Hydroxamic Acids as Weak Base Indicators: Protonation in Strong Acid Media

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The protonation equilibria of *N*-phenylbenzohydroxamic, benzohydroxamic, salicylhydroxamic, and *N*-*p*-tolylcinnamohydroxamic acids have been studied at 25 °C in concentrated sulfuric, hydrochloric, and perchloric acid media; the UV−vis spectral measurements were analyzed using the Hammett equation and the Bunnett−Olsen and excess acidity methods. The medium effects observed in the UV spectral curves were corrected with the Cox−Yates and vector analysis methods. The H_A acidity function based on benzamides provided the best results. The range of variation of the solvation coefficient *m** is similar to that of amides, this indicating similar solvation requirements for amides and hydroxamic acids. For the same substrate, the observed variations of pK_{BH^+} with the mineral acid used was justified by formation of solvent-separated ion pairs; for the same mineral acid, the observed changes in pK_{BH^+} can be explained by the solvation of BH^+. The change of the pK_{BH^+} values was in reasonably good agreement with the sequence of the catalytic efficiency of the mineral acids used, $HCl > H_2SO_4 > HClO_4$.

Introduction

The RCONHOH derivatives of hydroxylamine are generally called hydroxamic acids. These species are very interesting reagents due to their useful properties and important medical and biological applications; much of their biological activity is related to their ability to form very stable chelates with a wide variety of metal ions, especially with iron.[1] The ease in forming metal complexes and functioning as bioligands converts hydroxamic acids into potentially useful chelating agents in applications such as wastewater treatment.[2] Naturally occurring hydroxamic acids are involved as low-molecular weight iron chelators in the microbial transport of iron (siderophores) and play a key role in facilitating the proper function of enzymes in electron and oxygen transport and other life-sustaining processes.[3,4] They are also inhibitors of the urease activity and have been used therapeutically in the treatment of hepatic coma.[5] The observation that many oxidizing species can convert hydroxamic acids into reactive acylating agents confers a great deal of interest to this important acylation reaction in connection with the carcinogenicity of urethane and many aromatic amines biologically oxidizable to hydroxylamines.

Hydroxamic acids are acid species but also behave as weak bases due to the NC=O moiety;[6] despite their recognized importance, there are only a few experimental contributions on their acid−base behavior. The actual ionization sites have been long debated, but a strong controversy still remains; both OH-deprotonation and N-ionization have been proposed for unsubstituted hydroxamic acids, depending upon the solvent medium.[7] Hydroxamic acids are N-acids in DMSO and in the gas phase, but possibly OH-acids in water and alcohols;[8,9] although these equilibria have been investigated in different solvents and using a variety of experimental and theoretical tools, so far the structure of the anionic species has not unambiguously been determined.[10,11] In most metal chelates of hydroxamic acids the coordination involves deprotonation of the OH group, followed by metal (O,O) coordination to the carbonyl oxygen and the deprotonated OH group;[12] (N,O) coordination by normal hydroxamic acids should involve deprotonation of the NH group and formation of an unfavorable four-membered ring.

The anions of the hydroxamic acids and their N-substituted derivatives may serve as bidentate ligands toward metal ions such as Fe(III), Ni(II), and Cu(II); the resultant complexes are highly colored and, therefore, are

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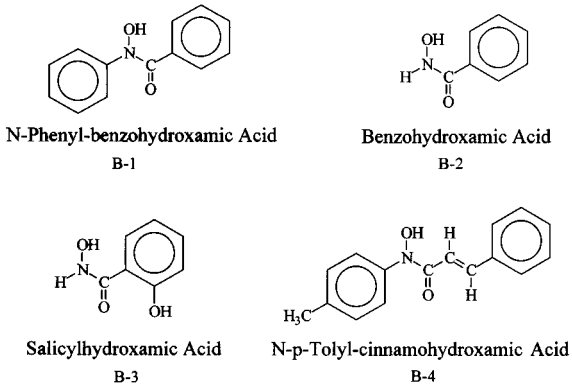
useful in colorimetric analyses of metal ions. With the aim of extending the study of the formation of metal chelates, *N*-phenylbenzohydroxamic acid (B-1, with only one acidic proton), benzohydroxamic acid (B-2, two acidic protons), and salicylhydroxamic acid (B-3, three acidic protons) were selected as model compounds. Except B-1, which serves as the reference compound, the other two acids are prone to multiple deprotonation reactions; this effect, together with the tautomeric forms that may arise from the anions, manifest a noticeable influence on the thermodynamics and kinetics of complex formation.[13,14] Tolylcinnamohydroxamic acid (B-4) possesses two aromatic rings and was synthesized in order to learn the differences in behavior with the other three, in particular with B-1. Likewise, contributions on the acidic behavior in different solvents were found only for B-1;[10] studies for the other three substrates either on their acid−base behavior or as complexing agents have not been reported.[15]

Recently, Ghosh et al.[16] reported on the protonation of some benzohydroxamic acid derivatives in acidic medium, but the UV spectral curves provided appeared distorted not only by the medium effects caused by protonation, but also by hydrolysis of the organic substrates;[17] in H_2SO_4 medium, this latter effect has been shown to become faster the higher the acidity used,[4] and often is the reason for erroneous and irreproducible pK_{BH^+} results. The hydrolysis of some hydroxamic acids in concentrated $HClO_4$ and HCl media has only very recently been investigated, and the results have been analyzed using the excess acidity method;[18,19] in aqueous $HClO_4$, the reaction rate increased initially with the acid concentration, reached a maximum, and then dropped with further increase in medium acidity. In HCl medium, however, no maximum in rate appeared, revealing a kinetic dependence on the nature of the mineral acid used;[20,21] this observation is of central importance to the study of the protonation equilibria and hydrolysis mechanisms.

The difference in the solvation states of reactants and products constitutes the major difference between the driving force of the protonation reaction in solution compared to the gas phase. Previously, we reported on the protonation of acetohydroxamic acid, either in the gas phase[22] or in solution;[23] the conclusions drawn point to a lower difference in stability between the N-protonated and the CO-protonated forms in solution compared to that in the gas phase, a result ascribed to an additional stabilization caused by the solvent polarity. Despite the difference in Gibbs energies, which suggests two possible equilibria, experimentally only the CO protonation was observed. In this work, we report on the protonation of B-1, B-2, B-3, and B-4 (Scheme 1) in concentrated solutions of sulfuric, perchloric, and hydrochloric acids; these substrates behave as weak bases prone to CO protonation and display medium effects.

Scheme 1. Investigated Hydroxamic Acids



Experimental Section

Reagents. *N*-Phenylbenzohydroxamic acid (Aldrich, 98%), benzohydroxamic acid (Aldrich, 99%), and salicylhydroxamic acid (Aldrich, 99%) were commercially available and used without further purification. *N*-*p*-Tolylcinnamohydroxamic acid was synthesized as described elsewhere;[24] since this compound was only sparingly soluble in water, to be able to compare the protonation parameters of all four substrates 10% v/v dioxane/water mixed solvent was used throughout.

Methods. The solutions used were always freshly prepared; appropriate amounts of sulfuric, hydrochloric, or perchloric acids were added to the working solutions to attain the required acidity. The equilibria were investigated at 25 °C by the UV spectrophotometric technique; the sample cell was prepared by syringing 0.2 mL of hydroxamic acid into 1.8 mL of solvent mixture, the resulting substrate concentration being 5×10^{-5} M in 10% dioxane/water of the required acid concentration. The blank of the reference cell was prepared by syringing 0.2 mL of pure dioxane (Biohit Proline Electronic micropipet, inaccuracy 0.5%, imprecision 0.2%) into 1.8 mL of mineral acid of the proper concentration. The spectral curves were recorded on a Hewlett-Packard 8453A spectrophotometer equipped with a diode array detection system and a temperature cell holder adapter, electrically regulated and controlled by computer. The absorbance measurements were performed at least in duplicate.

To exclude hydrolysis effects on the absorbance measurements, or to reduce them to a minimum, those experiments requiring conditions susceptible to give rise to appreciable hydrolysis were performed within a very short time interval. For this purpose the reagents were mixed directly in the measuring cell using a rapid mixing device with a dead time of only 6 ms; this extends the capabilities of the spectrophotometer and enables both multiwavelength data acquisition and stopped-flow measurements. The spectral curves were recorded rapidly under the control of a HP Kayak work station. Acidity function values in 10% dioxane−water were available in the literature only for aqueous perchloric acid;[25] therefore, the acidity functions used were those available for all three mineral acids in water.

Results and Discussion

Evaluation of the relative basicities and protonation parameters of weak organic bases is an important task

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that has attracted much interest both as a source of information on the molecular electronic structure and as a tool to interpret the reactivity of acid-catalyzed chemical reactions. The protonation−deprotonation equilibria in highly acidic media for the hydroxamic acids investigated are represented by eq 1.

$$BH^+ \rightleftharpoons B + H^+ \quad (1)$$

The equilibrium constants can then be described in terms of the ionization constants pK_{BH^+} of the protonated forms, using eq 2

$$pK_{BH^+} = \log I - \log C_{H^+} - \log(f_{H^+}f_B/f_{BH^+}) \quad (2)$$

where B = RCOR′, BH^+ = $RCOH^+R'$, $C_H{}^+$ is the hydrogen ion concentration, and I = $[BH^+]/[B]$ represents the ionization ratio. Although eq 2 is thermodynamically exact, a major problem lies on the evaluation of the molar activity coefficients (f_i) ratio term. The ionization ratios can be experimentally determined by measuring the variation with the change in medium acidity of a particular property of BH^+ compared to that of B; among the properties most commonly used are UV−vis and ^{1}H and ^{13}C NMR measurements.[11] The UV spectra of the investigated hydroxamic acids are distorted and exhibit shifts in wavelengths that could in principle be attributed to hydrolysis, medium effects, or both. In this work, the experimental procedure minimizes any hydrolysis effect on the equilibrium measurements; therefore, the medium effects are only responsible for the distortions observed in the spectral curves (Figure 1a). The medium effects, characteristic of the protonation of carbonyl compounds, were already observed in carbon acids such as amides[26] and ketones[27] and can be properly analyzed by the Cox−Yates and vector analysis methods.

(a) The Cox−Yates Method. This method enables the analysis of a large number of spectral curves over a wide wavelength range, yielding consistent and reliable results. Thermodynamic pK_{BH^+} values can only be determined from extrapolation to infinite dilution of the data pairs measured in aqueous solutions; however, a thorough description of equilibrium (1) in strongly acidic nonideal solutions requires the knowledge of two different parameters: (i) the protonation constant pK_{BH^+}, to be determined by a proper extrapolation from concentrated acids down to dilute solutions, or directly measured in a suitable way, and (ii) the solvation coefficient *m**. The latter parameter represents a measure of the solvation requirements of the protonated base and accounts for the sensitivity of the equilibrium to the large changes in the medium acidity needed to complete the protonation; experimental and theoretical aspects of this issue have been treated extensively.[28−30]

The thermodynamic K_{BH^+} constant is independent of the solvation effect; hence, the Cox−Yates eq 3, based on the excess acidity function *X* (defined later)

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \quad (3)$$

holds irrespective of the solvation states of the B and BH^+ species (which may differ from one another), thus eliminating the medium effects.[31] If the absorbance values for the unprotonated (A_B) and the protonated (A_{BH^+}) forms are accessible experimentally, then the method enables the ionization ratios to be determined using eq 4

$$I = (A_{BH^+} - A)/(A - A_B) \quad (4)$$

where *A* stands for the absorbance values at intermediate acidities. The method considers different situations depending on whether the medium effects stem from the protonated or from the unprotonated forms; if BH^+ is the only form responsible for the medium effects and the B form is not observable, then the following equations apply[31]

$$A = [A_B + I(A_{BH^+} + \delta A_{BH^+}I'_{BH^+})]/(1 + I) \quad (5)$$

$$I'_{BH^+} = (I_{BH^+} - 1)/(I_{BH^+} + 1) \quad (6)$$

$$\log I_{BH^+} = \Delta m^*_{BH^+} + X \quad (7)$$

where the Δm^* parameter for most compounds normally tends to 0.1; this method was not feasible in HCl medium, since the A_{BH^+} value was not accessible experimentally (Figure 2). Table 1 lists the pK_{BH^+} values provided by this method.

(b) TheVector Analysis Method. This method[32] decomposes the experimental absorbance readings into the minimum number of independent components capable of reproducing the spectral curves, from which reliable ionization ratios can be deduced. The absorbance readings *A*, measured at *n* different acidity levels and *r* wavelengths were arranged into an ($n \times r$) matrix array; if *p* independent components are needed to reproduce the experimental readings, then the absorbance values at every wavelength λ can be expressed for each C_{H^+} value by the set of equations

$$\begin{aligned} A_1 &= \bar{A}_1 + c_1\mathbf{v}_{11} + c_2\mathbf{v}_{21} + ... + c_p\mathbf{v}_{p1} \\ A_2 &= \bar{A}_2 + c_1\mathbf{v}_{12} + c_2\mathbf{v}_{22} + ... + c_p\mathbf{v}_{p2} \\ &- \\ A_r &= \bar{A}_r + c_1\mathbf{v}_{1r} + c_2\mathbf{v}_{2r} + ... + c_p\mathbf{v}_{pr} \end{aligned} \quad (8)$$

where $\bar{A}$ is the averaged absorbance corresponding to a particular wavelength for the *n* different C_{H^+} values, $\mathbf{v}_{pr}$ are the characteristic vectors, and c_p the weighing factors (or fitting coefficients). It was demonstrated[32] that in practice only two characteristic vectors are sufficient to describe the total effect, the first vector ($\mathbf{v}_{1r}$) accounting for the protonation effect caused by the change in the medium acidity, and the second ($\mathbf{v}_{2r}$) for the medium effects upon the protonation reaction. Values for *I* and pK_{BH^+} can be determined from the variation of c_1 with medium acidity; Table 2 lists the c_1 coefficients determined at different C_{H^+} values for all four substrates over the whole titration acidity ranges. As an example, Figure 1 shows the spectral curves of salicylhydroxamic acid

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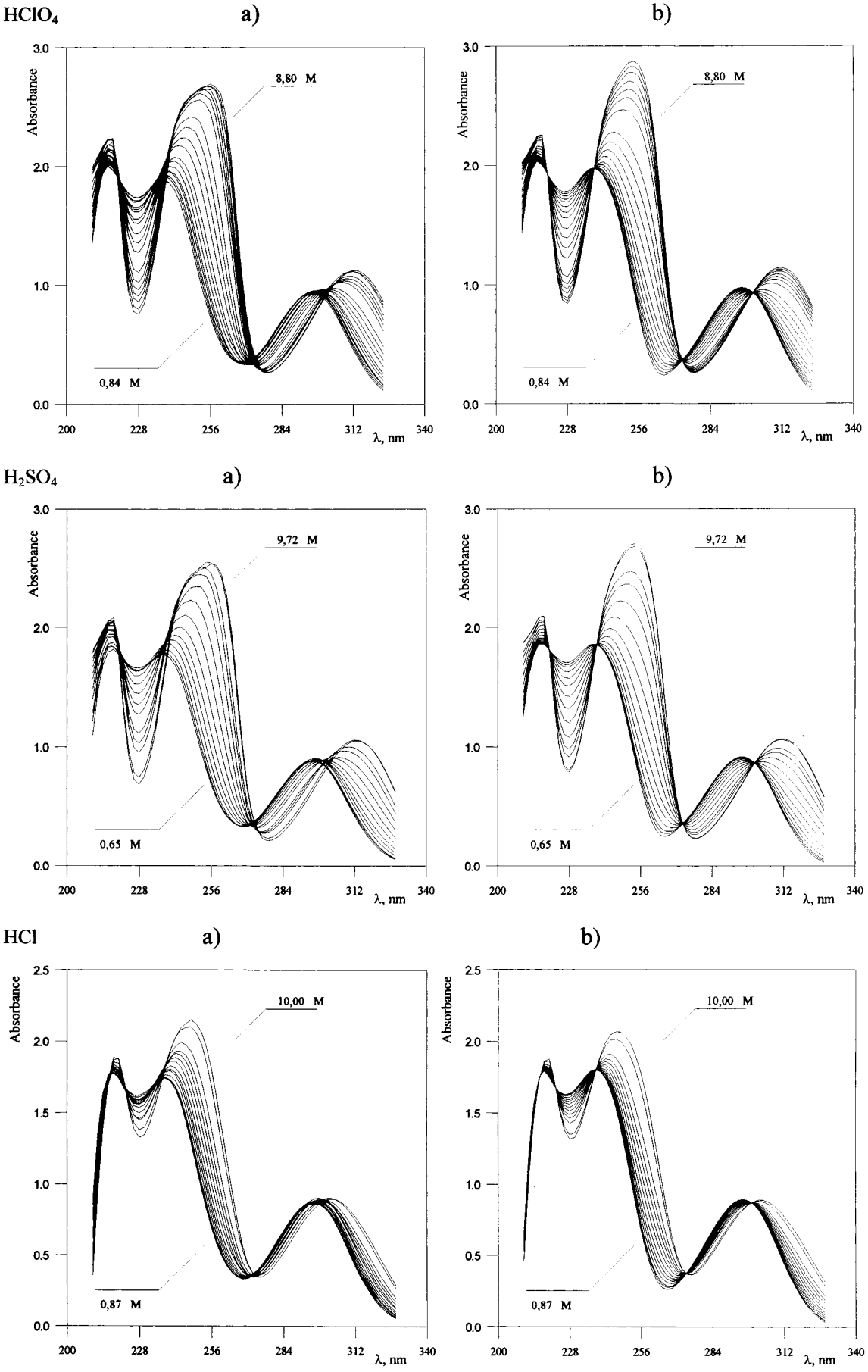

Figure 1. Sets of UV spectral curves of salicylhydroxamic acid recorded in three mineral acid media: (a) before and (b) after application of vector analysis.

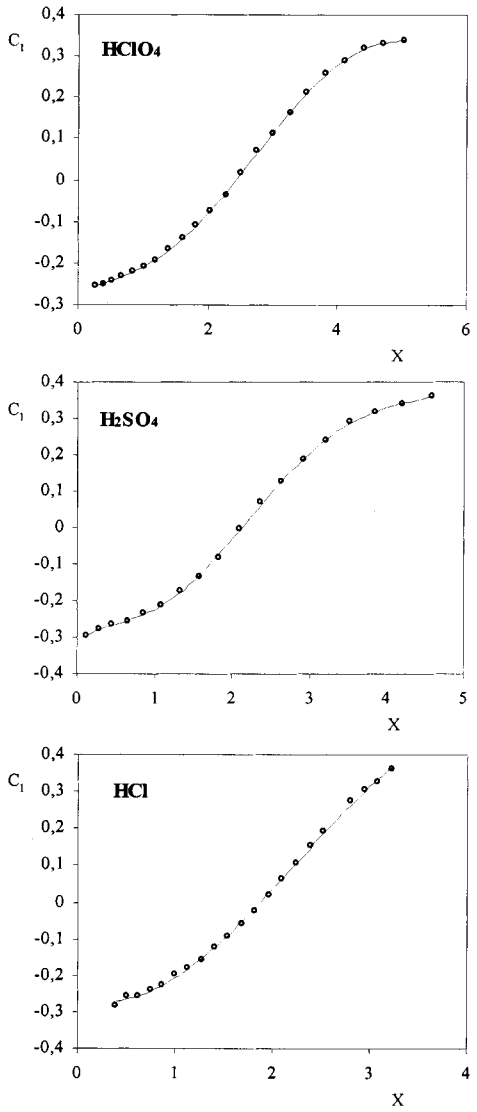

Figure 2. Variation of the c_1 coefficients vs the excess acidity function X for benzohydroxamic acid.

Table 1. Protonation Parameters, pK_{BH^+} and m^*, Determined by the Cox−Yates Method for Correction of Medium Effects

	$HClO_4$		H_2SO_4	
	pK	m^*	pK	m^*
B-1	−2.92 ± 0.09	0.66 ± 0.04	−2.30 ± 0.10	0.70 ± 0.10
B-2	−1.94 ± 0.02	0.40 ± 0.01	−2.10 ± 0.10	0.70 ± 0.10
B-3	−1.55 ± 0.03	0.57 ± 0.03	−2.10 ± 0.04	0.53 ± 0.03
B-4	−1.81 ± 0.03	0.63 ± 0.02	−1.89 ± 0.07	0.60 ± 0.07

recorded in three different acid media (a) before and (b) after correction of medium effects by the vector analysis method. If $c_{1,B}$ and c_{1,BH^+} are the coefficients for the fully unprotonated and the fully protonated base, then the ionization ratios can be readily determined with eq 9

$$I = \frac{c_{1,BH^+} - c_1}{c_1 - c_{1,B}} \tag{9}$$

where c_1 represents the coefficients at intermediate extents of protonation. Figure 2 shows the plots c_1 vs X, the excess acidity function of eq 3, corresponding to the titration of benzohydroxamic acid in three different acid media; H_2SO_4 and $HClO_4$ provided sufficient acidity to complete the protonation equilibria, and the titrations displayed the typical S-shaped curves, whereas HCl provided insufficient acidity, and the corresponding titration curve lacked the highest acidity curvature. In the latter case, the A_{BH^+} value was unaccessible, as was the characteristic c_{1,BH^+} vector needed to determine the equilibrium constant; this difficulty can be readily overcome as described below.

Once the c_1 characteristic vectors were determined by vector analysis as a function of the mineral acid concentration, the following thermodynamic equations were used to deduce accurate pK_{BH^+} values:

(1) The Hammett Equation. Hammett approached the problem of the unknown activity coefficients f_i, assuming that the log term of eq 2 cancels out; this zeroth-order approximation, however, is valid only for weak bases of similar structure. According to Hammett eq 10, the value for the acidity function H_o tends to pH in dilute acid solutions

$$H_o = -mH_x = pK_{BH^+} - \log I \tag{10}$$

where H_x is a Hammett-type acidity function. By a process similar to that of Chandler and Lee,[33] rearrangement of equations 9 and 10 results in eq 11

$$c_1 = \frac{c_{1,B} - c_{1,BH^+}}{1 - 10^{-mH_x + pK_{BH^+}}} + c_{1,BH^+} \tag{11}$$

$c_{1,B}$, c_{1,BH^+}, m, and pK_{BH^+} being unknown parameters that can be determined by iteration. The procedure requires introduction of initial values for $c_{1,B}$, c_{1,BH^+}, m, and pK_{BH^+}; few iterations were sufficient to achieve convergence, the minimum χ^2 value being used as a criterion for the goodness of the fit. Equation 11 was applicable in all cases and proved to be particularly useful for incomplete equilibria. Introduction of the H_o literature values (based on primary amines) available for different mineral acids[34−37] yielded results not fully satisfactory, since amines are structurally very distinct from the bases used here. The need for other scales different from H_o soon became evident, and more satisfactory results were achieved with the H_A acidity function, based on benzamides (Table 3a). This better agreement can be explained by the similar basic strength, similar solvation requirements, and closer structural similarity between benzamides and benzohydroxamic acids, in accordance with the requirements of the Hammett hypothesis. For $HClO_4$ and H_2SO_4, different H_A acidity functions are available in the literature,[35,37] but unfortunately, values for H_A values in HCl medium are lacking.

(2) The Bunnett−Olsen Method. This is a more general method; originally introduced by Bunnett−Olsen[38,39] and extended by Levi et al.,[40,41] the method is

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Table 2. Values for the c_1 Coefficients Determined by Vector Analysis for Four Hydroxamic Acids at Different Mineral Acid Molarities, *M*

$HClO_4$					H_2SO_4						HCl			
M	B-1	B-2	B-3	B-4	*M*	log C_H+	B-1	B-2	B-3	B-4	*M*	B-2	B-3	B-4
0.42					0.65	−0.111		−0.295	−0.331	0.358	0.87		−0.272	0.261
0.84			−0.299		1.30	0.197		−0.28	−0.317	0.341	1.31		−0.263	0.256
1.26		−0.255	−0.288		1.95	0.380	−0.297	−0.267	−0.302	0.32	1.74	−0.282	−0.256	0.248
1.68		−0.249	−0.275	0.325	2.59	0.511	−0.285	−0.255	−0.272		2.17	−0.259	−0.239	0.232
2.09		−0.244	−0.257	0.317	3.24	0.612	−0.277	−0.235	−0.229	0.259	2.61	−0.256	−0.222	0.214
2.51		−0.232	−0.242	0.303	3.89	0.693	−0.247	−0.211	−0.179	0.213	3.04	−0.24	−0.205	0.193
2.93		−0.221	−0.214	0.264	4.54	0.760	−0.217	−0.174	−0.112	0.139	3.48	−0.225	−0.183	0.181
3.35		−0.208	−0.183	0.227	5.19	0.818	−0.178	−0.133	−0.033	0.068	3.91	−0.195	−0.153	0.16
3.77		−0.191	−0.151	0.206	5.84	0.867	−0.148	−0.082	0.057	−0.029	4.35	−0.179	−0.126	0.12
4.19		−0.165	−0.094	0.164	6.48	0.910	−0.076	−0.006	0.153	−0.127	4.78	−0.156	−0.094	0.103
4.61		−0.141	−0.042	0.086	7.13	0.948	0.005	0.068	0.229	−0.213	5.22	−0.122	−0.064	0.05
5.03	−0.461	−0.109	0.014	0.035	7.78	0.981	0.086	0.125	0.278	−0.266	5.65	−0.094	−0.022	0.03
5.45		−0.073	0.071	−0.036	8.43	1.011	0.168	0.187	0.311	−0.323	6.09	−0.057	0.024	−0.011
5.87	−0.399	−0.035	0.121	−0.056	9.08	1.037	0.268	0.24		−0.36	6.52	−0.024	0.074	−0.056
6.28	−0.311	0.019	0.174	−0.189	9.73	1.060	0.337	0.29	0.365	−0.387	6.96	0.021	0.111	−0.094
6.70	−0.22	0.07	0.215	−0.226	10.37	1.081	0.412	0.319	0.375		7.39	0.062	0.159	−0.139
7.12	−0.138	0.115	0.243	−0.253	11.02	1.100	0.442	0.341			7.83	0.106	0.189	−0.177
7.54	−0.021	0.162	0.267	−0.257	11.67	1.117		0.359			8.26	0.153	0.237	−0.222
7.96	0.08	0.211	0.294	−0.286							8.70	0.191	0.273	−0.272
8.38	0.184	0.259	0.31	−0.306							9.57	0.275	0.336	
8.80	0.227	0.29	0.324	−0.327							10.00	0.307	0.353	−0.361
9.22	0.321	0.318									10.44	0.326		−0.385
9.64	0.371	0.333									10.87	0.361		
10.05	0.361	0.337												

Table 3. (A) Protonation Parameters Determined by Vector Analysis Using Different Equations. (B) Mean pK_{BH^+} Values Determined from Individual Values of Table 3A

(A)	B-1		B-2		B-3		B-4	
$HClO_4$								
eq 13	p*K*	ϕ	p*K*	ϕ	p*K*	ϕ	p*K*	ϕ
Ho[35]	−2.5 ± 0.2	0.44 ± 0.06	−1.87 ± 0.02	0.56 ± 0.01	−1.71 ± 0.04	0.36 ± 0.02	−2.0 ± 0.1	0.21 ± 0.06
Ho[35]	−2.8 ± 0.2	0.56 ± 0.04	−2.09 ± 0.03	0.67 ± 0.01	−1.81 ± 0.02	0.59 ± 0.01	−2.2 ± 0.1	0.48 ± 0.04
eq 14	p*K*	*m**	p*K*	*m**	p*K*	*m**	p*K*	*m**
X[42]	−2.9 ± 0.2	0.65 ± 0.06	−2.01 ± 0.03	0.44 ± 0.01	−1.67 ± 0.02	0.53 ± 0.01	−2.0 ± 0.1	0.67 ± 0.05
eq 11	p*K*	*m*	p*K*	*m*	p*K*	*m*	p*K*	*m*
H_A[35]	−3.4 ± 0.3	−1.2 ± 0.1	−2.13 ± 0.05	−0.81 ± 0.02	−2.02 ± 0.05	−1.01 ± 0.02	−2.5 ± 0.1	−1.21 ± 0.07
H_2SO_4								
eq 13	p*K*	ϕ	p*K*	ϕ	p*K*	ϕ	p*K*	ϕ
Ho[36]	−2.24 ± 0.05	0.60 ± 0.05	−2.02 ± 0.05	0.55 ± 0.03	−1.93 ± 0.04	0.37 ± 0.02	−1.94 ± 0.04	0.41 ± 0.02
Ho[36]	−2.48 ± 0.07	0.46 ± 0.04	−2.19 ± 0.05	0.48 ± 0.02	−2.09 ± 0.05	0.33 ± 0.03	−2.12 ± 0.05	0.35 ± 0.03
Ho[37]	−2.28 ± 0.05	0.54 ± 0.02	−2.01 ± 0.03	0.53 ± 0.01	−1.89 ± 0.03	0.36 ± 0.02	−1.91 ± 0.03	0.40 ± 0.02
eq 14	p*K*	*m**	p*K*	*m**	p*K*	*m**	p*K*	*m**
X[42]	−2.47 ± 0.06	0.54 ± 0.03	−2.15 ± 0.03	0.52 ± 0.01	−1.99 ± 0.03	0.66 ± 0.02	−2.01 ± 0.03	0.62 ± 0.02
eq 11	p*K*	*m*	p*K*	*m*	p*K*	*m*	p*K*	*m*
H_A[31]	−2.40 ± 0.09	−0.97 ± 0.04	−2.04 ± 0.03	−0.94 ± 0.02	−1.92 ± 0.04	−1.10 ± 0.03	−1.92 ± 0.04	−1.04 ± 0.03
HCl								
eq 13			p*K*	ϕ	p*K*	ϕ	p*K*	ϕ
Ho[42]			−1.94 ± 0.03	0.55 ± 0.02	−1.80 ± 0.02	0.50 ± 0.02	−1.81 ± 0.03	0.56 ± 0.02
eq 14			p*K*	*m**	p*K*	*m**	p*K*	*m**
X[42]			−1.94 ± 0.03	0.45 ± 0.02	−1.80 ± 0.02	0.49 ± 0.02	−1.80 ± 0.03	0.44 ± 0.02

(B)	B-1	B-2	B-3	B-4
$HClO_4$	−2.90 ± 0.40	−2.02 ± 0.11	−1.80 ± 0.15	−2.20 ± 0.20
H_2SO_4	−2.37 ± 0.11	−2.08 ± 0.08	−1.96 ± 0.08	−1.98 ± 0.08
HCl		−1.94 ± 0.03	−1.80 ± 0.02	−1.81 ± 0.03

based on the linear free energy relationship (12)

$$\log I + H_o = \Phi_e(H_o + \log C_{H^+}) + pK_{BH^+} \quad (12)$$

which provides the pK_{BH^+} value as the intercept and Φ_e as the slope parameter. Rearrangement of equations 9 and 12 results in eq 13:

$$c_1 = \frac{c_{1,B} - c_{1,BH^+}}{1 + 10^{H_o(\phi-1)+H_o\log C_H{}^+ + pK_{BH^+}}} + c_{1,BH^+} \quad (13)$$

After application of vector analysis, the fitting of eq 13 to the experimental data by the above iterative procedure enables the Φ, $c_{1,B}$, c_{1,BH^+}, and pK_{BH^+} parameters to be determined. A noticeable shortcoming to this method is the need for a Hammett-type acidity function, subject to the arbitrary cancellation assumption of the activity coefficients ratio term of eq 2.

(3) Excess Acidity Analysis. This method develops a recent version by Cox[42] of an earlier approach[43] and involves introduction of the excess acidity function *X*, which represents the difference between the observed

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(42) Cox, R. A. *Adv. Phys. Org. Chem.* **2000**, *35*, 1.

(43) Marziano, N. C.; Tomasin, A.; Traverso, P. G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 309.

acidity and that of the system if this would behave ideally.[34] The method is based on the free energy relationship (3), with the X acidity scales constructed for aqueous solutions of strong acids using a set of bases differently structured. Introduction in eq 3 of the c_1 coefficients provided by the vector analysis method results in eq 14, which differs from eq 11 by the replacement of $-mH_x$ by m^*X:

$$\boldsymbol{c}_1 = \frac{c_{1,B} - c_{1,BH^+}}{1 - C_{H^+}10^{m^*X+pK_{BH^+}}} + c_{1,BH^+} \qquad (14)$$

The iterative procedure applied to eq 14 provided the m^*, $c_{1,B}$, c_{1,BH^+}, and pK_{BH^+} values, the latter being evaluated with the X functions available for the mineral acids used.[42] Table 3a summarizes the results provided by vector analysis combined with the three thermodynamic equations, and allows comparison between the three approximations; the spectral curves were quite similar, specially in sulfuric and perchloric acids (Figure 1), but the pK_{BH^+} values appeared to be dependent on the nature of the mineral acid used, as inferred from the definition of pK_{BH^+}.

Previously,[22,23] we used both theoretical and experimental data to discuss the protonation sites of acetohydroxamic acid, concluding that the protonation preferentially occurs at the carbonyl oxygen; MP2 ab initio calculations, gave Gibbs free energies of formation in solution of −160.2 and −157.6 kcal mol^{-1} for the two stable cations $RCOH^+$ and $R'NH_2OH^+$, respectively; these data suggest that carbonyl is the most active site both in solution and in the gas phase.[23] The close similarity between the spectrophotometric behavior of hydroxamic acids and amides,[26] and the noticeable difference with amines[44] points to O-protonation. Bagno and Scorrano[45] demonstrated that N-protonation in formamide is disfavored by a sizable amount of some 14−15 kcal mol^{-1} with respect to O-protonation. However, the pK_{BH^+} values also involve an entropy contribution, and replacement of phenyl by methyl group is worth of +3 to +8 entropy units; for instance, in aqueous solution the entropy change associated with reaction 1 (in the protonation direction) is $\Delta S = -4.7$ eu for tetramethylammonium ion, whereas for anilinium ion is $\Delta S = +3.7$ eu.

The pK_{BH^+} values provided by eq 11, with $-mH_x$ replaced by H_o, were not reliable; these values do not fulfill, as expected, Hammett's cancellation assumption, according to which the $\log(f_A f_{BH^+}/f_B f_{AH^+})$ term vanishes, B denoting the hydroxamic acid and A the primary aromatic amine used to determine H_o. In view of the close structural similarity of amides and hydroxamic acids, it is reasonable to assume that the H_A acidity function, based on amides, would best fulfill the cancellation assumption. Table 3a lists the pK_{BH^+} values calculated with eq 11 using the $H_x = H_A$ acidity function. The pK_{BH^+} values obtained with H_o and equations 13 and 14 were in reasonably good agreement. From the definition of H_o (with aniline as the reference base), it follows that $-(H_o + \log C_{H^+}) = \log(f_A f_{H^+}/f_{AH^+})$, a result almost identical with that provided by eq 3, $m^*X = \log\{f_{B^*} f_{H^+}/f_{B^*H^+}\}$, particularly if B* = A.[46]

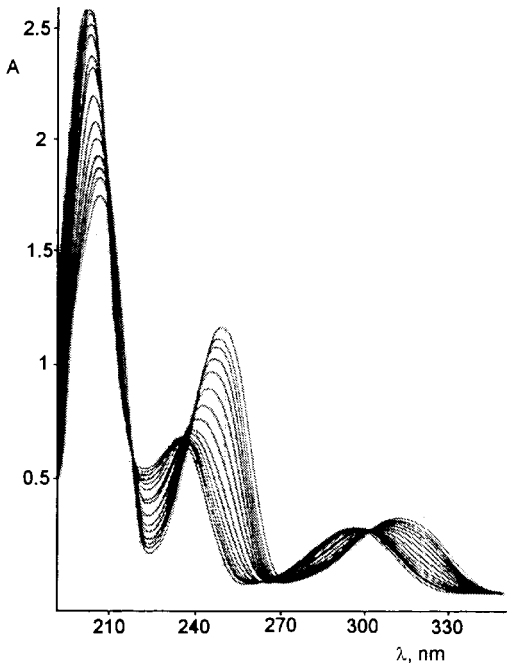

Figure 3. Set of UV spectral curves of 1.5×10^{-4} M salicylamide as a function of medium acidity within the 0−9.3 M $HClO_4$ acidity range.

As a rule, the Cox−Yates method for correction of medium effects[26] leads to pK_{BH^+} values lower than those obtained with the different thermodynamic equations and vector analysis (Tables 1 and 3b), a feature that stems from the difficulty of applying the Cox−Yates method to a wide wavelengths range.[47] Cox−Yates derived pK_{BH^+} values with eq 3 assuming that $(-H_o - \log C_{H^+}) = m^*X$. In strongly acidic solutions, the substrate basicity relies on pK_{BH^+} and m^*; the need for two parameters to describe the protonation equilibria is a consequence of the stabilization of BH^+ both by internal delocalization of the cationic charge and by solvation effects. The m* parameter characterizes the behavior of a variety of base types, and reflects the sensitivity of the protonated base to become stabilized by solvation, especially by hydrogen bonding; thus, $m^* = 0$ represents the upper limit of the solvation requirements on this scale (in water, H_3O^+ has the highest solvation requirements), whereas higher m^* values denote weaker solvation;[29] in the O-protonated bases, a positive charge is localized on a nonpolarizable electronegative atom with high solvation requirements.

The spectral changes of salycilhydroxamic acid (Figure 1) and salycilamide (Figure 3) in $HClO_4$ medium are similar, thus revealing similar protonation behaviors. The values $pK_{BH^+} = -1{,}57$, $m^* = 0.45$ for benzamide in $HClO_4$, and $pK_{BH^+} = -1.66$, $m^* = 0{,}48$ for salycilamide obtained with the Cox−Yates method,[26] compared to those of benzohydroxamic and salicylhydroxamic acids (Table 3), suggest that the hydroxamic group behaves as a weaker base than the amide group. The values $m^* = 0.56 \pm 0.11$ in $HClO_4$, $m^* = 0.63 \pm 0.08$ in H_2SO_4, and $m^* = 0.46 \pm 0.02$ in HCl deduced for hydroxamic acids, compared to the averaged value $m^* = 0.51 \pm 0.07$ reported for amides in $HClO_4$,[47] indicate similar solvation requirements for amides and hydroxamic acids.

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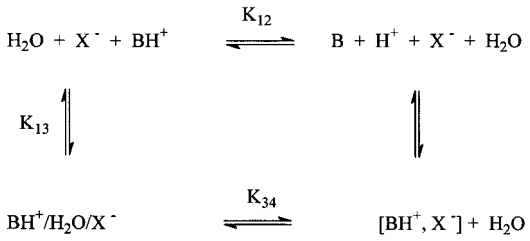
Scheme 2



The difference in the values of thermodynamic parameters of the substrates investigated could be rationalized on the basis of two different effects: the formation of ion pairs between X^- (the anions of the mineral acid used) and the BH^+ cations, and the stabilization of BH^+ due to the positive charge delocalization. The first effect can explain the dependence of the extent of protonation on the nature of the mineral acid; the relatively high concentrations of ClO_4^-, HSO_4^-, and Cl^- present in the solvent medium favor the formation of ion pairs with BH^+. It should be noted that sulfuric acid undergoes a variety of reactions where species such as $H_2S_2O_7$, $HS_2O_7^-$, $H_3SO_4^+$, H_2SO_4, and HSO_4^- are formed; however, under our experimental conditions the HSO_4^- anion becomes prevailing,[48] and therefore is the best candidate to forming ion pairs. Additionaly, also water is involved in the ion pairing process to an extent that depends on the medium permittivity, so that an equilibrium is established between "solvent-separated" and "contact" ion pairs.[49] In light of these considerations, it is clear that reaction 1 provides only an apparent picture of the protonation-deprotonation process, which now could be better described by the more detailed Scheme 2 where the protonated base is distributed among the BH^+ free form, the $BH^+/H_2O/X^-$ solvent-separated ion pair, and the $[BH^+,X^-]$ contact ion pair. According to the above scheme, the proton dissociation constant experimentally measurable is now defined as

$$K_{BH^+} = \frac{a_{H^+}a_B}{a_{BH^+} + a_{BH^+/H_2O/X^-} + a_{BH^+,X^-}} \qquad (15)$$

Introduction of the equilibrium constants of the individual reactions of Scheme 2 in eq 15 yields

$$K_{BH^+} = \frac{K_{12}}{1 + K_{13}a_{X^-}(a_{H_2O} + K_{34})} \qquad (16)$$

Since no deviations from the calculated trend were observed at the highest concentrations of mineral acid added, one can conclude that the denominator of eq 16 remains constant during the titration; this fact reveals that K_{34} is small compared to a_{H_2O}; i.e., the prevailing ion pair population is "solvent-separated". Actually, only for $K_{34} \ll a_{H_2O}$ could the increase in a_{X^-} due to the progress of the titration be compensated by the concomitant decrease in a_{H_2O}, in such a way that the $K_{13}.a_{X^-}.a_{H_2O}$ term could remain approximately constant; on the other hand, this term should depend on the nature of the mineral acid. Moreover, comparison of log a_{H_2O} values at the same molar concentration gives $a_{H_2O}(HCl) > a_{H_2O}(H_2SO_4) > a_{H_2O}(HClO_4)$,[50] and $a_{Cl^-} > a_{ClO4^-}$; i.e., Cl^- ions exhibit a stronger tendency to form ion pairs compared to ClO_4^- ions.[51] By applying these observations to eq 16, it follows that $K_{BH^+}(HCl) < K_{BH^+}(H_2SO_4) < K_{BH^+}(HClO_4)$. This behavior is clearly shown by *N*-*p*-tolylcinnamohydroxamic acid (B-4). For the other substrates, the trend observed for B-4 still remains with the exception of B-2 and B-3 in $HClO_4$, whose K_{BH^+} values were somewhat lower than expected according to the above argument; however, it should be noted that changing the nature of the mineral acids brings about changes in the physicochemical properties of the medium, which may affect the K_{13} value as well.

Concerning the second effect, i.e., the stabilization of BH^+ by charge delocalization, it should be noted that the structure of the O-protonated hydroxamic acid involves a large delocalization of the positive charge; as a consequence, the number and type of N and C substituents are expected to play an important role on the stability and solvation of BH^+, which are reflected in the pK_{BH^+} and m* values, respectively.[32]

The change in the electric field gradient calculated by means of ab initio methods for the O-protonated form is probably related to the involvement of the N-atom in localizing the positive charge formally residing on oxygen, thereby engaging the lone pair (which is normally responsible for most of the efg at nitrogen).[11] These calculations allow to predict the changes in the NMR line widths of the quadrupolar nuclei involved.[52] The positive charge of BH^+ is partially delocalized on the neighbor water molecules; this will be more difficult if NHOH is replaced by −NOHR regardless of the size of the R group. On the other hand, the C substituents also allow delocalization of the positive charge and favor the solvation of BH^+. The solvation parameters *m** vary between 0.5 and 0.7, a somewhat larger range than the usual 0.5−0.6 available for protonation of amides in sulfuric acid.[53] In contrast, the *m** value for B-2 is substantially lower, this indicating an increase in solvation. As a rule, the solvation is lower in N-substituted acids (less delocalization of the positive charge) and higher in HCl compared to $HClO_4$ and H_2SO_4; this feature is consistent with the stability of the ion pairs, since the larger the solvation (smaller *m**) the stronger the prevalence of the $BH^+/H_2O/X^-$ solvent-separated ion pairs compared to the $[BH^+,X^-]$ contact ion pairs.

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