medium greatly increases (h_0 rises faster than $C_{H_3O^+}$). These changes eventually disfavour the A-2 route, whose slow step involves H_2O (and whose rate may therefore pass through a maximum if most of the hydroxamic acid is protonated), but favour an A-1 path.

The kinetic data have been analysed by means of solvent isotope effect, salt effect, Bunnett-Olsen, Bunnett *w* and *w** parameters. It was suggested that hydrolysis of PBHA in H_2SO_4 and $HClO_4$ occurs by two distinct mechanisms.

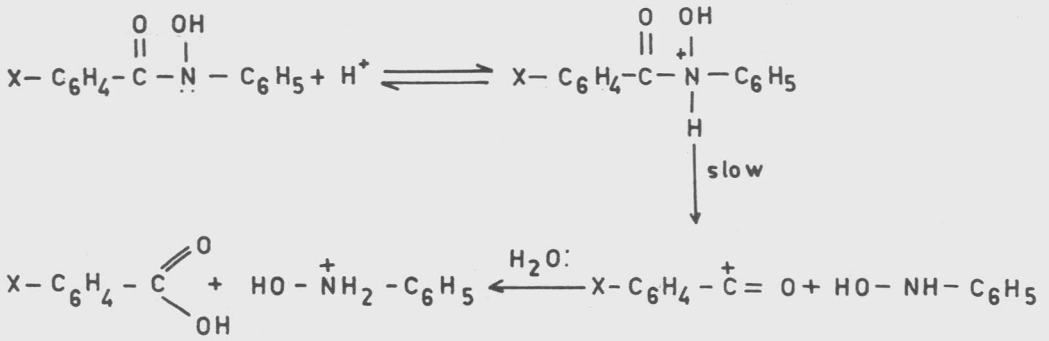
(i) In acid concentration upto 8.0 *M* H_2SO_4 and 7.5 *M* $HClO_4$ by an A-2 mechanism.

(ii) In acid concentration above 9.0 *M* H_2SO_4 and 7.0 *M* $HClO_4$ by an A-1 mechanism.

In addition of acidity function methods, other treatments involving Yates-McClelland[88] '*r*' parameter (which designates the number of water molecules on going from the protonated substrate to the transition state), excess acidity[90] and entropy of activation have been used to study the effect of changing acid concentration on the reaction rate, particularly with regard to mechanism. In the concentrated region where the mechanism is presumed to have changed from A-2 (Scheme IV) to A-1 (Scheme V) $\Delta H^{\ddagger}$ has increased significantly and $S^{\ddagger}$ has changed sign from the negative values typical of A-2 reactions to a small positive value more typical of an A-1 process (Table V). Another line of evidence indicating a change in mechanism comes from Yates-McClelland[88], *r* hydration parameter method. They argued that, for any given mechanism (A-2 or A-1), a plot of



Scheme IV



Scheme V

Table V—Activation parameters for the acidic hydrolysis of N-substituted hydroxamic acids, $R_1CO{\cdot}N(OH)R_2$

R_1	R_2	Temp. range °C	Acid	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ JK^{-1} mol^{-1}	$\Delta G^{\ddagger}$ kJ mol^{-1}	Ref.
$CH_3(CH_2)_2$	C_6H_5	30.2-60.2	HCl	66.7 (E_a)	−114.2	—	76
$2CH_3C_6H_4$	CH_3	70-90	HCl	87.0	−88.7	—	78
$4CH_3{\cdot}C_6H_4$	CH_3	61-84	HCl	81.1	−74.5	—	—
C_6H_5	C_6H_5	45-65	H_2SO_4 (2.9 *M*)	77.2	−79.5	102.5	79
			H_2SO_4 (11.0 *M*)	103.1	9.7	99.6	—
C_6H_5	$C_6H_5{\cdot}CH_2$	45-55	HCl (2.9 *M*)	74.6	−81.7	—	82
			H_2SO_4 (2.9 *M*)	71.6	91.3	101.5	—
			$HClO_4$ (2.9 *M*)	76.2	−78.9	—	—

$\log k_\psi - \log \frac{h_a}{h_a + K_{SH^+}}$ against $\log \alpha_{H_2O}$ (Eq. 6) will be rectilinear with slope r.

Thus,

$$\log k_\psi - \log \frac{h_a}{h_a + K_{SH^+}} = r \log a_{H_2O} + \text{constant} \quad \ldots (6)$$

Since the A-2 and A-1 mechanisms might sensibly be expected to involve different values of r for their slow steps, such plots should show discontinuities when changes in mechanism occur. The values of r obtained (Table IV) in different acid regions can be reasonably interpreted in terms of hydrolysis mechanism. Regions where $r \sim 2$ correspond to hydrolysis by an A-2 mechanism in which a protonated PBHA is attacked in the rate determining step by two water molecules, one acting as a nucleophile and the second assisting in dispersing the positive charge developing on oxygen in the transition state as progress is made towards the tetrahedral intermediate. Region where r becomes negative but is fairly close to zero (i.e. $r = -0.2$) correspond to A-1 mechanism. Further, the duality of mechanism was confirmed by the concept of the excess acidity (X) developed by Cox and Yates[90].

The excess acidity method is capable of revealing mechanistic features which other methods of analysing kinetic data in strong acids cannot. In this method it is argued that an A-2 mechanism should obey equation 7, and an A-1 mechanism an equation of the form (Eq. 8).

$$\log k_\psi - \log C_H^+ - 2 \log a_{H_2O} = (\log k_1/K_{SH^+} + m_2^{\ddagger} m^* X \quad \ldots (7)$$

$$\log k_\psi - \log C_{iH}^+ = (\log k_1/K_{SH^+}) + m_i^{\ddagger} m^* X \quad \ldots (8)$$

In these equations m^* is a parameter characteristic of the protonation of the substrate S, and $m^{\ddagger}$ a parameter characteristic of the transition state. For measurements of k over a significant range of acidity (X) a plot of left hand side of equation against X should be linear for an A-2

Table VI—Hammett reaction constants (ρ) for the hydrolysis off 4-substituted PBHA

[Acid]	H_2SO_4		HCl		Ref.
M	ρ	*r*	ρ	*r*	
0.87	—	—	0.288	0.998	
2.9	0.043	0.867	0.232	0.818	
					80
4.2	—	—	0.339	0.959	81
4.5	0.219	0.916	—	—	
5.8	—	—	0.394	0.984	
7.5	0.258	0.996	0.577	0.994	
8.5	—	—	0.653	0.998	
9.0	–0.906	0.984	—	—	
9.3	—	—	0.690	0.997	
12.0	–0.547	0.992			

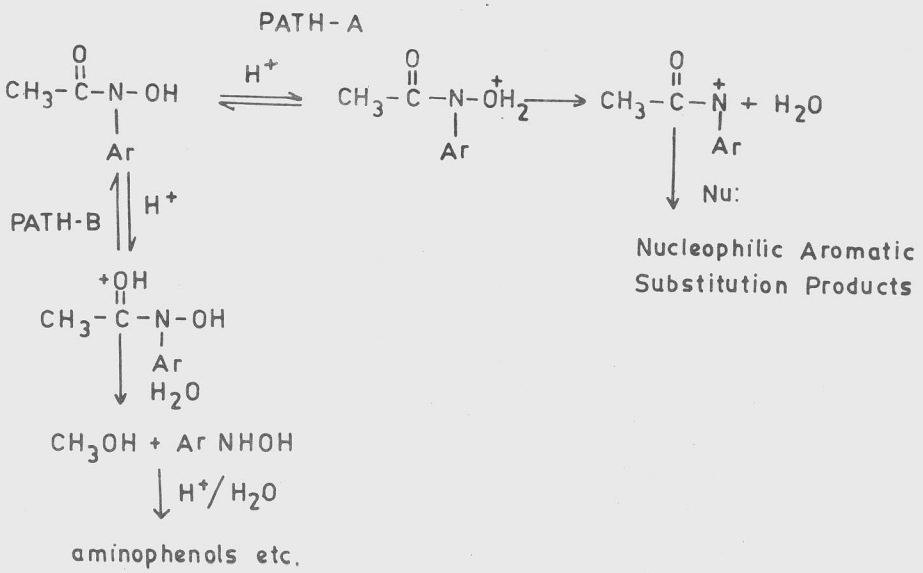
r=Correlation coefficient

mechanism. For the excess acidity method[94] it is normally found that for A-2 reactions $m_2^{\ddagger} \simeq 1$ and m^* for carbonyl oxygen protonation is 0.6 or less. Thus, a total slope against *X* of 0.6 or less should be expected for Eq. 8. For A-1 processes $m_1^{\ddagger} > 1$, probably above 2-3 and m^* for nitrogen protonation is 1, so an overall slope of 2-3 should be obtained. The slope values are given in Table IV. It was observed that the protonation behaviour of hydroxamic acids correlates better with H_A than H_0.

Hammett ρ values are valuable sources of mechanistic information. Surprisingly complete studies of Hammett equation for *N*-substituted hydroxamic acids are not available. It is an attempt to remedy this situation that the work described in this review was undertaken. A series of *para*-substituted PBHA have been studied[80,81] in H_2SO_4 and HCl. It can be seen from Table VI that the variation of ρ with acidity is quite large, with even a sign change for the A-2 reactions. The ρ values reflect the degree of interaction between the protonated transition state and water molecules. With increasing acidity, the water content decreases, and so solvation decreases, and the influence of sub-substituents (4-X=CH_3, OCH_3, F, NO_2) on the reaction centre should go up. 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.

Novak and coworkers[75] studied the acid-catalysed hydrolysis of *N*-hydroxyacetanilides in HCl solutions in the *p*H range of 0.3 to 3.0 at 50°C and found that these compounds undergo reaction (Scheme VI) primarily via path-B to yield the corresponding hydroxylamines, which also decompose and can be detected by HPLC or UV spectroscopy. Path-A is a minor contributor (<10%) to the hydrolysis.

They also examined the hydrolysis behaviour of the parent compound, *N*-hydroxyacetanilide in H_2SO_4 from 0.1 to 9.0 *M* to determine if a change in a_{H_2O} might lead to a change in mechanism and



Scheme VI

to compare the hydrolysis of *N*-hydroxyacetanilide with that of acetanilide in H_2SO_4. The pK_a of protonated substrate was also determined spectrophotometrically at 25°C. It has been suggested that protonation of carbonyl oxygen is favoured over the hydroxyl oxygen by a magnitude[75] of the order of *ca* 7.

Protonation Behaviour

The question concerning the actual site of protonation has been long debated. In principle protonation can take place at the carbonyl oxygen, at the nitrogen atom, or at the hydroxylamino oxygen. Because of the similarity of activity coefficient behaviour of hydroxamic acids and other carbonyl bases[95] (amides, anilides, etc.), it is generally accepted that the site of protonation is the carbonyl oxygen. On the other hand, it was claimed that a shift of the protonation site from N to CO takes place with increasing acidity[96] as now postulated for amides[97]. Some recent IR studies[98] are in favour of *N*-protonation. Gal *et al.*[99] studied gas phase basicities of acetohydroxamic acid and of its *N*-methyl and *O*-methyl derivatives. This gas phase basicity studies did not yield conclusive information. Hydroxamic acids and their ions have also been investigated theoretically; however high level quantum mechanical calculations have appeared only very recently in the literature[28,29]. Exner *et al.*[27] reported the results of systematic theoretical examination of formohydroxamic acid, its anion and protonated forms. The data clearly show that protonation proceeds on the carbonyl oxygen atom, in agreement with a parallel experimental study of acetohydroxamic acid in the gas phase. The protonation behaviour of some *N*-substituted and unsubstituted hydroxamic acids was studied in dioxane medium in sulfuric acid by UV method[99,100]. The experimental pK_{BH^+}values (–2 to –3) were obtained according to Hammett method. Recently, the site of protonation and deprotonation of hydroxamic acids (RCONHOH) has been investigated by heteronuclear (^{14}N, ^{15}N, ^{17}O) NMR relaxation and NOE experiments and *ab initio* theoretical methods by Bagno *et al.*[29] Theoretical calculations indicate that nitrogen deprotonation is favoured in all cases.

Electric field gradient calculations have been used to estimate the change in nuclear quadrupolar coupling constants at O and N atoms upon ionisation and compared to experimental line width changes. NMR relaxation rate and NOE measurements in aqueous solution indicate that acetohydroxamic acid in water is predominantly an oxygen acid, whereas benzohydroxamic acid is predominantly a nitrogen acid in methanol. Acetohydroxamic acid is protonated at the carbonyl oxygen[29]. More kinetic and thermodynamic studies are necessary to establish the protonation behaviour of hydroxamic acids. An effort to do this is in progress.

Conclusions

For acid catalyzed hydrolysis of hydroxamic acids investigated, I have presented the available experimental observations. For *N*-substituted hydroxamic acids both A-2 and A-1 paths were recognised. For primary hydroxamic acid no evidence for an A-1 pathway, such as changes in activation parameters, substituent constants or solvent isotope effects, was seen for the hydrolysis in the acidity range studied. If we ignore the worrying features regarding the *N*-versus *O*-protonation controversy, it is found that protonation involves specific acid protonation of the hydroxamic acid to activate it toward the attack by water. That attack is assisted by a second water molecule to directly yield the neutral tetrahedral intermediate T_0 and H_3O^+, which avoids the formation of a highly unstable *O*-protonated tetrahedral intermediate. The breakdown of T_0, in all cases we have investigated, involves protonation by H_3O^+ to yield T_{N^+} which then undergoes C-N cleavage. That process is assisted of simultaneous proton removal from OH in T_{N^+} by solvent water, so that the immediately formed products are hydroxylamine, carboxylic acid, and H_3O^+. The results of the hydrolysis could be useful for analytical reactions. A knowledge of mechanism of the reactions of this group of compounds can be of great assistance in planning their use as analytical reagents and also in explaining their role in biological reactions.

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