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Protonation Equilibrium of 4-Substituted Benzohydroxamic Acids in Mineral Acids

Kallol K. Ghosh,* Pankaj Tamrakar, and Surendra K. Rajput

School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur 492 010, India

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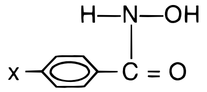
The protonation equilibria of some 4-substituted benzohydroxamic acids 4-X(C_6H_4CONHOH) (X = H, OMe, Cl) have been investigated in aqueous sulfuric, perchloric, and hydrochloric acids at 25 °C UV spectrophotometrically. The Hammett acidity function method, the Bunnett−Olsen method, Cox−Yates excess acidity function method, and Marziano−Cimino−Passerini method have been compared in order to rationalize the differences observed between pK_{BH^+} values determined by each method. An attempt has been made to apply multivariate analysis to separate the effect of protonation from the medium effect for benzohydroxamic acid.

Introduction

Hydroxamic acids possess a great variety of biological and pharmaceutical activities.[1−5] Recently, much attention has been directed toward their applications to DNA cleavage[6−8] and iron-chelators[9,10] as therapeutic agents. In spite of these important applications, hydroxamic acids remain one of the less well-characterized classes of organic compounds. Acid−base equilibria and overall stability of these compounds are known to have an important bearing on their general usefulness in many of these applications. An accurate knowledge of the ionization (protonation and deprotonation) behavior of hydroxamic acid is required both for structure−reactivity correlations and for the detailed kinetic analysis of acid-catalyzed reactions. A considerable amount of theoretical work[11−16] on the acidity and structure of hydroxamic acids has been conducted recently. Most of these have focused on their acid−base properties; thus, many of these studies also presented computations on hydroxamic acid anions.[13−16] Some also included the protonated species.[12−14] On the contrary, only scanty data are available[17−19] for the experimental determination of the protonation constant.

We aim, in this paper, to investigate a detailed study of the protonation behavior of a simple hydroxamic acid, i.e., benzohydroxamic acid (BHA) (**I**) and two of its 4-substituted derivatives in aqueous mineral acids.



(I)

(X=H, OMe, Cl)

Experimental studies usually rely on indirect methods like changes in NMR chemical shifts, UV or IR spectral changes,[20] etc. However, difficulties derived from the failure of the analytical technique or of data treatment procedures have led in the past to a good deal of confusion and a spread of values for the protonation parameters of typical carbonyl compounds such as aromatic ketones,[21] amides,[22,23] esters,[21] and anilides,[24] etc.

General formulation and treatment of protonation equilibria in nonideal acidic solutions are now available as the Bunnett−Olsen,[25] Cox−Yates excess acidity,[26] and Marziano−Cimino−Passerini[27] procedures. The pK_{BH^+}

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Table 1. **pK_{BH^+} Values for Benzohydroxamic Acid Calulated by Different Methods**

		λ_B : 228 nm		λ_{BH^+} : 252 nm	λ_B : 228 nm		λ_{BH^+} : 240 nm	λ_B : 228 nm		λ_{BH^+} : 240 nm
		A_B : 0.148		A_{BH^+} : 0.839	A_B : 0.460		A_{BH^+} : 0.723	A_B : 0.578		A_{BH^+} : 0.293
		H_2SO_4			HCl			$HClO_4$		
methods	slope parameters	pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a
HAFM	m	−2.06	0.82	0.998	−2.04	1.16	0.997	−2.03	0.97	0.999
BOM	ϕ	−1.86	0.38	0.987	−1.60	0.84	0.989	−1.74	0.62	0.990
EAM	m^*	−2.01	0.76	0.996	−1.99	1.25	0.982	−2.00	0.91	0.996
MCP	n_B	−1.79	0.26	0.984				−1.82	0.62	0.997

[a] r = correlation coefficient.

values obtained by the methods can be regarded as thermodynamically defined ones. The protonation of weak bases in strong acids gives rise to problems that have yet to be satisfactorily resolved. The chief problems are as follows:

(i) Estimation of the position of half protonation (pK_{BH^+}) in terms of acid concentration is unequivocal only if a tight isobestic is observed between two species. What does it mean if this isobestic appears to drift? Are there (a) alternative cations, or (b) is one observing a medium effect?

(ii) Translation of acid concentration into an acidity scale is required to arrive at pK_{BH^+}. Ideally, the slope with respect to degree of protonation should be unity, as it is protonation equilibria at infinite dilution in water. What is the significance of the nonunit slopes almost invariably found?

(iii) Again, ideally, any derived pK_{BH^+} should be independent of the strong acid used; just as in dilute aqueous solution, it is independent of the buffer. If not, why not?

(iv) Which approach is more profitable and suitable? We therefore thought it of interest to investigate protonation behavior of benzohydroxamic acids in mineral acids (HCl, H_2SO_4, $HClO_4$) in the hope to seriously address these questions. As protonation equilibrium do reflect the electronic environment of the protonation site, two 4-substituents have also been taken in order to separate protonation from the medium effect the characteristic vector analysis on the protonation data of benzohydroxamic acid have been applied.[28]

Results and Discussion

The protonation equilibrium of a weak base, B, may be written as

$$B + H^+ \xrightleftharpoons{K_{BH^+}} BH^+ \tag{1}$$

Calculation of K_{BH^+} ($pK_{BH^+} = -\log K_{BH^+}$) requires the measurement of the ionization ratios, $I = C_{BH^+}/C_B$. The most widely applied method is UV spectrophotometry using the relationship

$$I = (A - A_B)/(A_{BH^+} - A) \tag{2}$$

where A, A_B, and A_{BH^+} are the absorbances of the solution, the free base, and its conjugate acid, respectively. The UV spectra of benzohydroxamic acid and its derivatives at different acidities (H_2SO_4 0−14.4 M, $HClO_4$ 0−8.0 M, and HCl 0−9.3 M) are illustrated in Figures 1−5. As the substrates became protonated there was a definite shift in spectrum.

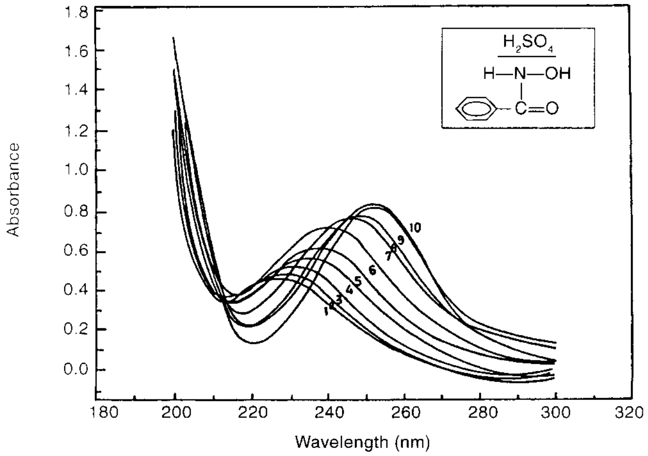

Figure 1. Absorption curves of BHA in aqueous sulfuric acid: (1) 0.0 M, (2) 1.80 M, (3) 3.60 M, (4) 5.40 M, (5) 6.30 M, (6) 7.20 M, (7) 9.00 M, (8) 10.8 M, (9) 12.6 M, (10) 14.4 M.

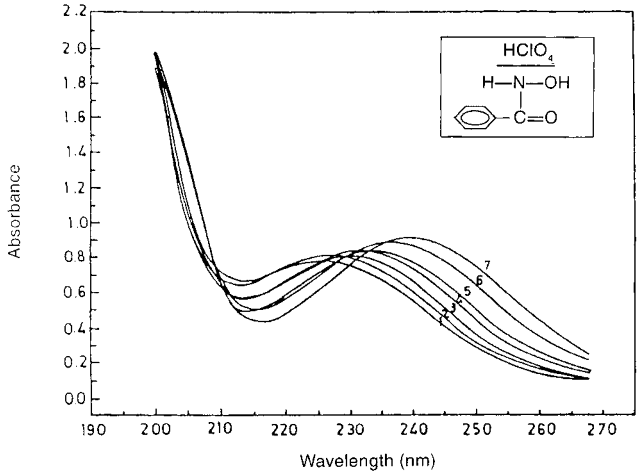

Figure 2. Absorption curves of BHA in aqueous perchloric acid: (1) 0.0 M, (2) 2.00 M, (3) 4.0 M, (4) 5.0 M, (5) 6.0 M, (6) 7.0 M, (7) 8.0 M.

In the case of BHA in sulfuric acid at low acidities a peak is present at 228 nm, which shifts to some 236 nm at intermediate acidities and continues shifting to the 240−250 nm region in strongly acidic solutions. Similar shifting and medium effects have also been observed in hydrochloric and perchloric acids. The position of λ_{max} of 4-MeO and 4-Cl remained constant in dilute solutions of mineral acids, but in more concentrated acid there was a steady bathochromic shift in λ_{max}. The wavelength of light absorption corresponds to the energy differences between the normal ground state and excited state.

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[28] The characteristic vector analysis method (CVA program and UV spectral studies) applied by Professor Jose M. Leal, University of Burgos, Spain.

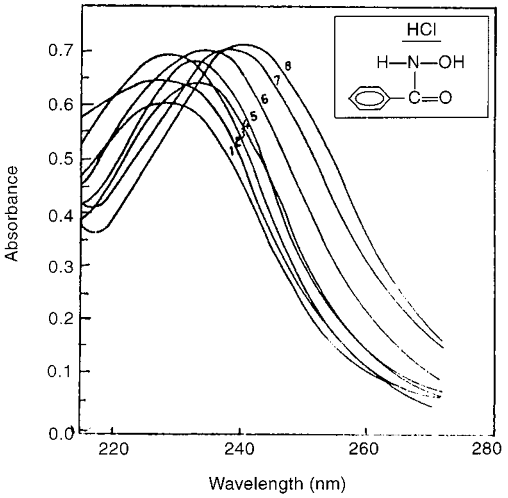

Figure 3. Absorption curves of BHA in aqueous hydrochloric acid: (1) 0.0 M, (2) 2.32 M, (3) 3.48 M, (4) 4.64 M, (5) 5.80 M, (6) 6.96 M, (7) 8.12 M, (8) 9.28 M.

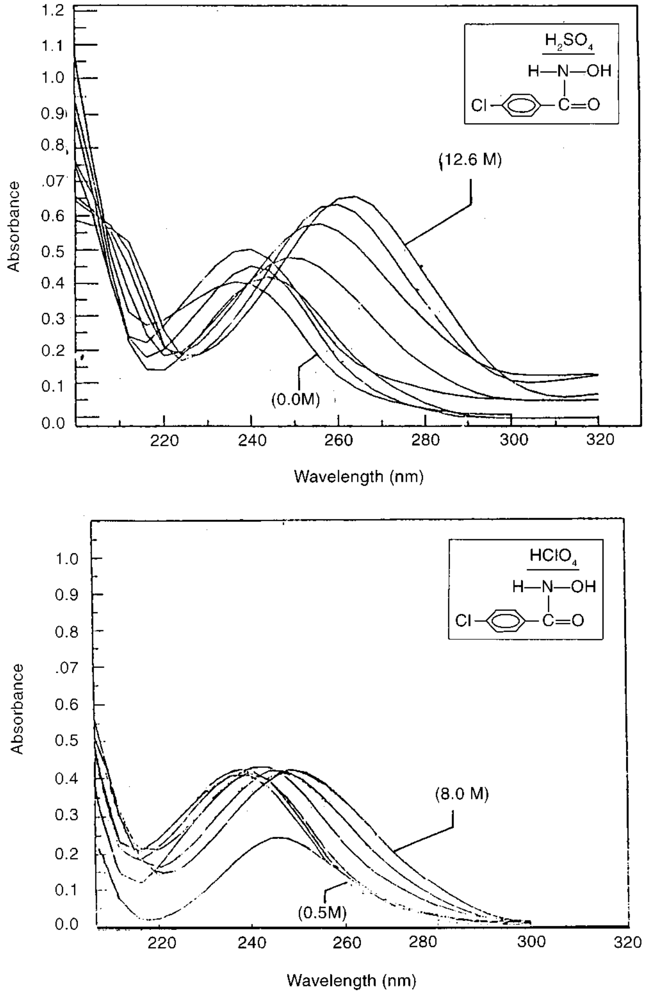

Figure 4. Experimental absorbances of 4-Cl BHA as a function of mineral acids.

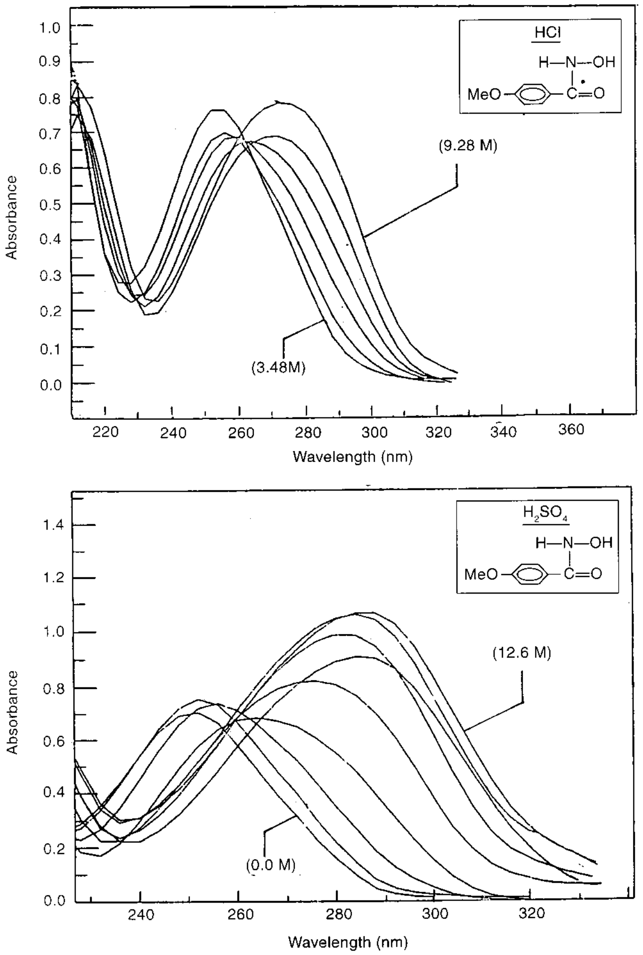

Figure 5. Experimental absorbances of 4-OMe BHA as a function of mineral acids.

Incorporation with different substituents results in a change in ground-state and excited-state energies, which is reflected as shift in ultraviolet spectra (in aqueous solution λ_{max} of BHA = 228 nm, 4-Cl-BHA, λ_{max} = 236 nm, and 4-MeO BHA λ_{max} = 252 nm). The shifts are generally in order of mesomeric effects of substituents. A chloro substituent has a relatively small effect on the benzenoid B band, but polar substituents such as the OMe group alter the benzene spectrum considerably.

The UV absorption spectra of all the hydroxamic acids at different acid concentrations undergo changes not only because of the protonation process but also as a consequence of the medium effect. Therefore, no good isobestic points have been seen (Figures 1−5). At lower acid concentration, the concentration of conjugate acid is small. The small bathchromic shift in this region can be explained by increasing interaction between the carbonyl group and the solvent. In intermediate acidities, the concentration of unprotonated species is small. Again there is small bathochromic shift with increasing acid concentration as a result of the changing interaction between cation and solvent. The gradual shift in λ_{max} results in the convergence of the absorbance curves into an apparent isobestic point. In spite of these problems, all the methods give rather similar results. By analogy with the larger spectral changes found for benzamide,[29] we ascribe this spectral change to the tautomeric change of the cation from N-protonated to O-protonated. At higher acid concentrations the activity of water falls, which is essential for the stabilization of N-protonated cations. Similar changes have been reported in the UV spectra of *N*-methyl-*p*-tolyhydroxamic acid[30] between 60 and 96% sulfuric acid and have also been ascribed to the

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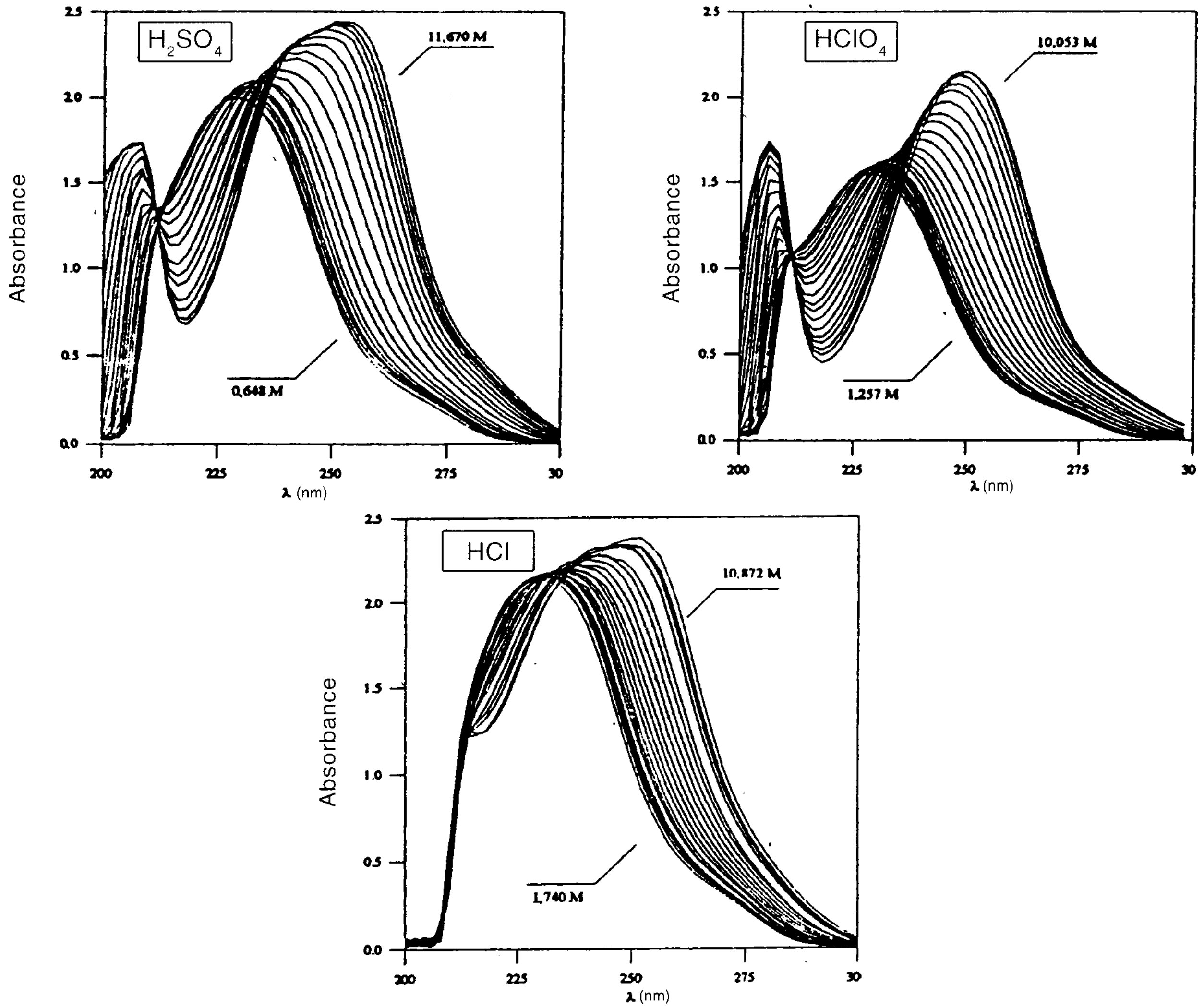

Figure 6. Experimental absorbances of BHA as a function of mineral acids.

Table 2. pK_{BH^+} Values for 4-OMe-BHA Calculated by Different Methods

		λ_B : 252 nm A_B : 0.080	λ_{BH^+} : 284 nm A_{BH^+} : 1.065		λ_B : 252 nm A_B : 0.201	λ_{BH^+} : 272 nm A_{BH^+} : 0.778		λ_B : 252 nm A_B : 0.075	λ_{BH^+} : 280 nm A_{BH^+} : 0.365	
		H_2SO_4			HCl			$HClO_4$		
methods	slope parameters	pK_{BH^+}	*s*	r^a	pK_{BH^+}	*s*	r^a	pK_{BH^+}	*s*	r^a
HAFM	*m*	−1.88	0.84	0.971	−1.81	1.08	0.980	−1.86	0.86	0.999
BOM	ϕ	−1.62	0.36	0.993	−1.61	0.77	0.978	−1.62	0.49	0.998
EAM	*m**	−1.91	0.75	0.997	−1.87	1.07	0.996	−1.85	0.79	0.995
MCP	n_B	−1.72	0.31	0.980				−1.70	0.50	0.999

[a] *r* = correlation coefficient.

tautomeric change in the structure of the cation from N-protonated in aqueous acid to O-protonated in concentrated acid. However, this controversial question of site of protonation and medium effect for hydroxamic acid have not been answered so far.

The question of the site of protonation cannot be answered in a straightforward way from our results. Recently, the acid−base equilibria of a series of monofunctional and polyfunctional bases and acids have been investigated with theoretical and heteronuclear NMR relaxation rate methods by Bagno et al.[31,32] NMR relaxation rate and NOE experiments indicate that acetohydroxamic acid ($CH_3CONHOH$) protonates at the carbonyl oxygen.[14] The basicity of the hydroxylamino oxygen has been estimated[33] to be lower than that of the carbonyl oxygen by some 7 p*K* Units, which is confirmed by theoretical calculations of Bagno et al.[14] The site of protonation of formohydroxamic acid (HCONHOH) is also clearly borne out by theoretical results, which favor the carbonyl-protonated form.[11] Estrada et al.[12] also studied protonation and deprotonation of a series of seven hydroxamic acids by ab initio molecular orbital calculations.

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Table 3. pK_{BH^+} Values for 4-Cl-BHA Calculated by Different Methods

		λ_B : 236 nm A_B : 0.083		λ_{BH^+} : 264 nm A_{BH^+} : 0.657	λ_B : 236 nm A_B : 0.109		λ_{BH^+} : 260 nm A_{BH^+} : 0.350	λ_B : 236 nm A_B : 0.148		λ_{BH^+} : 248 nm A_{BH^+} : 0.750
		H_2SO_4			HCl			$HClO_4$		
methods	slope parameters	pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a
HAFM	m	−2.17	0.90	0.998	−2.16	0.97	0.999	−2.19	0.98	0.991
BOM	ϕ	−1.92	0.41	0.974	−1.90	0.67	0.988	−1.95	0.69	0.989
EAM	m^*	−2.16	0.86	0.999	−2.17	0.96	0.998	−2.17	0.91	0.997
MCP	n_B	−1.91	0.28	0.978				−1.92	0.56	0.981

[a] r = correlation coefficient.

Their results show that hydroxamic acids are predominantly in the E-TS form and that the most probable protonation site is the carbonyl oxygen atom, while deprotonation proceeds by loss of NH hydrogen. The relative energies indicate that the most favorable protonation site is the O atom.

As solutions of hydroxamic acid cation are made still more acidic, the UV spectra continue to undergo changes. Liler[29] interpreted these types of changes as a medium effect on the equilibrium with the N-protonated forms, which will be strongly hydrogen-bonded to water, being displaced by the O-protonated forms in the concentrated acid. The O-protonated ions possess considerable charge delocalization, and it is argued that they will be less affected by the removal of water from the medium than will be the N-protonated form. Accordingly, the equilibrium will be tipped from the N- to the O-protonated form as the concentration of acid becomes high. This will not constitute the subject of the present paper, the aim of which is to compare the pK_{BH^+} values obtained by different classical methods.

Three strongly acidic systems were used in order to check whether the pK_{BH^+} values obtained would really be independent of the nature of the strong acid. Protonation constants (pK_{BH^+}) were calculated from the following equations:

Hammett acidity function method (HAFM)[23]

$$\log I = -mH_A + pK_{BH^+} \tag{3}$$

Bunnett−Olsen method (BOM)[25]

$$\log I - \log C_{H^+} = (1-\phi)(H_0 + \log C_{H^+}) + pK_{BH^+} \tag{4}$$

Cox−Yates excess acidity method (EAM)[26]

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \tag{5}$$

Marziano−Cimino−Passerini (MCP) method[27]

$$\log I - \log C_{H^+} = -n_B M_c + pK_{BH^+} \tag{6}$$

Here C_{H^+} is the molar concentration of solvated protons, H_0 and H_A are acidity functions, M_c is the activity coefficient function, X is the excess acidity function, and m, m^*, n_B, and ϕ are the slope parameters.

The influence of solvation may be assessed on a semiquantitative basis from the m^* values. To a reasonable approximation $m^* \approx (1-\phi)$ and the two are inconvertible, $H_0 + \log C_{H^+} \approx -X$. These slope parameters are of paramount importance in defining the protonation behavior of weak bases. The need for two parameters to describe protonation equilibria may be considered as reflecting stabilization of the protonated base both by internal delocalization of its cationic charge and by solvation through hydrogen bonding. The m^* values of amides[35] are in the range 0.5−0.6. These values, which are low if compared to those of nitrogen bases such as primary anilines (m^* values of 1.00), are believed to be primarily evidence of strong hydrogen-bonding of the O-protonated BH^+ with water.

Table 4. Comparison of pK_{BH^+} Values of BHA and Its 4-Substituted Derivatives

hydroxamic acid	mineral acids	HAFM	BOM	EAM	MCP
BHA	H_2SO_4	−2.06	−1.86	−2.01	−1.79
	HCl	−2.06	−1.60	−1.99	
	$HClO_4$	−2.03	−1.74	−2.00	−1.82
4-OMe-BHA	H_2SO_4	−1.88	−1.62	−1.91	−1.72
	HCl	−1.83	−1.61	−1.87	
	$HClO_4$	−1.86	−1.62	−1.85	−1.69
4-Cl-BHA	H_2SO_4	−2.17	−1.92	−2.16	−1.91
	HCl	−2.16	−1.90	−2.17	
	$HClO_4$	−2.19	−1.95	−2.17	−1.92

The obtained values of pK_{BH^+} and slopes are given in Tables 1−3. All the linear regression plots are good but showed a scattering of points, which could only be resolved into straight lines by omitting certain points. The condition of the HAFM method is that the slope of $\log C_{BH^+}/C_B$ against H_X must be unity. All three compounds investigated closely follow the H_A function. The slopes (m) of $\log I$ vs H_A plots are 0.91 ± 1. Only an appropriate acidity function will give a slope of unity. Unfortunately, no acidity function has been developed for hydroxamic acid. While the need for individual acidity functions can be overcome by the Bunnett−Olsen,[25] Marziano−Cimino−Passerini,[27] or Cox−Yates[26] excess acidity methods.

The pK_{BH^+} values show a regular variation (Table 4) with substituents: an electron-withdrawing group (Cl) decreases and an electron-donating group (OMe) increases the pK_{BH^+}. This means that the OMe group is capable of increasing the electron density at the carbonyl oxygen.

It was observed that the pK_{BH^+} values are not influenced by the different mineral acids. In aqueous hydrochloric and perchloric acids, the BHA studied seems to be stronger base than in aqueous sulfuric acid solutions. It should also be noted that the ion pair formation ($BH^+ + A^- \rightleftharpoons BH^+{\cdot}A^-$, $A^- = SO_4^{2-}, ClO_4^-, Cl^-$) is less favored in perchloric and hydrochloric acid solutions because of

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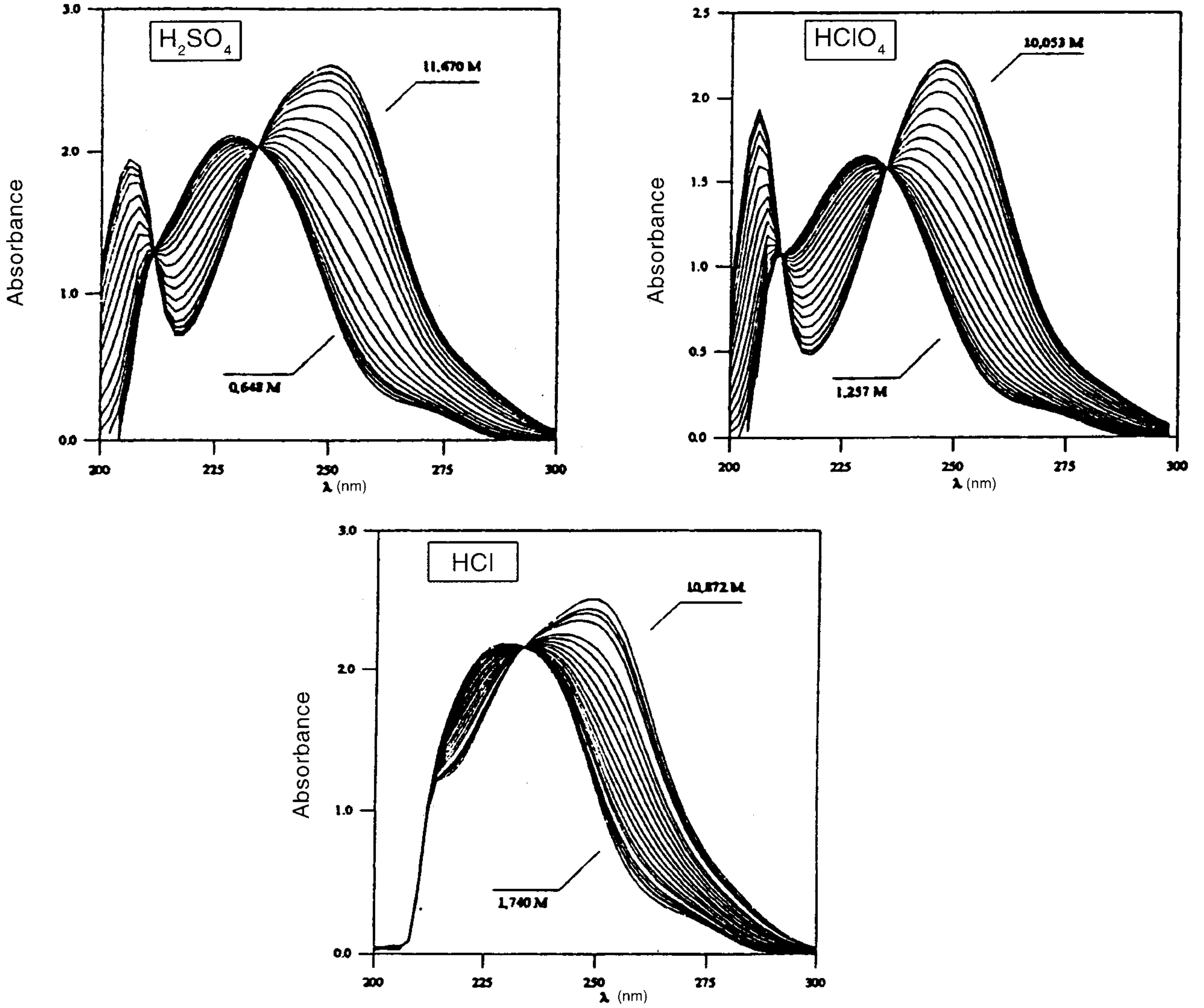

Figure 7. Reconstituted UV spectra of BHA in different acidities of mineral acids resulting from CVA.

Table 5. pK_{BH^+} Values of Benzohydroxamic Acids in Mineral Acids by Different Methods Using Characteristic Vector Analysis

methods	slope parameter s	H_2SO_4			$HClO_4$			HCl		
		pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a	pK_{BH^+}	s	r^a
HAFM	m	−2.05	0.99	0.997	−2.31	0.92	0.999	−1.82	0.90	0.996
BOM	ϕ	−2.02	0.52	0.999	−2.20	0.63	0.999	−1.94	0.33	0.999
EAM	m^*	−2.08	0.52	0.979	−2.07	0.48	0.999	−2.04	0.59	0.991

[a] r = correlation coefficient.

lower charge density on ClO_4^- and Cl^-. Thus, if the ion pairs BH^+ and SO_4^{2-} are being formed, there should be some differences in the protonation of hydroxamic acids in different mineral acids. The good agreement of pK_{BH^+} and m^* values in different mineral acids (HCl, $HClO_4$, H_2SO_4) for all the compounds studied indicates that the ion pairs BH^+ and A^- are not formed in any detectable quantities. In the case of sulfuric acid, the four different methods give pK_{BH^+} values that agree closely with each other. The slope values depend on the degree of solvation[35] of the conjugate acid−base pair. It must be noted that our data analyzed by the four classical methods generally gave almost nearly coincident results. However, the excess acidity[26] method has been suggested for treating spectra that reflect protonation and medium shift simultaneously. An analysis of medium effects in the protonation reaction of amides has been reported in terms of the excess acidity method, claiming to permit accurate calculations of pK_{BH^+} and m^* values in the presence of these methods. The pK_{BH^+} values obtained by BOM and MCP are slightly lower than those obtained by the EAM and HAFM methods. The agreement among pK_{BH^+} values obtained by HAFM and EAM is very good. It is very difficult to say which method gives the more accurate estimate of the real thermodynamic quantity.[36]

The m^* values reported in this work are >0.5. This indicates low solvation requirements for the conjugate acids, BH^+ of BHA. Various factors[35] influence the qualitative magnitude of m^*. The degree of charge localization on an electronegative atom forming a site of solvation, the nature of atom (N or O), and the number

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[36] (a) Johnson, C. D.; Stratton, B. *J. Org. Chem.* **1986**, *51*, 4100. (b) Johnson, C. D.; Stratton, B. *J. Org. Chem.* **1987**, *52*, 4798.

of hydrogens bound at the site participating in hydrogen bonding and steric hindrance of solvation are the major factors. A large m^* value denotes a larger difference from H_3O^+ (for which $m^* = 0$) and hence weaker solvation. According to Scorrano et al.,[35a] when BH^+ has the positive charge buried in a large and polarizable molecule, its solvation is less than that of BH^+ $m > 1$, and when BH^+ has the positive charge buried in a small and not very polarizable molecule and solvation is greater than BH^+ $m < 1$ and ϕ is positive. The present results also indicate that the protonation of hydroxamic acids follows the H_A scale.

Characteristic Vector Analysis. The problem of medium effects and isobestic points has remained a vexation in studies of protonation behavior of carbonyl compounds. For compensating the medium effect, Reeves[37] applied characteristic vector analysis. This is the method of analyzing multivariate response data by characteristic vector analysis.[38] The absorbance A at r wavelengths is obtained in n different concentrations of acid, and the data are arrayed to form an n-row, r-column data matrix. The description of multivariate response data in terms of characteristic vectors involves the determination of linear transformations of the data to an intrinsic minimum number of parameters containing all the information in the original data. According to this analysis, the absorbance is expressed as an average absorbance, $\bar{A}$, corrected by two characteristic vectors, v_1 and v_2:

$$A = \bar{A} + c_1 v_1 + c_2 v_2 + ... \qquad (7)$$

In the present investigation, the weighing factors c_1 and c_2 were determined for the absorbances of benzohydroxamic acid.[28] The sets of spectral curves for benzohydroxamic acids, averaged curves, and first characteristic vectors were obtained. Using the resulting sets of c_1 values, ionization ratios were measured for each acid concentration and applied to the calculation of pK_{BH^+} values. It is reasonable on chemical grounds to associate the first vector with the effect of protonation and the second vector with the medium effect, although this is not required by the mathematical analysis. The experimental absorbance curves of benzohydroxamic acid in mineral acids are shown in Figure 6. The reconstituted curves are shown in Figure 7. The pK_{BH^+} values obtained by the characteristic vector analysis are very similar to those obtained by simple methods (Table 5). This indicates that without applying characteristic vector analysis it is also possible to determine pK_{BH^+} accurately.

Experimental Section

Benzohydroxamic acid and its derivatives were prepared as per literature procedure.[39]

All the acids were analytical reagent grade (AnalaR grade). The acid solutions used were made up by dilution of the concentrated acid with double-distilled water, and their concentrations were determined by titration with standard alkali.

A Unicam UV2 300 spectrometer and matched 10 mm cuvettes were used for UV measurements with the cell holders thermostated at 25 °C. Ultraviolet spectra in the 190−300 nm range were measured in at least 10 acids covering water to the 10 M acid region. The sample was prepared by dilution of 2 mL of an aqueous solution of BHA with the appropriate acid solution. Solutions were cooled in an ice bath before and during the addition. The resulting cold solution was then thermostated at 25 °C, and the volumetric flask (10 mL) was eventually filled to the mark with water. The reference cell contained the same solvent (acid solutions) as the sample under measurement. Hydrolysis of the hydroxamic acid is negligible during the time required to measure the spectra.

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