Contribution from the Department of Chemistry,
University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Kinetics of Complexing of Nickel(II) by Tautomeric Forms of Histamine

P. DASGUPTA and R. B. JORDAN*

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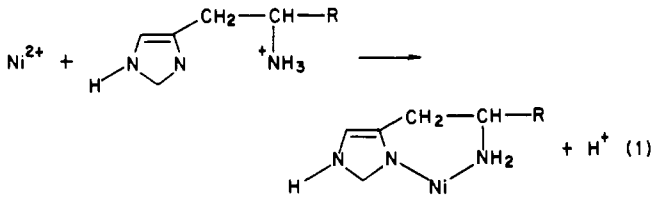
A detailed kinetic analysis of the reaction of $Ni(OH_2)_6^{2+}$ with histamine (pH 5.8–6.6, 25 °C, 0.50 M $LiClO_4$) indicates that the biphasic kinetic behavior is due to parallel complexing of the histamine tautomers deprotonated at imidazole N-1 and N-3. The N-3 complex leads to the stable chelated product, but the N-1 complex formed initially must dissociate in the slower step to give the chelated product. The rate constants for initial complexing at N-1 and N-3 are $(2.3 \pm 0.15) \times 10^3$ and $(1.4 \pm 0.5) \times 10^3$ M^{-1} s^{-1}, respectively. The formation equilibrium constant for the N-1 monodentate complex is $(7.5 \pm 0.8) \times 10^2$ M^{-1}.

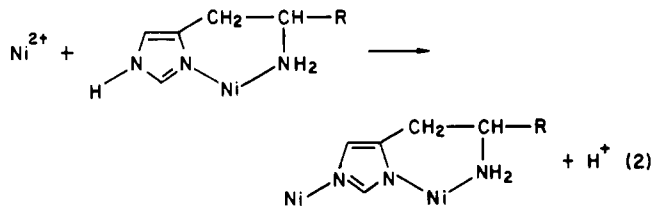
In an earlier study[1] of the complexing of $Ni(OH_2)_6^{2+}$ by histidine and histidine methyl ester, the reaction was observed to be biphasic. The faster reaction was assigned to the expected chelate formation



(1)

I

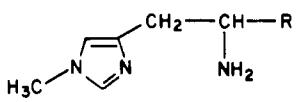
and it was proposed that the slower step was due to the following reaction



(2)

II

This proposal was supported by the later observations[2] that the 1-methyl derivatives (III) did not show any slow reaction (R ≡ $-CO_2^-$ or $-CO_2CH_3$).

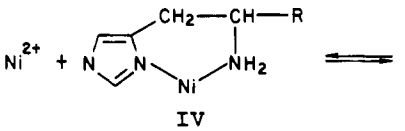


III

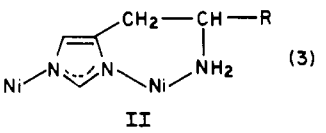
In the interim Cassatt et al.[3] found that complexing of $Ni(OH_2)_6^{2+}$ by histamine is also biphasic. The slower reaction was attributed to formation of small amounts of $Ni(hist)(OH_2)_3OH^+$ (hist = histamine), but this seems unlikely in view of the studies of the 1-methyl derivatives and the fact that this biphasic behavior seems unique to histidine derivatives.

However, there are two problems with the explanation of the slower reaction 2. First, and most serious, the biphasic behavior is not observed with imidazole; second, if reaction 2 occurs to a significant extent, the equilibrium constant for (3) must be $\gtrsim 10^5$ M^{-1},[4] but the analogous formation constant for $(H_2O)_5Ni(im)^{2+}$ (im = imidazole) is only $\sim 10^3$ M^{-1}.

Recent NMR studies on histidine[5] and histamine[6,7] show that there are significant concentrations of the two tautomeric forms



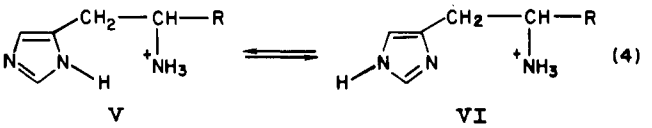
IV



(3)

II

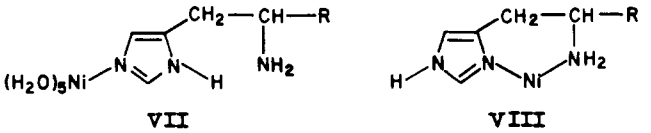
V and VI. These observations suggest another explanation for



(4)

V VI

the slower reaction when histidine derivatives are complexed by $Ni(OH_2)_6^{2+}$. Reaction with V to give VII will be a dead-end



VII VIII

process because chelation cannot occur in VII. Therefore, any VII formed initially must dissociate before it can convert to the stable chelate VIII.

To test this hypothesis, the kinetics of the reaction of $Ni(OH_2)_6^{2+}$ with histamine and 1-methylhistamine have been studied. There are several reasons for choosing histamine for this study. Since histamine shows the largest fraction (~25%) of tautomer V, the second reaction should be most evident and easy to study with histamine. Furthermore, there are no published quantitative data for the slower reaction, except that Cassatt et al.[3] state that it is independent of $[Ni^{2+}]$ for pH 6.5–7.0 and has $k \approx 2$ s^{-1}. Finally, the published data[3] for histamine relate only to the first reaction at four pH values and give an unusually large rate constant of 6×10^5 M^{-1} s^{-1}. This was attributed to an internal conjugated base (ICB) mechanism.[8] However, it has been proposed recently[9] that the rate acceleration observed with aliphatic diamines is not due to an ICB effect but results from the labilizing of coordinated water[10] by coordinated H_2NCH_2- in the monodentate intermediate. On this basis histamine should not show an unusually large complexation rate constant because the coordinated imidazole nitrogen in the monodentate intermediate should not greatly labilize the coordinated water molecules.[11]

Experimental Section

Materials. The histamine dihydrochloride (Aldrich Chemical Co, Inc.) and 1-methylhistamine (Sigma Chemical Co.) were used as supplied.

Aqueous nickel(II) perchlorate was prepared from nickel carbonate and perchloric acid and standardized as described previously.[12] The

(1) Letter, J. E., Jr.; Jordan, R. B. *Inorg. Chem.* **1971**, *10*, 2692.
(2) Letter, J. E., Jr.; Jordan, R. B. *Inorg. Chem.* **1974**, *13*, 1152.
(3) Cassatt, J. C.; Johnson, W. A.; Smith, L. M.; Wilkins, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 8399.
(4) This calculation assumes that [II]/[IV] = 0.15 for $[H^+] = 1 \times 10^{-6}$ M and $[Ni^{2+}] = 1.5 \times 10^{-2}$ M and the acid dissociation constant for I is $\leq 1 \times 10^{-10}$ M.
(5) Blomberg, F.; Maurer, W.; Ruterjans, H. *J. Am. Chem. Soc.* **1977**, *99*, 8149.
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Table I. Kinetic Results for the Reaction of $Ni(OH_2)_6^{2+}$ with Histamine (25 °C, 0.50 M $LiClO_4$)[a]

pH	$10^2[Ni^{2+}]$, M	γ_-, s^{-1} [b]	γ_+, s^{-1} [b]
5.78	4.026		1.36 (1.27)
5.81	4.026	10.6 (11.0)	1.59 (1.30)
5.83	4.026	11.1 (11.3)	1.16 (1.32)
5.91	2.013		1.35 (1.29)
5.94	2.013	8.45 (8.03)	1.23 (1.32)
5.94	4.026	14.1 (13.7)	1.44 (1.44)
5.97	6.002		1.52 (1.51)
5.98	2.013		1.42 (1.37)
5.99	2.013		1.47 (1.38)
5.99	4.026		1.48 (1.49)
6.04	2.013		1.64 (1.43)
6.15	8.052		1.67 (1.69)
6.16	2.013	10.4 (10.9)	1.21 (1.56)
6.16	4.026		1.65 (1.65)
6.17	6.039		1.66 (1.69)
6.18	2.013	12.1 (11.2)	1.60 (1.58)
6.45	2.013		1.92 (1.80)
6.47	4.026		1.82 (1.88)
6.55	1.098	10.0 (10.5)	1.98 (1.76)
6.58	2.013		1.95 (1.88)
6.60	4.026		2.02 (1.95)

[a] When γ_- is not given, γ_+ only was determined from the last 30% of the reaction. [b] Observed values are given first, with calculated values in parentheses.

buffer MES (Sigma) was used as supplied. Aqueous lithium perchlorate was prepared by dissolving lithium perchlorate (AMED Drug and Chemical Co.) in a minimum volume of water and filtering through filter paper. Lithium perchlorate was standardized by titration of protons eluted from Dowex 50W-X8 (H^+) resin.

Kinetic Measurement. A standard Aminco-Morrow stopped-flow system was used to mix a solution containing $Ni(ClO_4)_2$, buffer (5.00×10^{-2} M), lithium perchlorate (0.50 M), and bromothymol blue indicator (5×10^{-5} M) with a solution of the ligand, buffer (5.0×10^{-2} M), and lithium perchlorate (0.50 M). The Ni^{2+} concentration was always in excess of the ligand to maintain pseudo-first-order conditions. The pH of each solution[12] was adjusted to the desired value before mixing. The reported pH is that of the solution after mixing and generally was within 0.04 pH unit of the initial value. The change in transmittance of the indicator due to the small pH change was monitored at 620 nm.

The rate constants for monophasic reactions or the slower step of biphasic reactions were determined by an analogue comparison technique described elsewhere.[13] For biphasic reactions the data was stored on a Tracor-Northern NS-570 signal averager and then output to a Hewlett-Packard 7004B-XY recorder. The recording rate was changed for two or three traces to give similar resolution of the time axis for the faster and slower reactions. The data was hand digitized, with 25–30 points taken over a reaction time up to 1.25 s, and then fitted by nonlinear least squares as described in the next section.

Results and Discussion

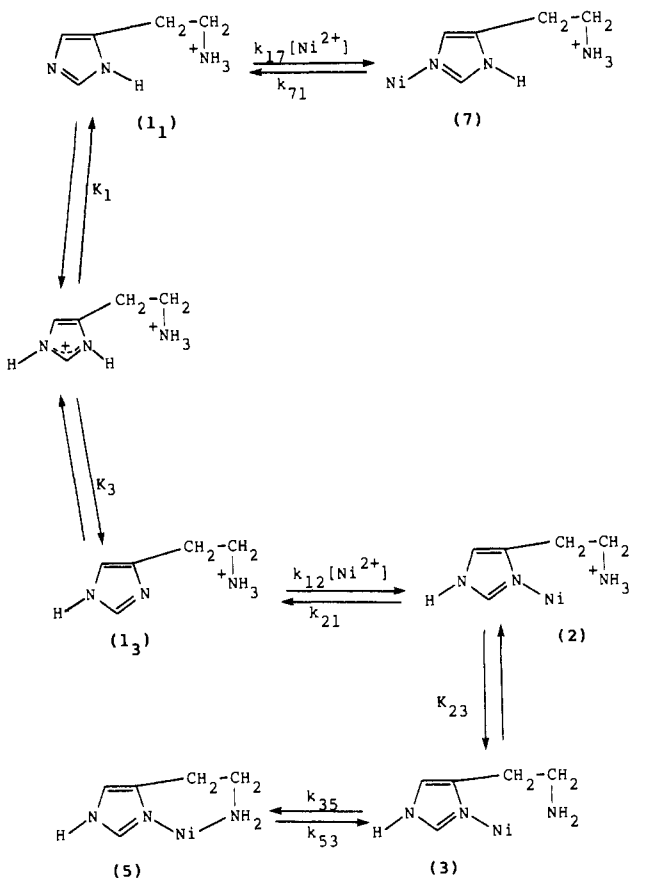
The qualitative observations of this study are similar to those of Cassatt et al.[3] in that reaction of $Ni(OH_2)_6^{2+}$ with histamine is biphasic. However, the two processes give rather similar absorbance changes, contrary to the implication of Cassatt et al. that the slower process is a minor one.

Under our conditions, the rates of the two reactions were not sufficiently different for them to be analyzed separately. The rate constant for the slower reaction could be determined by an analogue comparison technique[13] if only about the last 30% of reaction was used. This was not possible with the faster reaction because the infinite-time absorbance was too undefined. To obtain the rate constants for both reactions, the data were digitized and fitted by nonlinear least squares to the equation

$$A_t = A_\infty + A_1 e^{-\gamma_- t} + A_2 e^{-\gamma_+ t} \qquad (5)$$

The values of γ_- and γ_+ from the least-squares fits[14] and γ_+ from the analogue comparison are given in Table I.

Scheme I



The magnitude of γ_+ at pH 6.6 and its insensitivity to $[Ni^{2+}]$ at pH 5.94, 6.15–6.18, and 6.45–6.47 are consistent with the qualitative observations of Cassatt et al.[3] However, the more extended pH range reported here shows that γ_+ does increase with increasing pH. It is noteworthy that the absorbance change of the indicator for the slower reaction with histamine is ~30% of the total absorbance change. This compares to ~5–10% for the histidine and histidine methyl ester systems studied previously. This is consistent with the proposal that the slower reaction is associated with tautomer V, since this form is much more prevalent with histamine than with histidine.[5-7]

The above conclusion is also consistent with the observation that the reaction of $Ni(OH_2)_6^{2+}$ with 1-methylhistamine is *monophasic*. This shows again, consistent with previous studies on 1-methylhistidine,[2] that the biphasic character is associated with reaction of N-1 of the imidazole function. The study with 1-methylhistidine was much more limited because of the cost of the ligand. These results are given in Table II and will be discussed quantitatively later.

The biphasic nature of the histamine reaction can be rationalized in terms of Scheme I. The faster reaction involves parallel formation of monodentate (**7**) and chelate (**5**), and the slower reaction is dissociation of the monodentate (**7**) with fast formation of the thermodynamically stable chelate product (**5**).

The theoretical rate law for Scheme I has been developed under the assumption that species **2** and **3** are at a steady state and that the proton-transfer steps K_1, K_3, and K_{23} are rapidly established equilibria. Then the observed rate constants (γ_+, γ_-) are the negative roots of a quadratic equation and have the expected form

$$\gamma_\pm = \frac{b \pm (b^2 - 4c)^{1/2}}{2} \qquad (6)$$

where

$$b = X_1 + X_2 + X_3 + X_4 \qquad c = X_2(X_3 + X_4) + X_1X_4$$

and

(12) Bajue, S. A.; Dasgupta, P.; Jordan, R. B.; Lalor, G. C. *Inorg. Chem.* **1985**, *24*, 726.
(13) Pinnell, D.; Jordan, R. B. *Inorg. Chem.* **1979**, *18*, 3191.
(14) The value of A_∞ was held fixed at the value between 3.8 and 4.0 s, which is over 7 half-times for the slower reaction.

$$X_1 = \frac{k_{12}k_{35}K_{23}K_3[Ni^{2+}]}{(k_{21}[H^+] + k_{35}K_{23})(K_{a1} + [H^+])}$$

$$X_2 = \frac{k_{12}k_{35}K_{23}[H^+]}{(k_{21}[H^+] + k_{35}K_{23})(K_{a2}K_f)}$$

$$X_3 = \frac{k_{17}K_1[Ni^{2+}]}{K_{a1} + [H^+]} \qquad X_4 = \frac{k_{17}}{K_7} = k_{71}$$

$$K_{a1} = \frac{[\mathbf{1}_1 + \mathbf{1}_3][H^+]}{[LH_2^{2+}]} \qquad K_7 = \frac{[7]}{[\mathbf{1}_1]} = \frac{k_{17}}{k_{71}}$$

$$K_{a2} = \frac{[L][H^+]}{[HL]} \qquad K_f = \frac{[Ni{=}L^{2+}]}{[Ni^{2+}][L]}$$

The $[H^+]$ and $[Ni^{2+}]$ dependence of γ_+ and γ_- can be understood in a useful qualitative way if the binomial expansion is applied to eq 6. Then

$$\gamma_+ \approx \frac{c}{b} \qquad \gamma_- \approx b \tag{7}$$

Further analysis using probable values for the rate and equilibrium constants shows that, for pH >6.2, the order of terms in b and c is such that

$$X_1 > X_3 > X_4 > X_2 \tag{8}$$

Then

$$\gamma_- \approx b \approx X_1 + X_3$$
$$\gamma_+ \approx \frac{c}{b} \approx \frac{X_2X_3 + X_1X_4}{X_1 + X_3} \approx X_4 = k_{71} \tag{9}$$

This conforms to the intuitive expectations described in the previous paragraph in that the larger rate constant (γ_-) depends on k_{12} and k_{17} while the smaller one depends on k_{71}. However, the approximations used are too poor to be of quantitaive use. This is most easily apparent when it is noted that the pH dependence of γ_+ is not explained by eq 9. Furthermore, the approximations are not at all valid for pH $\lesssim$6.2. Therefore, it has been necessary to fit the data to the complete form of eq 6. Since γ_+ and γ_- depend on many of the same variables, it is useful to fit them simultaneously by defining

$$\gamma = J_+\gamma_+ + J_-\gamma_- \tag{10}$$

where J_+ and J_- are two dummy independent variables such that, if $\gamma = \gamma_-$, then $J_+ = 0$ and $J_- = 1$, and if $\gamma = \gamma_+$, when $J_+ = 1$ and $J_- = 0$. Then γ_+ and γ_- can be fitted simultaneously with the four independent variables $[Ni^+]$, $[H^+]$, J_+, and J_-. The values of K_{a1}, K_{a2}, and K_f determined by Gergely and Sovago[15] were used.

The least-squares analysis of the data gave a good fit, as can be seen from the comparison of the observed and calculated values in Table I. The parameters obtained and their standard deviations are as follows: $k_{12} = 1.4\ (\pm 0.5) \times 10^3\ M^{-1}\ s^{-1}$; $k_{17} = 2.3\ (\pm 0.15) \times 10^3\ M^{-1}\ s^{-1}$; $K_7 = 7.5\ (\pm 0.8) \times 10^2\ M^{-1}$; $k_{35}K_{23}/k_{21} = 4.5\ (\pm 1.6) \times 10^{-7}$ M.

The values of the parameters are reasonable when compared to analogous simpler systems. For example, k_{17} is similar to the values for imidazole and *N*-methylimidazole of 2.8×10^3 and $4.5 \times 10^3\ M^{-1}\ s^{-1}$, respectively.[2] The value of k_{12} can be expected to be smaller than k_{17} because of the steric and charge effects of the $-CH_2CH_2NH_3^+$ substituent on the formation of the precursor "ion pair". The formation equilibrium constant for the $(H_2O)_5Ni(im)^{2+}$ complex is $\sim 10^3\ M^{-1}$ and should be similar to K_7, as found. The magnitude of $k_{35}K_{23}/k_{21}$ can be estimated to see if the experimental value is reasonable. One expects K_{23} to be larger than K_{a2} for histamine (1.5×10^{-10} M); k_{35} should be similar to the water-exchange rate on $Ni(OH_2)_6^{2+}$ ($3 \times 10^4\ s^{-1}$) and k_{21} should be larger than the dissociation rate of $(H_2O)_5Ni(im)^{2+}$ ($2\ s^{-1}$) because of the basicity differences (pK_{a1} of 7.1 vs. 6.2 for hisamine). Therefore, $k_{35}K_{23}/k_{21} \approx (3 \times 10^4)(3 \times 10^{-10})/20 = 4.5 \times 10^{-7}$ M in fortuitous exact agreement with the observed value.

Table II. Kinetic Results for the Reaction of $Ni(OH_2)_6^{2+}$ with 1-Methylhistamine[a] (25 °C, 0.50 M $LiClO_4$)

pH	$10^2[Ni^{2+}]$, M	k, s^{-1}
6.05	2.013	3.76
6.03	4.026	7.02
6.04	6.039	10.3

[a] The 1-methylhistamine concentration is 2.18×10^{-3} M at pH 6.05 and 1.04×10^{-3} M otherwise.

The results for 1-methylhistamine are consistent with those for histamine if the value of k_{21} is changed in proportion to K_{a1} (8.1×10^{-7} and 6.7×10^{-7}, respectively) and K_{23} is changed in proportion to K_{a2} (0.94×10^{-10} and 1.3×10^{-10}, respectively). Then $k_{34}K_{23}/k_{21}$ for 1-methylhistamine is $\sim 2.7 \times 10^{-7}$. The rate law for 1-methylhistidine is easily derived from eq 6 by noting that $k_{17} = 0$, from which $c = 0$ and $b = X_1 + X_2 = k_{obsd}$. Therefore

$$k_{obsd} = \frac{k_{12}k_{35}K_{23}/k_{21}}{[H^+] + k_{35}K_{23}/k_{21}}\left\{\frac{K_{a1}[Ni^{2+}]}{K_{a1} + [H^+]} + \frac{[H^+]}{K_{a2}K_f}\right\} \tag{11}$$

As predicted from this equation, a plot of k_{obsd} vs. $[Ni^{2+}]$ at constant $[H^+]$ is linear and the slope to intercept ratio can be used to calculate $K_f = 7.4 \times 10^6\ M^{-1}$. This is very similar to the value of $7.08 \times 10^6\ M^{-1}$ for histamine.[15] Without further assumptions, the k_{obsd} values in Table II and eq 11 can be combined to calculate k_{12}. With increasing $[Ni^{2+}]$ the calculated k_{12} values are 1.59×10^3, 1.55×10^3, and $1.54 \times 10^3\ M^{-1}\ s^{-1}$, respectively. These values are constant, and the k_{12} value is quite similar to that given above for histamine as one would expect. The important feature of 1-methylhistamine is that reaction with $Ni(OH_2)_6^{2+}$ is not biphasic, but the quantitative similarity of the kinetic results provides further support to the proposed reaction scheme for histamine.

The observed rate constants of Cassatt et al.[3] (for histamine) are 1.5–2 times smaller than those predicted from the present study. This may be due to the effect of the slower reaction on the final absorbance values used to calculate the rate constants in the earlier study. The unusually large rate constant ($6 \times 10^5\ M^{-1}\ s^{-1}$) for histamine free base in the previous study is not confirmed by the present results. At pH 6.6 the free-base path is contributing 65% to k_{obsd} according to Cassatt et al. but the present data can be fitted by completely neglecting the reaction of the free base. This does not mean that the free base is unreactive but simply that its contribution is small at pH 6–7 because pK_{a2} is so large that, with normal reactivity, it will not contribute even at pH 7. This confirms the earlier analysis,[9] which predicts that histamine free base should not show unusual reactivity.

Finally, two aspects of these results can be mentioned. The explanation for the biphasic behavior given in Scheme I removes the apparently anomalous normal behavior of imidazole implied in the earlier explanations.[1,2] Since the two nitrogens in imidazole are equivalent, it would not be expected to give biphasic kinetics.

A recent *T*-jump study[17] has shown that the cobalt(II)–histamine system also shows biphasic kinetics. These observations might be explained by Scheme I, although this seems to have been discarded by Feliz and Capparelli[17] only because the species analogous to **7** had not been observed in previous studies at equilibrium.

Acknowledgment. We wish to acknowledge the financial support for this work from the Natural Sciences and Engineering Research Council of Canada.

Registry No. Ni, 7440-02-0; histamine, 51-45-6.

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