Inorg. Chem. **1985**, *24*, 2717-2720 2717

Comparison of the titration data for Zn^{2+} and Cu^{2+} complexes of **1** and **3** reveal an intriguing phenomenon. Although a similar coordination environment is expected in the metal complexes of **1** and **3**, a large difference exists in the pK_a of the metal-bound waters. In particular, titrations at 50 °C have previously shown a pK_a of 7.1 for **1**-Cu^{2+}-OH_2, while a pK_a for **1**-Zn^{2+}-OH_2 could not be observed due to precipitation.[6,7] That **1**-Cu^{2+}-OH_2 and **3**-Cu^{2+}-OH_2 have similar coordination geometries is evidenced by the fact that λ_{max} for each complex is about 735 nm.[19] Thus, the lower pK_a values for the metal-bound water in Zn^{2+} and Cu^{2+} complexes of **3** must be due in part to factors other than the net Lewis acidity of the metal ion. Differential solvation effects in **1**-M^{2+} and **3**-M^{2+} is one attractive explanation since the metal-bound water in **3**-M^{2+}-OH_2 may lie in a more hydrophobic environment in the boat conformation of the azalactam than in the chair. Hydrophobic effects have been shown to affect metal-bound water acidity in Zn^{2+} and Cu^{2+} complexes[21] and have been proposed to account for lowered pK_a for a zinc-bound water in the zinc metalloenzyme carbonic anhydrase.[22] An electrophilic interaction of the nearby amide carbonyl in **3**-M^{2+}-OH_2 with the metal-bound water could also lower the pK_a.

In summary, the development here of a Zn^{2+} model complex that exhibits a rate enhancement of 10^7 for Zn^{2+}-promoted amide hydrolysis and a pK_a of 7 for a zinc-bound water offers compelling evidence that a "zinc hydroxide" mechanism is viable in this model system. A similar mechanism should be considered for CPA. Indications that the Glu-270 may assist in the deprotonation of the zinc-bound water in CPA[23,24] are consistent with this suggestion.

Acknowledgment. Partial support of this work by the National Science Foundation is gratefully acknowledged.

Registry No. **1**-Cu^{2+}-OH_2, 69896-33-9; **3**, 97278-41-6; **3**-Cu^{2+}-OH_2, 97278-39-2; **3**-Zn^{2+}-OH_2, 97278-40-5; **4**, 81879-64-3; **5**, 97278-42-7; **6**, 97278-43-8; 6-(bromomethyl)-2-(ethoxycarbonyl)pyridine, 97278-44-9; proteinase, 9001-92-7.

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Articles

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Kinetic Study of the Complexing of 2-Aminophenol Derivatives by Nickel(II)

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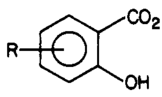
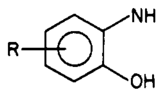
Received November 19, 1984

The systems 2-aminophenol + $Ni(OH_2)_6^{2+}$ and 2-aminophenol-4-sulfonic acid have been investigated by measuring the ligand acid dissociation constants, monoligand complex formation constants, and the kinetics of complexing for pH 6.4-7.0 in 0.30 M $LiClO_4$ at 25 °C. The kinetic results indicate that first-bond formation at the OH function is rate limiting with a rate constant of 2.7×10^3 M^{-1} s^{-1} and 2.9×10^3 M^{-1} s^{-1} for 2-aminophenol and 2-aminophenol-4-sulfonate, respectively. The results are compared and rationalized with respect to earlier studies of salicylate derivatives and acetohydroxamic acid.

A recent kinetic study[1] of the reaction of $Ni(OH_2)_6^{2+}$ with salicylate derivatives (I) provided information on the reactivity of these systems and the acidity of the coordinated OH. This information should be useful in the interpretation of results on 2-aminophenol derivatives (II), where the initial reaction site (OH or NH_2) is less certain and intramolecular hydrogen bonding might reduce the reactivity of II. The dissociative ion-pair mechanism[2] would lead one to predict that the anion I should react more rapidly than the neutral ligand II. As will be seen, the simple formation rate constants are actually in the opposite order because the rate-limiting step is chelate ring closing with I but first-bond formation with II.



I



II

The complex formation constants with 2-aminophenol and 2-aminophenol-4-sulfonic acid have been measured because the earlier values of Sims[3] and Perrin[4] have been put into question by recent results.[5]

Experimental Section

Materials. 2-Aminophenol (Aldrich Chemical Co.) and 2-aminophenol-4-sulfonic acid (Riedel-de Haenag-Seelze) were recrystallized twice by dissolution in aqueous $NaHCO_3$ followed by addition of HCl to pH 4, under an argon atmosphere. The solid was collected and dried under vacuum.

Anal. Calcd for 2-aminophenol (C_6H_7NO): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.90; H, 6.46; N, 12.73. Calcd for 2-aminophenol-4-sulfonic acid hemihydrate ($C_6H_7NO_4S{\cdot}{}^1/_2H_2O$): C, 36.40; H, 4.04; N, 7.06. Found: C, 36.16; H, 4.08; N, 6.93.

Aqueous nickel(II) perchlorate was prepared from nickel carbonate and perchloric acid and standardized as described previously.[6] The buffers PIPES (Aldrich) and MES (Sigma) were used as supplied.

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(2) Wilkins, R. G. *Acc. Chem. Res.* **1970**, *3*, 408; *Pure Appl. Chem.* **1973**, *33*, 583.

(3) Sims, P. *J. Chem. Soc.* **1959**, 3648.

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(5) Rola-Szustkiewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1977**, *25*, 179.

(6) Bajue, S. A.; Dasgupta, P.; Jordan, R. B.; Lalor, G. C. *Inorg. Chem.* **1985**, *24*, 726.

0020-1669/85/1324-2717$01.50/0

Aqueous lithium perchlorate was prepared from Li_2CO_3 and $HClO_4$ and standardized by titration of protons eluted from Dowex 50W-X8 (H^+) resin.

Potentiometric Titrations. The ligand acid dissociation constants and complex formation constants with Ni(II) were determined by standard titration under an argon atmosphere in a vessel sealed with rubber serum caps. Solid 2-aminophenol was dissolved in a deoxygenated solution of $LiClO_4$ and $HClO_4$, and $Ni(ClO_4)_2$ if necessary, and titrated with 2×10^{-2} M NaOH in $LiClO_4$ at the same ionic strength. The titration curves were analyzed by least-squares methods to determine the equilibrium constants.

Kinetic Measurements. On the stopped flow system, a solution containing $Ni(ClO_4)_2$, buffer (1.0×10^{-2} M), lithium perchlorate (0.30 M), and bromothymol blue indicator (5×10^{-5} M) was mixed with a solution of the ligand buffer (1.0×10^{-2} M) and lithium perchlorate (0.30 M). The Ni(II) concentration was always in excess of the ligand to maintain pseudo-first-order conditions. The pH of each solution was adjusted to the desired value before mixing. The reported pH is that of the solution after mixing and generally was within 0.04 unit of the initial value. The reaction was monitored by the change in the spectrum of the indicator at 620 nm. Reported rate constants are the average of five to eight replicate determinations.

Equipment. A standard Aminco-Morrow stopped-flow system was used as described previously.[7,8] Electronic spectra were recorded on a Cary 219 spectrophotometer. The pH was measured on a Corning 125 meter with a combination electrode standardized at pH 4 and 9 with commercial buffers.

Results and Discussion

The acid dissocation constants and complex formation constants, determined by potentiometric titration, are given in Table I. The constants are defined by reactions 1–3, where R ≡ H or SO_3^-. The results in Table I are in satisfactory agreement with earlier results,[3,4] considering the differences in temperature and ionic strength, but do not confirm the more recent values.[5]

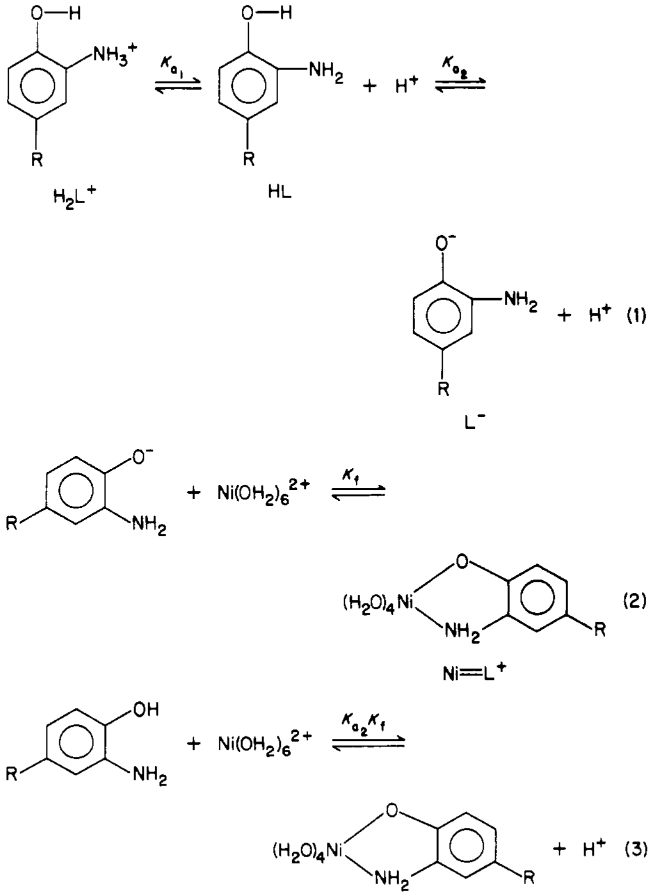

Table I. Equilibrium Constant Values (25 °C, 0.30 M $LiClO_4$)[a]

	2-aminophenol	2-aminophenol-4-sulfonate
pK_{a_1}	4.99_6 (4.816)[b]	3.89_8 (4.096)[b]
pK_{a_2}	9.58_5 (9.932)[b]	8.84_3 (9.052)[b]
$10^5K_{a_2}K_f$[a]	1.17 ± 0.17 (2.6)[c,d]	3.78 ± 1.1[d]

[a] Errors quoted are 95% confidence limits and are about twice the standard error. [b] Values from ref 4, at 20 °C and 2.5×10^{-3} to 7.5×10^{-3} M ionic strength. [c] Value from ref 3, at 20 °C and $\sim 1 \times 10^{-3}$ M ionic strength. From ref 5, log K_f = 7.25; therefore, $K_{a_2}K_f = 4.5 \times 10^{-3}$, in disagreement with previous and present results. [d] This discrepancy between $K_{a_2}K_f$ values from the kinetic and titration results can be removed if the formation constant for Ni═LH is ~ 40 M^{-1}; however, the effect of inserting this species on the quality of the data fitting is too small to assign it with any certainty.

Table II. Kinetic Data for the Reaction of Nickel(II) with 2-Aminophenol (25 °C, 0.30 M $LiClO_4$)

		k_{obsd}	
$10^3[Ni^{2+}]$, M	pH	exptl	calcd
11.17	6.47	79.5	76.4
	6.53	78.0	70.4
	6.60	68.7	64.3
	6.68	66.7	58.5
	6.82	51.7	50.5
	6.96	41.5	44.8
	7.00	42.6	43.4
	7.03	41.3	42.5
	7.14	37.0	39.6
	7.20	33.8	38.3
10.05	6.79	52.1	49.5
8.375	6.72	56.8	48.5
7.816	6.63	53.2	53.1
	6.82	39.0	41.6
	7.03	34.1	33.6
5.583	6.62	55.2	47.9
	6.74	38.5	39.9
	6.82	38.6	35.7
	6.84	43.6	34.8
	6.88	32.7	33.0
4.466	6.83	27.2	32.3
	7.09	24.0	23.1
4.02	6.66	43.4	40.8
2.233	6.87	22.1	24.6
	7.14	19.5	15.9
1.954	6.68	27.6	34.0

Table III. Kinetic Data for the Reaction of Nickel(II) with 2-Aminophenol-4-sulfonate (25 °C, 0.30 M $LiClO_4$)

		k_{obsd}	
$10^3[Ni^{2+}]$, M	pH	exptl	calcd
11.17	6.74	41.0	39.8
	6.76	46.4	39.5
	6.84	41.1	38.4
	7.00	33.5	36.7
11.08	6.82	36.0	38.4
	6.94	33.5	37.0
8.933	6.56	37.5	36.7
7.816	6.76	29.3	29.6
5.583	6.37	35.1	32.5
	6.49	28.6	28.7
	6.56	24.0	26.8
	7.00	17.4	20.2
	7.11	20.0	19.4
	7.16	20.6	19.1
	7.16	21.8	19.1
4.466	6.60	21.0	22.6
3.350	6.79	15.4	15.9
2.233	6.64	15.8	15.2
	7.02	12.0	10.2

The pseudo-first-order rate constants are given as a function of pH and $[Ni^{2+}]$ for 2-aminophenol and 2-aminophenol-4-sulfonate in Tables II and III, respectively. A consideration of the values of $K_{a_2}K_f$ (Table I) shows that the reaction does not go to completion under the experimental conditions of pH and $[Ni^{2+}]$. For example, at pH 6.68 and $[Ni^{2+}] = 1.95 \times 10^{-3}$ M, the ratio

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(7) Voss, R. H.; Jordan, R. B. *J. Am. Chem. Soc.* **1976**, *98*, 6926.
(8) Pinnell, D.; Jordan, R. B. *Inorg. Chem.* **1979**, *18*, 3191.

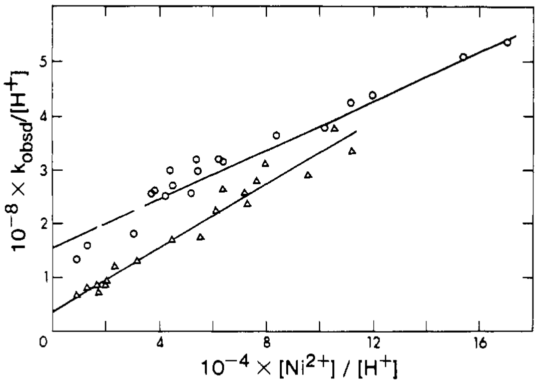
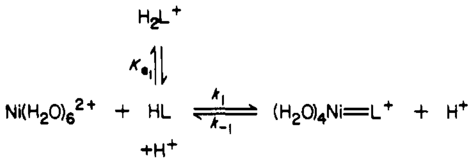
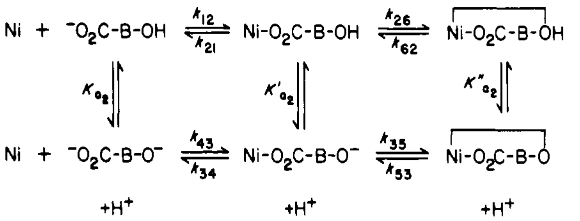


Figure 1. Variation of $k_{obsd}[H^+]^{-1}$ with $[Ni^{2+}][H^+]^{-1}$ for 2-aminophenol (○) and 2-aminophenol-4-sulfonate (△).

Scheme I



Scheme II



of complex to free 2-aminophenol is 1.1. Then, it is not surprising that the variation of the pseudo-first-order rate constant with $[H^+]$ and $[Ni^{2+}]$ is given by

$$k_{obsd} = k_f[Ni^{2+}] + k_r[H^+] \qquad (4)$$

as expected for a system coming to equilibrium. In Tables II and III the experimental values of k_{obsd} are compared to those calculated from least-squares fits to eq 4. The adequacy of eq 4 is shown also by the plots of $k_{obsd}[H^+]^{-1}$ vs. $[Ni^{2+}][H^+]^{-1}$ shown in Figure 1.

For 2-aminophenol, the least-squares fit gives $k_f = (2.65 \pm 0.50) \times 10^3$ M^{-1} s^{-1} and $k_r = (1.38 \pm 0.15) \times 10^8$ M^{-1} s^{-1}, and for 2-aminophenol-4-sulfonate the values are $(2.95 \pm 0.45) \times 10^3$ M^{-1} s^{-1} and $(3.78 \pm 1.2) \times 10^7$ M^{-1} s^{-1}, respectively.

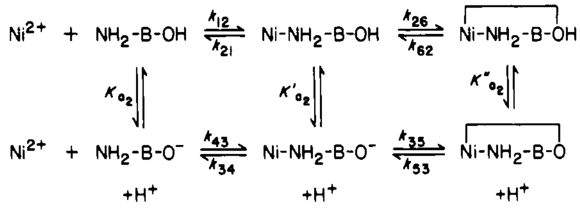
The simplest method of describing the system is shown in Scheme I. Since $K_{a_1} >> [H^+] >> K_{a_2}$, Scheme I gives

$$k_{obsd} = k_1[Ni^{2+}] + k_{-1}[H^+] \qquad (5)$$

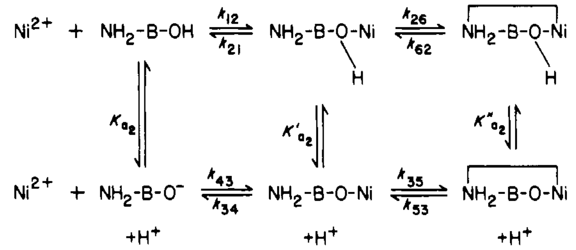
Then k_f (eq 4) is equivalent to k_1, and the value of $\sim 3 \times 10^3$ M^{-1} s^{-1} for the two ligands is in the typical range[2] for complexing of a neutral ligand by $Ni(OH_2)_6^{2+}$, as expected for the dissociative ion-pair (DIP) mechanism.[2]

This type of analysis when applied to the $Ni(OH_2)_6^{2+}$–salicylate system gives $k_f \sim 2.5 \times 10^2$ M^{-1} s^{-1}, about 10 times less than for the 2-aminophenols. This relative rate difference is the opposite of that expected because the salicylate anion should be more reactive than the neutral 2-aminophenol according to the DIP mechanism. It might be argued that hydrogen bonding inhibits the complexation rate for salicylate but is not effective in the 2-aminophenol systems. However, a number of previous examples[1,7,9] have shown that the simple representation given by Scheme I is neither realistic nor informative in assessing the mechanism of chelate formation.

Scheme III



Scheme IV



In the salicylate system it has been shown[1] that one must consider a more detailed reaction sequence as shown in Scheme II, where $B \equiv C_6H_4$.

If a steady state is assumed for the monodendate intermediates and if $k_{12}[H^+] >> k_{43}K_{a_2}$ since $[H^+] >> K'_{a_2}$ then it has been shown that

$$k_{obsd} = \frac{k_{12}[H^+](k_{26}[H^+] + k_{35}K'_{a_2})}{(k_{21} + k_{26})[H^+] + k_{35}K'_{a_2}} \times \left(\frac{[Ni^{2+}]}{[H^+]} + \frac{K''_{a_2}}{K_{a_2}K_f(K''_{a_2} + [H^+])}\right) \qquad (6)$$

Further arguments for the salicylate system indicate that $k_{26}[H^+] >> k_{35}K'_{a_2}$, so that

$$k_{obsd} = \frac{k_{12}k_{26}}{k_{21} + k_{26}}\left([Ni^{2+}] + \frac{K''_{a_2}[H^+]}{K_{a_2}K_f(K''_{a_2} + [H^+])}\right) \qquad (7)$$

Comparison of eq 3 and 7 shows that $k_f = k_{12}k_{26}/(k_{21} + k_{26})$ for salicylate, and the small value of k_f ($\sim 2.5 \times 10^2$ M^{-1} s^{-1}) is rationalized if $k_{21} >> k_{26}$.

An analogous reaction sequence for 2-aminophenols is shown in Scheme III.

The analysis leading to eq 7 should apply also to Scheme III. The only modification might be that $K''_{a_2} >> [H^+]$, because K_{a_2} for the 2-aminophenols ($\sim 10^{-9}$ M) is larger than that for salicylate ($<10^{-10}$ M) and $K''_{a_2} \approx 6 \times 10^{-7}$ for the latter. Then eq 7 simplifies to

$$k_{obsd} = \frac{k_{12}k_{26}}{k_{21} + k_{26}}\left([Ni^{2+}] + \frac{[H^+]}{K_{a_2}K_f}\right) \qquad (8)$$

Comparison to eq 3 shows that $k_f = k_{12}k_{26}/(k_{21} + k_{26}) \approx 2.8 \times 10^3$ M^{-1} s^{-1}. Since the magnitude is that expected for k_{12} for a neutral ligand reacting with nickel(II),[2] the implication is that $k_{26} >> k_{21}$ and $k_f \sim k_{12} \sim 2.8 \times 10^3$ M^{-1} s^{-1} for the 2-aminophenols.

The requirement of Schemes II and III that $k_{26} >> k_{21}$ for 2-aminophenols but $k_{21} >> k_{26}$ for salicylates is not really very reasonable. The rate of the ring-closing step (k_{26}) is probably controlled by coordinated water elimination and should be about the same in both systems.[10] Then one must say that k_{21} for

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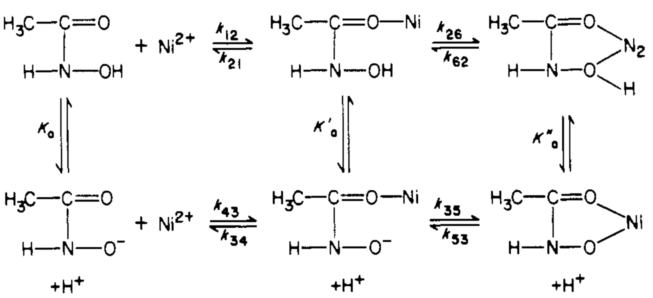
(9) Cavasino, F. P. *J. Phys. Chem.* **1965**, *69*, 4380.

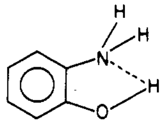
(10) A reviewer has suggested that k_{26} might be larger for 2-aminophenols because of a labilizing effect of coordinated NH_2 on coordinated water release, as has been observed with ammonia and ethylenediamine. This seems unlikely if the amine pK_a values are used as a measure of electron donation and thereby labilizing influence. The aromatic amines (pK_a = 4–5) are much poorer bases than aliphatic amines (pK_a = 9–10).

Scheme V



salicylate is larger than k_{21} for 2-aminophenol, but this seems contrary to steric and charge effects of B–CO_2^- compared to those of B–NH_2.

A reasonable explanation of the difference between 2-aminophenols and salicylates can be given if a different reaction sequence is used for the aminophenols. This sequence acknowledges the probability that the 2-aminophenol conjugate base may have a hydrogen-bonded structure such as



Then the unshared electron pair on NH_2 is less available for coordination to nickel(II) than one of the two electron pairs on the phenolic oxygen, and the latter is the site of first-bond formation as shown in Scheme IV. Now first-bond formation is at OH, and K'_{a_2} is for proton dissociation from a B–OH coordinated to Ni^{2+}. This should greatly increase K'_{a_2} in Scheme IV compared to K'_{a_2} in Scheme III, and K'_{a_2} in Scheme IV should be analogous to K''_{a_2} in Scheme II. Since the latter is $\sim 10^5$ times larger than K_{a_2} for the salicylates, one can estimate for Scheme IV that $K'_{a_2} \approx 10^5 \times 10^{-9} = 10^{-4}$ M. With this magnitude for K'_{a_2}, the experimental conditions give $K'_{a_2} >> [H^+]$, and if $k_{26} \approx k_{35}$, then $k_{35}K'_{a_2} >> k_{26}[H^+] \geq k_{21}[H^+]$, and eq 6 simplifies to

$$k_{\text{obsd}} = k_{12}\left([Ni^{2+}] + \frac{[H^+]}{K_{a_2}K_f} \right) \tag{9}$$

A comparison to eq 4 shows that $k_f \equiv k_{12}$ and k_f has the expected magnitude for a neutral ligand reacting with $Ni(OH_2)_6^{2+}$ if first-bond formation is rate limiting.[2]

In conclusion, the difference in reactivity between salicylates and 2-aminophenols with $Ni(OH_2)_6^{2+}$ can be explained by differences in the position of first-bond formation. Charge and steric effects promote first-bond formation at the CO_2^- in salicylate, while hydrogen bonding favors complexing at the OH in the 2-aminophenols.

Another system that can be analyzed similarly is the reaction of nickel(II) with acetohydroxamic acid.[11] The ligand pK_a of 9.35 is similar to that of 2-aminophenols (Table I) but the rate constant for the neutral ligand (750 M^{-1} s^{-1}) is about 4 times less. Dominey and Kustin[11] suggested that the small rate constant was due to rate-controlling proton transfer in the chelate formation. However, this seems unlikely for several reasions: (i) The rate constant for cobalt(II) is 50 times larger than that for nickel(II), although the acidity difference should be less than two times. (ii) An analysis following that of Voss and Jordan[7] (Appendix) indicates that the relative rate conditions for proton-transfer control are improbable. (iii) The 2-aminophenols appear to react "normally" but have pK_a values similar to that of acetohydroxamic acid. It seems more probable that acetohydroxamic acid is reacting by a sequence analogous to that of salicylate (Scheme II), as shown in Scheme V. The conditions leading to eq 7 should still apply, so that

$$k_f = \frac{k_{12}k_{26}}{k_{21} + k_{26}} = 750 \text{ M}^{-1} \text{ s}^{-1} \tag{10}$$

The apparent rate constant (k_f) is smaller than expected because $k_{21} > k_{26}$. If k_{12} and k_{26} have normal values of $\sim 3 \times 10^3$ and 3×10^4, then $(k_{12}/k_{21}) \approx 3.3 \times 10^{-2}$. This small value is much more consistent with expectations than that of $\gtrsim 30$ required if proton transfer is rate controlling (Appendix).

Acknowledgment. The authors are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support.

Appendix

If a steady state is assumed for monodentate intermediates in Scheme V and the proton-transfer rate constants, k_{65} and k_{56}; are defined for the K''_a step, then

$$k_{\text{exptl}} = \frac{k_{12}k_{26}k_{65}}{k_{21}(k_{62} + k_{65}) + k_{65}k_{26}}\left([Ni^{2+}] + \frac{[H^+]}{K_aK_f} \right) \tag{A.1}$$

where

$$\begin{aligned} k_{56} &= k_{-1}[H_3O^+] + k_{-2}[BuH^+] + k_{-3}[H_2O] \\ k_{65} &= k_1[H_2O] + k_2[Bu] + k_3[OH^-] \end{aligned} \tag{A.2}$$

and by definition $K''_a = k_{65}[H^+]/k_{56}$.[7] Under the conditions of Dominey and Kustin[11] no buffer was used; therefore, [Bu] = [BuH$^+$] = 0. The values of k_{-1} and k_3 should be close to the diffusion-controlled limit, $\sim 10^{10}$ M^{-1} s^{-1}, and for pH 6–7, the dominant term gives

$$k_{56} \approx k_{-1}[H_3O^+] \qquad k_{65} = k_{56}K''_a/[H_3O^+] = k_{-1}K''_a \tag{A.3}$$

Consideration of eq A.1 shows that proton transfer will influence the rate only if $k_{62} \gtrsim k_{65}$; otherwise, k_{65} cancels in eq A.1. Application of detailed balance to Scheme V and the condition $k_{62} \gtrsim k_{65}$ gives

$$k_{62} = \frac{k_{12}k_{26}K''_a}{k_{21}K_aK_f} \geq k_{-1}K''_a \tag{A.4}$$

Rearrangement, cancellation, and substitution of the values of K_aK_f (9×10^{-5}), k_{-1} (10^{10}), and k_{26} ($\sim 3 \times 10^4$) expected for water elimination on nickel(II) give

$$\frac{k_{12}}{k_{21}} \geq \frac{k_{-1}K_aK_f}{k_{26}} \approx 30 \tag{A.5}$$

This equilibrium constant is much larger than expected for nickel(II) complexing at a carbonyl oxygen.

Registry No. 2-Aminophenol, 95-55-6; 2-aminophenol-4-sulfonic acid, 98-37-3; $Ni(OH_2)_6^{2+}$, 15365-79-4.

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(11) Dominey, L. A.; Kustin, K. *Inorg. Chem.* **1984**, *23*, 103.