Inorg. Chem. **2003**, *42*, 5434–5441

NMR Studies of Phenylbenzohydroxamic Acid and Kinetics of Complex Formation with Nickel(II)

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Received February 14, 2003

The behavior of *N*-phenylbenzohydroxamic acid (PBHA) in organic solvents has been investigated by ^{1}H and ^{13}C NMR spectroscopy. Measurements in acetone at different temperatures and concentrations enable one to individualized two signals, in a 20/80 area ratio, which were ascribed to partition of PBHA between two isomers, HZ (*cis*) and HE (*trans*). The dependence of the low-intensity peak on concentration and temperature strongly suggests dimer formation. Since only the HZ form can give dimers, it may be concluded that in acetone PBHA is present mainly in the HE form. ^{13}C NMR measurements in methanol yielded a 50/50 [HZ]/[HE] ratio. The equilibria and kinetics of complex formation in aqueous solutions between Ni(II) and PBHA were investigated by spectrophotometric and stopped-flow techniques at 25 °C and 0.2 M ionic strength. Two reaction paths, involving the binding of Ni^{2+} to the neutral PBHA and to its anion, were observed. The rate constants of the forward and reverse steps are $k_1 = (7.1 \pm 0.3) \times 10^2\ M^{-1}\ s^{-1}$ and $k_{-1} = (4.9 \pm 0.6)\ s^{-1}$ for the step involving the undissociated PBHA and $k_2 = (5.5 \pm 0.7) \times 10^4\ M^{-1}\ s^{-1}$ and $k_{-2} = (1.2 \pm 0.1)\ s^{-1}$ for the step involving the anion. The k_2 value indicates that the PBHA anion reacts with Ni^{2+} according to Eigen's mechanism and that in water the *cis* form prevails. The k_1 value is lower by a factor of 13 compared to the value estimated on the basis of Eigen's mechanism, suggesting that at least 90% of the neutral ligand is present in a nonreactive conformation.

Introduction

Hydroxamic acids (RCONROH) are weak acids with a broad variety of applications; they are used as flotation agents in metal extraction, as inhibitors of copper corrosion, and also as therapeutic agents due to their antibacterial and antimalaria action.[1] These species are inhibitors of urease activity and have been used in the treatment of hepatic coma.[2] All these properties are related to the ability of these acids to form complexes with metal ions. Much attention has been devoted to binding of iron(III) to hydroxamic acids, as many microorganisms may synthesize compounds containing the hydroxamate residue susceptible to binding iron(III),[3] thus providing a way to dissolve the metal ion under physiological conditions.[4] Hydroxamic acids may also act as ligands toward many other metal ions such as Al(III),[5] Cr(III),[6] Ga(III),[7] Os(III),[8] Eu(III),[9] Be(II),[10] Co(II),[11] Ni(II),[12] Cu(II),[13] Zn(II),[14] V(V),[15] Pu(IV),[16] Np(IV),[16] U(VI),[16] Mo(VI),[17] and La (III).[18]

However, despite these interesting applications, hydroxamic acids still remain poorly characterized; very recently it has been demonstrated that these compounds can accept a second proton under high-acidity conditions, and the protonation constants have been determined in strong mineral acid media for aceto-, benzo-, and salicylhydroxamic acids.[19] On the other hand, despite the number of experimental and theoretical investigations on this issue, assignment of the preferred deprotonation sites is still puzzling; moreover, it should be noted that the structure of hydroxamic acids in solution has not yet unambiguously been determined.

A major difficulty in assigning the proper structures stems from their distribution among the tautomer forms,[20,21] and further complications may arise from the possible geometric

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10.1021/ic034161q CCC: $25.00
Published on Web 07/29/2003

isomerization and internal or solvent-including hydrogen bonding. The HZ ⇌ HE equilibrium for monoalkylbenzohydroxamic acids was investigated in several solvents,[22] and it has been suggested that the HZ (*cis*) conformation of monoalkylhydroxamic acids become stabilized in water by solvent-including hydrogen bonding; the latter kind of interaction has been attributed to NH compounds, whereas intramolecular hydrogen bonding has been attributed to N-substituted hydroxamic acids.[23] To gain additional insight into this aspect of the chemistry of hydroxamic acids in solution, the behavior of phenylbenzohydroxamic acid has been investigated in organic solvents by NMR spectroscopy, and the kinetics and mechanism of its binding to nickel(II) have been studied in aqueous solution by the stopped-flow technique. *N*-Phenylbenzohydroxamic acid, PhCONOHPh (PBHA), bears a single OH proton unambiguosly bound to the oxime group, and hence only two tautomer forms, HZ and HE, are feasible. Therefore, difficulties in connection with the uncertainty about the deprotonation site, required for complex formation, should be disregarded in the system investigated. On the other hand, Ni(II) has been chosen to investigate the metal binding to PBHA in aqueous solution since it is well established that this metal ion reacts ordinarily by the interchange dissociative (I_d) mechanism; sound conclusions about the ligand structure in solution can be drawn only if the rate of solvent exchange at the metal ions is known with good precision, and this is the case for Ni(II) ion.

Experimental Section

Chemicals. All chemicals were analytical grade. PBHA was from Merck (purity >99%). Solutions of PBHA for NMR measurements were prepared by weighing the appropriate amount of acid just before use and were always kept under a dry nitrogen atmosphere. The NMR solvents used were acetone-d_6, acetonitrile-d_3, DMSO-d_6, and methanol-d_4, SDS ≥99.8% purity. Acetone was dried and deareated as follows: first it was frozen by liquid nitrogen and degassed under vacuum, and then it was distilled under a nitrogen atmosphere that had been previously dried. Finally it was left in contact with molecular sieves AW500.[24] The solvent was kept under nitrogen in bottles able to maintain for long time intervals a 10^{-6} atmosphere pressure. In this way the NMR spectra did not show the H_2O signal. The solubility of PBHA in water was too low to allow NMR measurements. Twice distilled water was used both to prepare the solutions and as a reaction medium. The Ni(II) concentration was measured by titration with EDTA.[25] Perchloric acid and sodium perchlorate or potassium chloride were used to attain the desired medium acidity and ionic strength, respectively.

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Methods. The NMR measurements were performed with a Unity Inova Varian 400 MHz instrument at 9.4 T (operating at 399.941 and 100.574 MHz for ^{1}H and ^{13}C, respectively). The spectra were recorded over the −90 to +40 °C temperature range using a spectral window of 15 ppm for ^{1}H and 250 ppm for ^{13}C. Acquisition times were 3.74 and 1.20 s for ^{1}H and ^{13}C, respectively, and pulse angles of $\pi/2$ (^{1}H) and $\pi/4$ (^{13}C) were used. The solvent signal was used as a reference. The exchange rate constants were evaluated with the gNMR program (4.1 version), which is capable of simulating one-dimensional NMR spectra.

The hydrogen ion concentrations of solutions with $[H^+] \leq 0.01$ M were determined by pH measurements performed by a PHM 84 Radiometer Copenhagen instrument or by PHM Titrino DMS. A combined glass electrode was used after the usual KCl bridge was replaced by 3 M NaCl to avoid precipitation of $KClO_4$. The electrode was calibrated according to a procedure described elsewhere,[26] which enables conversion of the pHmeter output into $-[\log [H^+]]$ values.

Absorption titrations were performed on a Perkin-Elmer Lambda 17 double-beam spectrophotometer, and on an HP 8453 diode array spectrophotometer equipped with an HP 89090A Peltier accessory to control the temperature. Experiments were performed at 5, 15, 25, 35, and 45 °C since PBHA undergoes hydrolysis above 55 °C and pH 8. Increasing amounts of titrant were added by a microsyringe to a solution of PBHA already thermostated in the measuring cell.

The kinetic experiments were performed at 260 nm using a stopped-flow apparatus constructed in our laboratory. A Hi-Tech SF-61 mixing unit was coupled to a spectrophotometric line through two optical guides. The UV radiation produced by a Hamamatsu L248102 "quiet" lamp was passed through a Bausch and Lomb 338875 high-intensity monochromator and then split into two beams. The reference beam was sent directly to a 1P28 photomultiplier. The measuring beam was sent, through a quartz optical guide, to the observation chamber, and then through a second optical guide to the 1P28 measuring photomultiplier. The outputs of the two photomultipliers were balanced before each shot. The signal revealing the course of the reaction was sent to a Tektronix TDS 210 oscilloscope equipped with a digital storage unit capable of memorizing 2500 data points at a maximum sampling rate of 60 MHz. Finally, the acquired signal was transferred to a personal computer via a GPIB interface, using the wavestar 2.0 program, and analyzed by a nonlinear least-squares procedure.[27] The observed time constants used in this work were averaged over at least six repeated experiments, the maximum spread being within 10%. Temperature fluctuactions were within ±0.1 °C throughout. The medium acidity and ionic strength were kept constant at the desired values during each experiment.

Results

NMR Measurements in Organic Solvents. (a) Solvent Effects. The ^{1}H NMR spectra of PBHA were recorded in the deuterated solvents acetone, acetonitrile, dimethyl sulfoxide, methanol, and methanol/water. In the first three solvents only a singlet, associated with the H(OH) of the hydroxamate group, could be observed at 25 °C. The donor strengths of acetonitrile-d_3, acetone-d_6, and dimethyl sulfoxide-d_6 are 60.3, 75.7, and 105.5 kJ mol^{-1}, respectively,[28] and the corresponding measured chemical shifts are 8.45, 9.48, and 10.63 ppm. The linear dependence of the chemical shift upon the solvent donor numbers (not shown) could indicate strong solvent interactions with the polar PBHA forms. In methanol and methanol/water the ^{1}H NMR signals of the aromatic hydrogen atoms are very broad, hinting at the presence of a fast equilibrium; here, the above-mentioned H(OH) signal disappears as a consequence of the fast exchange with the deuterium of methanol and water, in keeping with the lability of the acidic proton.

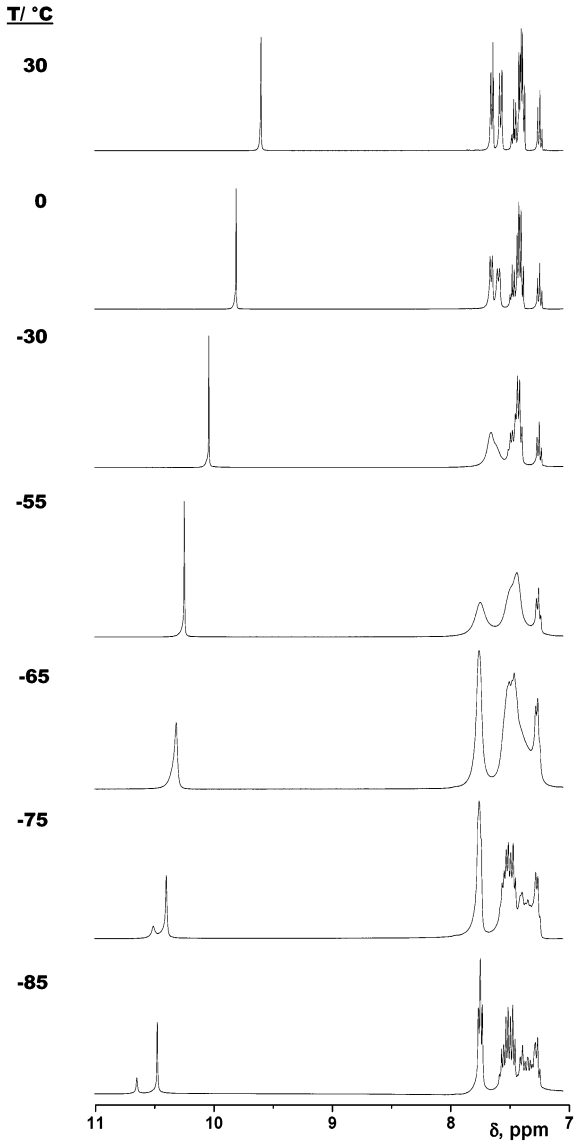

Figure 1. ^{1}H NMR spectra of PBHA recorded in acetone at different temperatures. $C_{PBHA} = 0.29$ M.

(b) Temperature Effect. The ^{1}H NMR spectra of PBHA in acetone were recorded at different concentrations and temperatures, from −85 to +30 °C, keeping the substrate concentration constant at 0.29 M (Figure 1). The H(OH) signal at around 10.5 ppm is split into two peaks, indicating the occurrence of an equilibrium between two conformation

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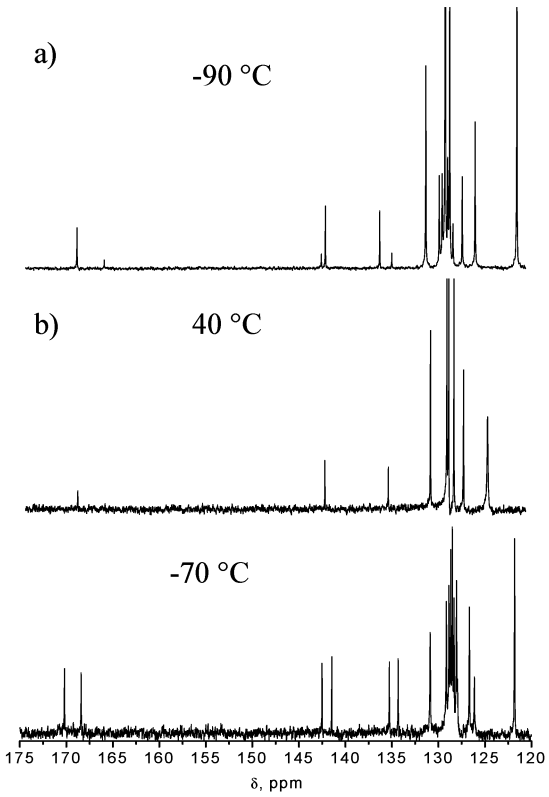


Figure 2. ^{13}C NMR spectra of PBHA recorded in (a) acetone at −90 °C and (b) methanol at 40 and −70 °C.

isomers in a 20/80 ratio, as deduced from the area integration. The signals of the aromatic protons, ranging from 7.2 to 7.8 ppm, indicate that coalescence occurs at about −60 °C. The multiple signals displayed at 30 °C should be attributed to the coalesced spectra of the two isomeric forms. Likewise, the ^{13}C NMR spectrum of PBHA, recorded in acetone at −90 °C (Figure 2a), shows two signals of different intensities at 169.5 and 167 ppm attributed to the CO group of each of the two isomers, whose presence is also evidenced by the splitting of the aromatic C signals. The ^{13}C NMR spectra of PBHA have also been recorded in methanol at 10 different temperatures between −80 and +40 °C. Two representative spectra are shown in Figure 2b. The number of peaks displayed at temperatures below −50 °C was twice that of those above 20 °C; coalescence occurs at about −40 °C, which proves the presence of the two isomers in methanol. The chemical shifts in the low exchange limit of the CO group were 170.2 and 168.3 ppm. Comparison with the results in acetone (coalescence at −60 °C) enables one to advance the hypothesis of a slower HZ−HE interconversion in methanol, possibly due to hydrogen bonding with solvent. The ratio of the peak areas is about unity, thus revealing that in methanol the two isomers are present in about the same concentration.

The increase of the amount of the minor isomer on changing from acetone to methanol suggests this isomer adopts the HZ configuration since this form can bind protic solvents by hydrogen bonding more firmly than the HE form. On this basis one can expect that in water the HZ form would prevail.

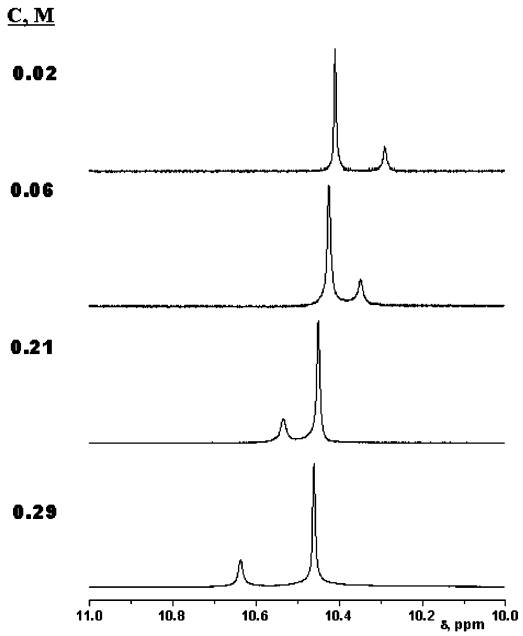
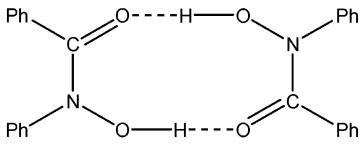


Figure 3. ^{1}H NMR spectra of PBHA recorded in acetone at different substrate concentrations. $T = -85$ °C. The low- and high-intensity peaks correspond, respectively, to HZ and HE hydroxamate hydrogens.

(c) Effect of PBHA Concentration. Figure 3 shows the effect of the substrate concentration on the ^{1}H NMR spectra of PBHA in acetone at −85 °C. By increasing the PBHA content, the lower intensity signal moves to the lower field region, whereas the higher intensity signal is also displaced but to a much less extent. Displacement to lower fields reveals an increase of hydrogen bonding;[25] hence, the observed behavior finds a simple explanation by assuming dimerization of PBHA. This peak is rather broad, which means that the monomer ⇌ dimer equilibrium is fast, even at low temperatures. In this regard, PBHA behaves like carboxylic acids, which may exist as stable hydrogen-bonded dimers in nonpolar solvents even in highly diluted solutions. The dimer structure could be represented by the following diagram:



If one assumes that the extent of displacement is proportional to the dimer concentration, then the δ value should change according to the total PBHA concentration; this behavior was experimentally found (Figure 4, circles). The linear trend indicates that the dimer prevails over the HZ monomer. On the other hand, the small displacement displayed by the high-intensity peak (Figure 4, squares) could be ascribed to hydrogen bonding between the E form and acetone.

Figures 1 and 5 show the variation of the N(OH) signals of 0.29 M PBHA in acetone with temperature. The two peaks shift toward higher fields with increasing temperature; the low-intensity peak presents a much larger shift, an effect attributed to the decrease in the dimer content as a conse-

Table 1. Rate Constant k_V (s^{-1}) at Different Concentrations and Temperatures and Activation Parameters for the HZ → HE Reaction of PBHA in Acetone

	k_V (s^{-1})							
[PBHA] (M)	−80 °C	−75 °C	−70 °C	−65 °C	−60 °C	−55 °C	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
0.02	0.051	0.147	0.349	0.720	1.07	5.27	61 ± 2	49 ± 11
0.06	0.187	0.422	0.941	1.930	3.79	8.44	51.0 ± 0.7	9 ± 3
0.29	1.930	2.690	4.730	6.460	9.90		25.7 ± 0.8	−102 ± 4

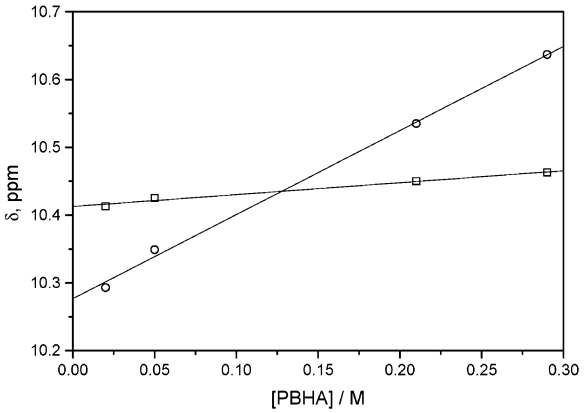


Figure 4. Concentration dependence of the chemical shift of the peak associated with the (○) HZ and (□) HE forms of PBHA. $T = -85$ °C.

quence of the hydrogen-bonding reduction.[29] Both the concentration and temperature effects on the low-intensity peak reveal that this signal should be assigned to the Z form. Scheme 1 can then be proposed for the monomer ⇌ dimer

Scheme 1

$$(HZ)_2 \overset{K_D}{\rightleftharpoons} 2HZ \overset{K_{EZ}}{\rightleftharpoons} 2HE$$

equilibrium. $K_D = [HZ]^2/[(HZ)_2]$ and $K_{EZ} = [HE]/[HZ]$; the dimerization equilibrium is fast compared to the conformation transition.

Concerning the high-intensity signal associated with the HE form, the small displacement observed can be ascribed to reduction of the weak hydrogen bonding between the HE form and acetone as the temperature increases. Table 1 lists the values for the exchange rate constant, k_V (s^{-1}), and the apparent activation parameters enthalpy, $\Delta H^{\ddagger}$, and entropy, $\Delta S^{\ddagger}$, for the HZ → HE conversion of PBHA, deduced by line shape simulation, considering the exchange between the two positions (Figure 5). Possible exchange with trace water can be discarded, since dried solvent was used. The k_V values are concentration dependent, providing an additional indication that this process could not be represented by a single first-order reaction. The presence of dimers in the system can be inferred from the concentration dependence of the apparent activation enthalpy of the overall process depicted in Scheme 1.

Again, the application of the Eyring equation to the data of Table 1 shows that the activation entropy decreases with increasing PBHA concentration until becoming negative for the highest concentration, which is consistent with displacement to the left of the equilibrium of Scheme 1 with increasing PBHA concentration.

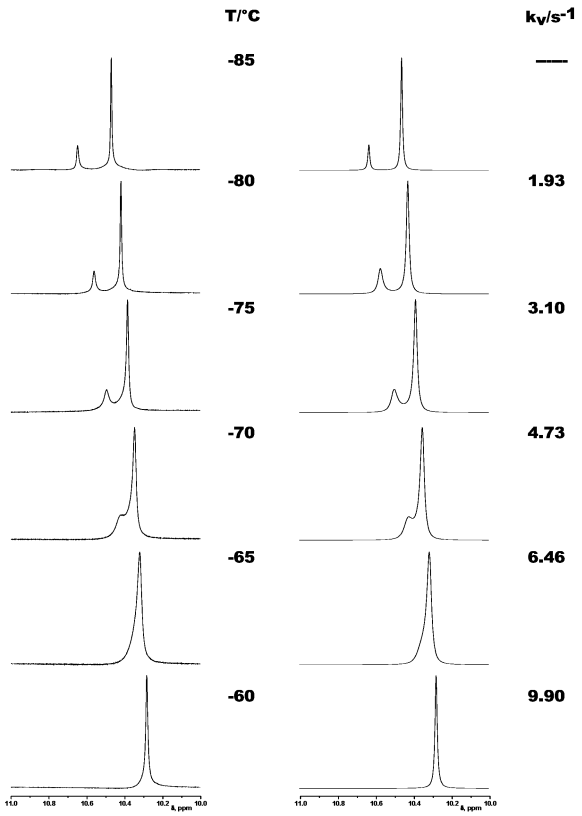


Figure 5. Left: experimental signals associated with the N(OH) proton of PBHA at different temperatures. $C_{PBHA} = 0.29$ M. The two peaks are ascribed to the HZ → HE transition. Right: simulation obtained with the k_V (s^{-1}) rate constants associated with the above transition. The low- and high-intensity peaks correspond, respectively, to HZ and HE hydroxamate hydrogens.

Equilibria in Aqueous Solution. (a) Acid Dissociation Constant. Within the ordinary pH range PBHA behaves as a simple monoprotic acid whose dissociation is represented by reaction 1. So far, the pK_{HA} values published appear to

$$HA \rightleftharpoons A^- + H^+ \quad (1)$$

be rather scattered ($pK_{HA} = 8.55$,[30] 6.63,[31] 8.0,[32] and 8.22[33] in water); therefore, we have reinvestigated equilibrium 1 by UV titrations at ionic strength 0.2 M and different temperatures. The absorbance−pH data pairs are analyzed according to the relationship

$$A = \frac{A_{A-} - A_{HA}}{1 + 10^{-mpH + mpK_{HA}}} + A_{HA} \quad (2)$$

where A is the absorbance measured during titration, A_{A^-} and

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Table 2. Acid Dissociation Constant of PBHA (pK_{HA}) at Different Temperatures and Thermodynamic Parameters from vant'Hoff Analysis ($I = 0.2$ M)

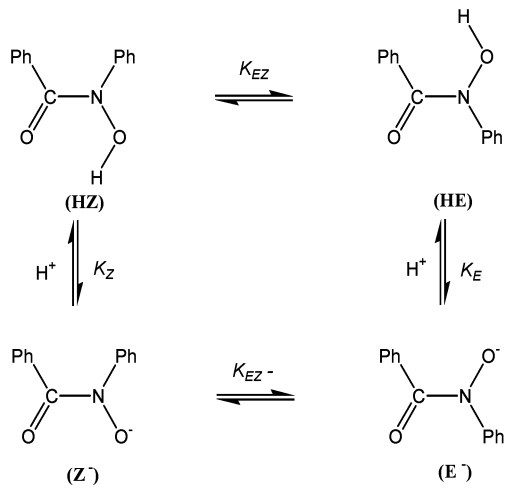
T (°C)	pK_{HA}	$\Delta S°$ (J K^{-1} mol^{-1})	$\Delta H°$ (kJ mol^{-1})
5	8.73 ± 0.11		
15	8.63 ± 0.09		
25	8.50 ± 0.10		
	8.53 ± 0.13[a]		
35	8.35 ± 0.12		
45	8.28 ± 0.13		
		-95 ± 4	20.1 ± 0.8

[a] From the proton exchange reaction HL + In ⇌ HIn + L, where L and HL refer to PBHA and In and HIn refer to thymol blue.

A_{HA} stand for the absorbances of the anion and of the undissociated acid, respectively, K_{HA} is the acid dissociation constant, and the parameter m is close to unity in aqueous solutions of pH 3−11.[34] An iterative minimization procedure allows the A_{A^-}, A_{HA}, and pK_{HA} values to be determined. Table 2 lists the pK_{HA} values at different temperatures along with the $\Delta H°$ and $\Delta S°$ values of reaction 1. To ensure that the changes of the UV spectra during titration are due to only the H^+ dissociation, the pK_{HA} value for PBHA was evaluated as well by titration at $\lambda = 585$ nm by coupling to reaction 1 the dissociation reaction of thymol blue, an indicator whose dissociation constant ($pK_{HIn} = 8.50$ at 25 °C and $I = 0.2$ M)[35] is close to that of PBHA. The equilibrium constant for the proton exchange between the indicator and PBHA ($K = K_{HA}/K_{HIn}$) was evaluated following a procedure described earlier,[35] and from the K_{HIn} value the K_{HA} value has been derived (Table 2).

The distribution of PBHA among different isomer species makes it difficult to decide which of these forms preferentially dissociates. Assuming that dimer formation in aqueous solution could be neglected at the low PBHA concentrations used in the titrations, the H^+ dissociation process can be depicted as in Scheme 2, according to which the macroscopic

Scheme 2



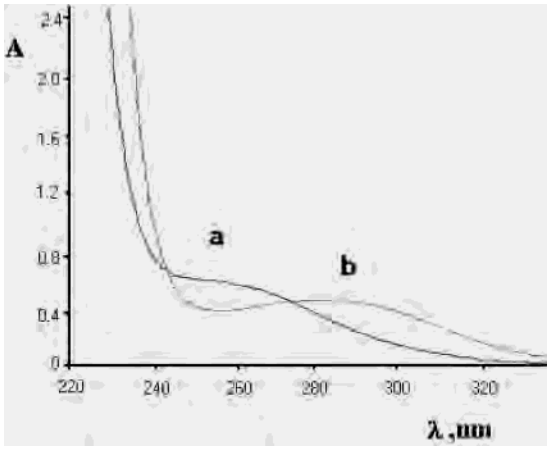


Figure 6. Absorption spectra of the PBHA/Ni(II) system in aqueous solution at pH 6.5, $I = 0.2$ M, and $T = 25$ °C: (a) 4×10^{-5} M PBHA; (b) 4×10^{-5} M PBHA + 5×10^{-3} M $Ni(ClO_4)_2$.

dissociation constant K_{HA} results in the combination of one of the two acid dissociation constants K_Z and K_E and of the ratios $K_{EZ} = [HE]/[HZ]$ and $K_{EZ^-} = [E^-]/[Z^-]$:

$$K_{HA} = K_Z(1 + K_{EZ^-})/(1 + K_{EZ}) \quad (3)$$

The kinetic experiments have shown that in water $[E^-] \ll [Z^-]$ and $[HE] \ll [HZ]$; therefore, it turns out that $K_{HA} \approx K_Z$ in aqueous solution.

(b) Complex Formation Constants. The bathochromic shift observed in the UV spectrum of the acid upon metal addition (Figure 6) reveals interaction of PBHA with Ni(II). Under excess metal conditions ($C_M \gg C_L$) only 1/1 complexes are formed. At constant pH the equilibria could be described by the apparent complex formation reaction 4, where $[M_f] = [M^{2+}]$, $[L_f] = [HL] + [L^-]$, and $[ML_T] = [MHL^{2+}] + [ML^+]$.

$$M_f + L_f \rightleftharpoons ML_T \quad (4)$$

The equilibrium constant of reaction 4, K_{app}, was evaluated[36] at different pH values by spectrophotometric titration (280 nm) of PBHA with $Ni(ClO_4)_2$. The K_{app} values were found to decrease as $[H^+]$ increases. The dependence of K_{app} on $[H^+]$ is given by eq 5

$$K_{app}/\alpha\beta = K_{MHL} + K_{ML}K_{HA}/[H^+] \quad (5)$$

which has been derived according to Scheme 3.

Scheme 3

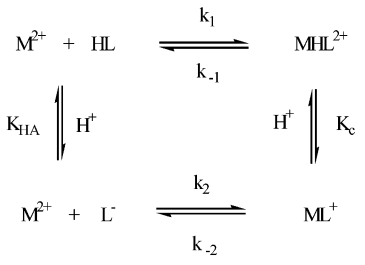


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Table 3. Reaction Parameters for the Complex Formation Reaction between Nickel(II) and PBHA (I = 0.2 M, T = 25 °C)

$10^{-2}k_1$ ($M^{-1}s^{-1}$)	k_{-1} (s^{-1})	$10^{-4}k_2$ ($M^{-1}s^{-1}$)	k_{-2} (s^{-1})	$10^{-2}K_{MHL}$ (M^{-1})	$10^{-4}K_{ML}$ (M^{-1})	$10^{9}K_{HA}$ (M)
7.1 ± 0.3	4.9 ± 0.6	5.5 ± 0.7	1.2 ± 0.1	1.5 ± 0.2	5.2 ± 0.7	2.9 ± 0.4
$10^{6}K_C$ (M)	$\Delta H_f^{\ddagger}$ (kJ mol^{-1})	$\Delta S_f^{\ddagger}$ (J mol^{-1} K^{-1})	$\Delta H_d^{\ddagger}$ (kJ mol^{-1})	$\Delta S_d^{\ddagger}$ (J mol^{-1} K^{-1})	$\Delta H_{app}°$ (kJ mol^{-1})	$\Delta S_{app}°$ (J mol^{-1} K^{-1})
1.0 ± 0.1	67.3 ± 0.8	31	58 ± 2	−46	9.2[a] 8.8[b]	75[a] 88[b]

[a] From activation parameters. [b] From van't Hoff analysis.

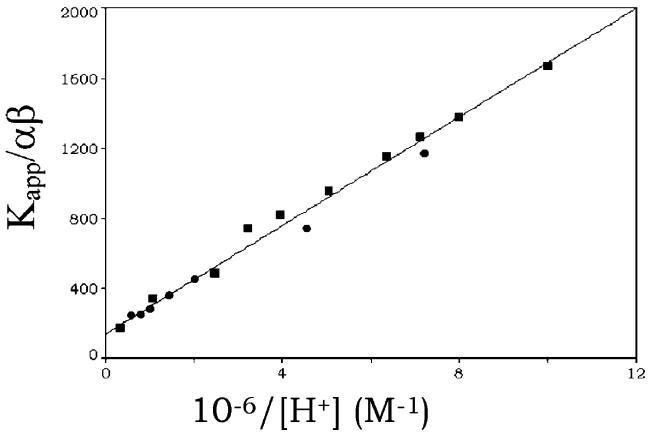

Figure 7. Dependence of the apparent equilibrium constant, K_{app}, on the reciprocal hydrogen ion concentration for the PBHA/Ni(II) system at I = 0.2 M and T = 25 °C: (●) kinetic data, (■) thermodynamic data.

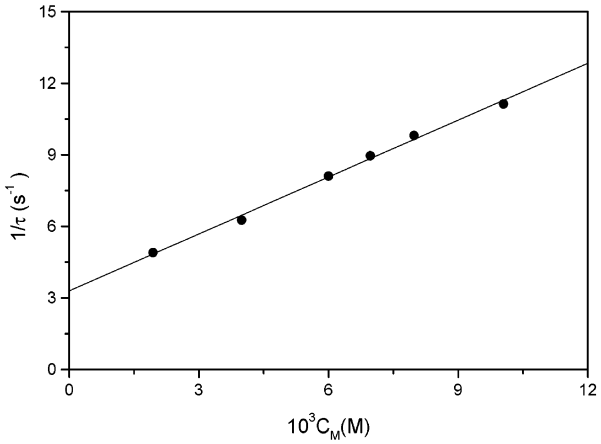

Figure 8. Dependence of the reciprocal the relaxation time on the metal ion concentration for the PBHA/Ni(II) system. $[H^+] = 1.3 \times 10^{-6}$ M, I = 0.2 M, and T = 25 °C.

$K_{MHL} = k_1/k_{-1}$ and $K_{ML} = k_2/k_{-2}$ are the equilibrium constants of steps 6 and 7, respectively, $\alpha = [HL]/[L_f]$, and $\beta = [M^{2+}]/[M_f]$. Figure 7 shows that the dependence of $K_{app}/\alpha\beta$ upon $1/[H^+]$ is linear, in agreement with eq 5; the intercept yields the K_{MHL} value, and the slope divided by the acid dissociation constant of PBHA yields K_{ML}. The values of the equilibrium parameters are quoted in Table 3.

Kinetics in Aqueous Solution. The kinetic curves for complex formation are single exponential, meaning that the apparent reaction 4 adequately represents the kinetic behavior of the PBHA/Ni(II) system. For $C_M \gg C_L$, the time constant $1/\tau$ is independent of the PBHA concentration, but depends on the metal concentration according to eq 8, as shown in

$$\frac{1}{\tau} = k_d + k_f C_M \qquad (8)$$

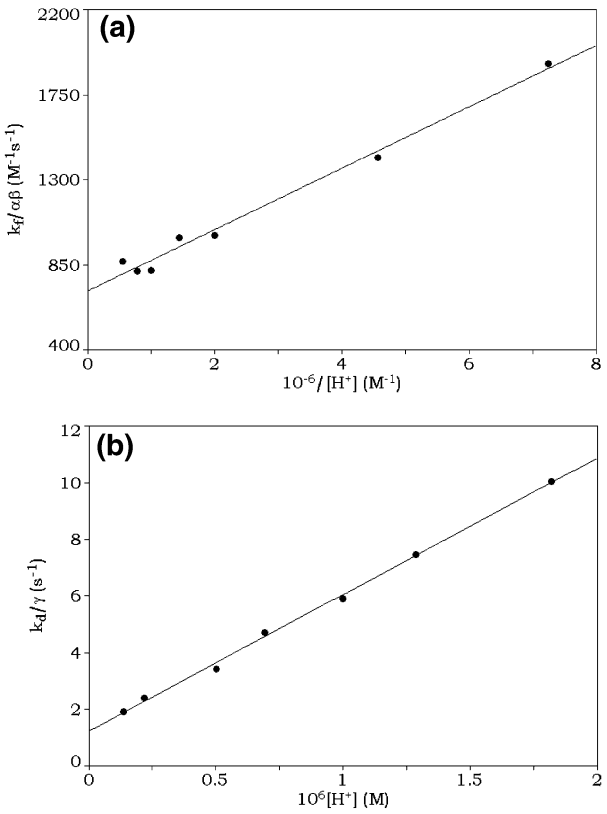

Figure 9. Dependence of the apparent kinetic constants on the medium acidity for the PBHA/Ni(II) system at I = 0.2 M and T = 25 °C: (a) complex formation; (b) complex dissociation.

Figure 8. Both the k_f and k_d values were found to depend on the medium acidity. According to Scheme 3 the dependence of the apparent rate constants on $[H^+]$ is given by the relationships

$$k_f = (k_1 + k_2 K_{HA}/[H^+])\alpha\beta \qquad (9)$$

and

$$k_d = (k_{-2} + k_{-1}[H^+]/K_C)\gamma \qquad (10)$$

where $\gamma = [ML]/[ML_T] \cong 1$. The $k_f/\alpha\beta$ vs $1/[H^+]$ plot (Figure 9a) enables one to obtain k_1 and k_2, the forward rate constants of steps 6 and 7, respectively, whereas the k_d/γ vs $[H^+]$ plot (Figure 9b) yields k_{-1}/K_C and k_{-2}. Table 3 lists the values of the individual rate constants.

The temperature dependence of K_{app}, k_f, and k_d was investigated at pH 6.5 and at 15, 25, 35, and 45 °C. The reaction parameters are listed in Table 3.

Discussion

NMR. The NMR results reveal that PBHA in acetone and methanol solutions is distributed between a *trans* (HE) isomer

and a *cis* (HZ) isomer. The latter, in turn, forms a dimer in acetone. The [HE]/[HZ] ratio, [HZ] being the sum of the dimer and monomer concentrations, changes from 80/20 in acetone to 50/50 in methanol. NMR measurements in water cannot be performed due to the scarce solubility of PBHA in this solvent. ^{1}H NMR spectra were not capable of directly indicating which of the two peaks appearing around 10 ppm should be assigned to the HE and HZ forms. However, the concentration and temperature effects on the low-intensity peak strongly suggest that this should be associated with HZ, since this is the only form capable of giving dimers. Hence, we can conclude that in acetone the HZ form is the minority. On going from acetone to methanol and then to water, it is conceivable to assume that the dimer population could be small in methanol and negligible in water, since protic solvents tend to form hydrogen bonds with the monomer; if noticeable amounts of dimer were present in aqueous solution, then both the equilibrium and the kinetic experiments would become affected.

Kinetics. The rate-limiting step of the metal binding reaction of Ni(II) to PBHA is the loss of water from the inner coordination shell of Ni^{2+}, following the formation of an outer-sphere complex.[37] Subsequent ring closure is generally rapid in an aqueous medium. The rate of loss of water is identified with the rate of solvent exchange, k_{H_2O}; for Ni^{2+} $k_{H_2O} = 3.1 \times 10^4$ s^{-1}.[38] On the other hand, the equilibrium constant, K_{OS}, for the step of formation of the outer-sphere complex can be calculated by the Fuoss equation[39] with a maximum uncertainty of 300%, due to the arbitrary choice of the distance of closest approach of the reactants. According to the above-described I_d mechanism, the second-order rate constant of a complex formation reaction is $k = K_{OS}k^*$. This relationship allows k^* to be evaluated from the measured value of k and the calculated value of K_{OS}. For "normal" ligands the value of k^* should be similar to k_{H_2O}, the main source of uncertainty arising from K_{OS}. This feature is common to all complex formation reactions between normal ligands and Ni^{2+}. We have chosen Ni^{2+} as a candidate to bind PBHA since any deviation from the relatioship $k^* = k/K_{OS} = k_{H_2O}$ should be ascribed to a particular behavior of the ligand. Using for the distance of closest approach the usual value of 5×10^{-8} cm, one obtains for the binding step involving L^- $K_{OS} = 1.6$ M^{-1} (25 °C, $I = 0.1$ M) and $k_2^* = 3.4 \times 10^4$ s^{-1}. The excellent agreement of k_2^* with k_{H_2O} indicates that Ni^{2+} reacts with the anion of PBHA "normally"; namely, the rate-determining step of the binding process is the loss of the first water molecule from $Ni(H_2O)_6^{2+}$, while the subsequent step of chelation is relatively fast. This behavior implies that in water L^- should be present mainly in the Z form, the only one capable of undergoing chelate formation. Actually, owing to the partial double bond character of the C−N bond, the change of the ligand configuration from E to Z should be slow, as shown by the NMR measurements of Table 1. On the basis of this observation, if substantial amounts of the E form were present, then the reaction rate would tend to become independent of [Ni^{2+}] at the highest metal concentrations, contrary to the results shown in Figure 8.

Concerning the Ni(II) binding to HL, it turns out that $k_1^* = 2.4 \times 10^3$ s^{-1}, a value 13 times lower than that of k_{H_2O}. One could not ascribe this large reduction of rate to a slow ring closure, since this process has been found to be fast with L^-. An alternative mechanism, based on slow HL and MHL deprotonation, has been proposed to explain the reduced rate of binding of the neutral acetohydroxamic acid to Ni^{2+}, Co^{2+}, and Zn^{2+}.[40] This mechanism does not apply to our system since in 3×10^{-3} M sodium cacodylate buffer the vertical steps of Scheme 3 are very fast. In particular, the rate constant for the $MHL^{2+} + B^- \rightarrow ML^+ + HB$ step is diffusion controlled, since this process is thermodynamically favored ($pK_{HB} = 6.19$)[26] and $pK_{MHL} = 5.99$.

Once the mechanisms outlined above have been ruled out, a plausible explanation which reasonably accounts for the reduced reactivity of HL is based on the distribution of the protonated PBHA species among different forms, only one of which is capable of reacting with Ni^{2+}. Since it is reasonable to exclude dimer formation in aqueous solution and since the HE form seems to be negligible, a reaction scheme fitting the experimental data is shown in Scheme 4,

Scheme 4

$$HZ_c \overset{K_{CO}}{\rightleftharpoons} HZ_o \xrightarrow{Ni^{2+}} MHL^{2+}$$

where HZ_C is an HZ form in which the reaction site is blocked by an intra- or an intermolecular (water-involving) hydrogen bond and HZ_O is the corresponding HZ open form. If HZ_C prevails and HZ_O reacts with Ni^{2+} at a normal rate, then $k_1^* = k_{H_2O}K_{CO}/(1 + K_{CO})$. With the above quoted values of k_1^* and k_{H_2O} one obtains $K_{CO} = 0.07$. This means that in water 93% of the PBHA is present in the closed Z configuration. Similar behavior has been found in reactions of Ni^{2+} and Co^{2+} with salicylates,[41,42] where, owing to intramolecular hydrogen bonding, the binding rates are about 1000 times below their normal values.

Acknowledgment. Financial support by Junta de Castilla y León (Spain), Project BU26-02, Ministerio de Ciencia y Tecnología (Spain), Project BQU2002-01061, and COFIN 2002 is gratefully acknowledged. We are indebted to Prof. L. Di Bari (Università di Pisa) and Dr. Delgado (Universidad de Burgos) for their useful comments.

IC034161Q

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