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Kinetic Study of the Complexing of Nickel(II) by *N*-Methylimidazole and 1- and 3-Methylhistidine

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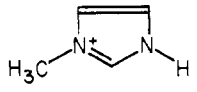
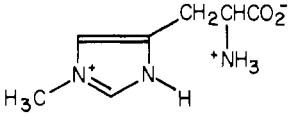
The kinetics of complexation of nickel(II) by *N*-methylimidazole, 3-methylhistidine, and 1-methylhistidine have been studied at 23.7° in 0.10 *M* KNO_3. For *N*-methylimidazole the protonated cation ($k = 2.3 \times 10^2\ M^{-1}\ sec^{-1}$) and neutral molecule ($k = 4.5 \times 10^3\ M^{-1}\ sec^{-1}$) are observed to react with nickel(II). Only reaction of the neutral form of 3-methylhistidine ($k = 2.1 \times 10^3\ M^{-1}\ sec^{-1}$) was detected. This system was different from the previously studied histidine in that it did not show a second slow reaction. This observation is consistent with the previous proposal that the second reaction involves coordination of a second nickel(II) at the pyrrole nitrogen of the coordinated imidazole part of histidine. A two-step reaction was observed for 1-methylhistidine, the first step being attributed to complexing at the imidazole part of the molecule and the second step involving coordination of a second nickel(II) at the glycine part of 1-methylhistidine. Thus the latter ligand acts as two complexing units and does not show any tendency to chelate in a histidine-like manner.

Introduction

A previous study[1] in this laboratory of the reaction of nickel(II) with histidine and related ligands indicated that initial complexing of nickel takes place at an imidazole nitrogen of histidine. It was also found that the rate constants showed a correlation with net ligand charge, as expected for a dissociative ion-pair mechanism.[2] The present work explores this correlation further with the methyl-substituted derivatives *N*-methylimidazole (I), 3-methylhistidine- (II), and 1-methylhistidine (III).



I



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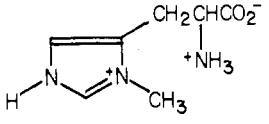
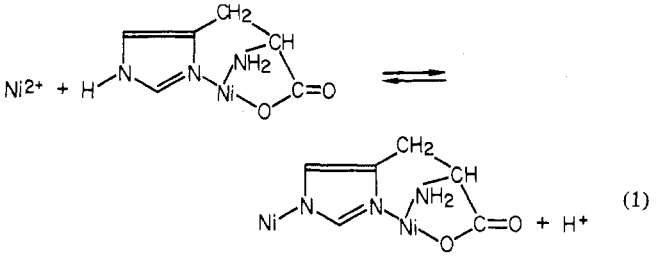


III

Another important reason for studying these ligands was to determine the nature of a second slower reaction which was observed[1] between nickel(II) and histidine and between nickel(II) and histidine methyl ester. This slower reaction is rather difficult to study kinetically because it produces only about 10% of the absorbance change associated with the reaction. As a result it is not possible to obtain very precise kinetic data for the second step. Therefore it seemed more profitable to study the chemically modified ligands in the hope that their qualitative behavior would indicate the site involved in the second step.

It should be noted that the kinetic results are obtained by monitoring the hydrogen ion released with nickel(II) in about tenfold molecular excess over ligand. The earlier study indicated that the second reaction was first order in nickel(II) and involved the release of about 10% of the hydrogen ion produced in the first step. The rate constants for the first step clearly show that it involves complexing at an imidazole nitrogen ($pK_a \approx 6$) rather than the amino nitrogen ($pK_a \approx 9$).

It was originally proposed[1] that the second reaction involved formation of a binuclear species according to the reaction

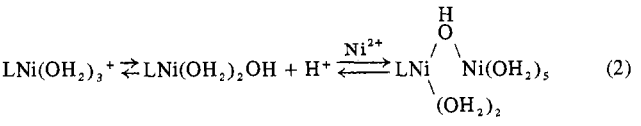


(1)

If this is the case, then no second reaction should be observed with 3-methylhistidine because the CH_3 group would inhibit addition of the second nickel(II), and no hydrogen ion would be released in any case. It may be noted that if reaction 1 proceeds about 10% at $[H^+] = 1.5 \times 10^{-7}\ M$ and $[Ni^{2+}] = 1.5 \times 10^{-2}\ M$, then the equilibrium constant is $\sim 10^{-6}$. If a K_a of $\sim 10^{-7}$ is taken for the species on the left, then a normal formation constant of $\sim 10\ M$ is calculated. As expected this is smaller than the analogous value of $\sim 2 \times 10^3\ M$ for imidazole.

Other explanations for the second reaction should also be mentioned. First of all it might seem that formation of the bis complex could explain the second reaction. However, the stability constants for the histidine[3] and methyl ester[4] systems indicate that, under our experimental conditions of ~10-fold excess nickel(II) at pH 6–7, the amount of bis complex is $\gtrsim$100 times less than the mono complex. The amount of hydrogen ion released on formation of this small amount of bis complex could not be detected in our experiments and is at least an order of magnitude less than the amount observed to be produced by the second reaction. However, if these estimates are incorrect, then 3-methylhistidine should show behavior similar to that of histidine and its methyl ester.

In principle, the second reaction could be caused by hydrolysis and polymerization reactions. If the tridendate histidine ligand is represented by L, then one could envisage the reactions



(2)

(1) J. E. Letter, Jr., and R. B. Jordan, *Inorg. Chem.*, 10, 2692 (1971).

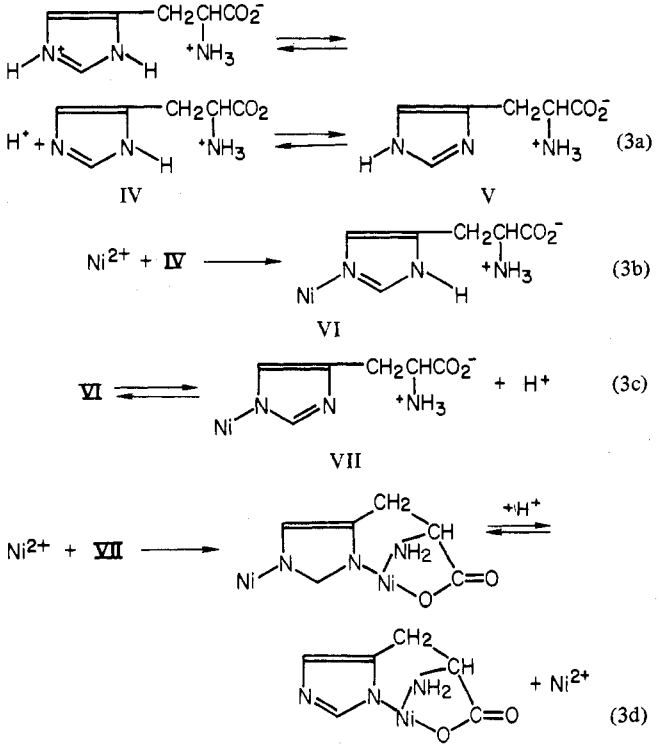
(2) (a) K. Kustin and J. Swinehart, *Progr. Inorg. Chem.*, 13, 107 (1970); (b) R. G. Wilkins, *Accounts Chem. Res.*, 3, 408 (1970).

(3) D. R. Williams, *J. Chem. Soc. A*, 1550 (1970).

(4) R. W. Hay and P. J. Morris, *J. Chem. Soc. A*, 1518 (1971).

The equilibrium constant for the hydrolysis equilibrium is probably about equal to that of $Ni(OH_2)_6^{2+}$ ($K_a \approx 10^{-10}$ *M*), in which case proton transfer to water, the forward reaction in the first equilibrium in reaction 2, could have a rate like the observed second reaction. However, the basic buffer component (lutidine) would provide a general base catalyst and make the first step in reaction 2 too fast to measure. In addition this first step would produce far too little hydrogen ion to be detectable unless the hydrolysis constant is two orders of magnitude larger than our estimate. If polymerization provides the driving force for the reaction, then the product of the hydrolysis and polymerization equilibrium constants must be $\sim 5 \times 10^{-7}$ to generate the required amount of hydrogen ion under our experimental conditions. This would seem to require that both constants be rather high for a nickel(II) system. However, if 3-methylhistidine shows the second reaction, this explanation would remain a possibility.

Another potential mechanism involves complexation of nickel(II) at the 3-nitrogen atom in the first step. This could be followed by ionization of the imidazole proton and then attack of a second nickel(II) to produce the tridendate product. (See eq 3a-d.) This scheme is included



primarily for completeness and for pointing out the possible effect of different modes of ionization of histidine (*i.e.*, IV and V). The second reaction with histidine cannot be explained by this mechanism because the second step must release an amount of hydrogen ion at least equal to that from the first step, and possibly greater depending on the position of the final equilibrium. This mechanism also appears unlikely since recent ^{13}C nmr studies[5] indicate that V is greatly favored over IV for histidine, and one would have to propose that IV is much more reactive toward nickel(II) to overcome this unfavorable equilibrium.

In summary, the study of 3-methylhistidine should serve either to support or to eliminate reaction 1 as the source of the slower reaction observed with histidine and its methyl ester. If the 3-methyl derivative shows a slower reaction step, then one would have to look more quantitatively at the hydrolysis-polymerization and bis complex formation mechanisms, or perhaps search for other paths for binding of nickel(II) to histidine systems.

In the latter connection the study of 1-methylhistidine might prove useful. Models indicate that this ligand cannot be brought into a configuration to allow both the 3 nitrogen and the amino nitrogen to coordinate to nickel(II). Therefore this ligand is much more likely to react *via* a path analogous to eq 3a-d and could provide rate constants useful in testing such a mechanism.

Experimental Section

The *N*-methylimidazole (Aldrich Chemical Co.), L-1-methylhistidine (Calbiochem), L-3-methylhistidine (Calbiochem), Bromothymol Blue (British Drug Houses), and 2,6-lutidine (Eastman Organic Chemicals) were used as supplied. The solutions of $Ni(NO_3)_2 \cdot 6H_2O$ (May and Baker) were analyzed for nickel(II) by EDTA titration as described previously.[1]

The kinetic measurements were made on an Aminco-Morrow stopped-flow system by monitoring the change in transmittance of the indicator, Bromothymol Blue ($\sim 10^{-5}$ *M*), at 620 nm. The reaction half-times, determined from the usual semilogarithmic plot of absorbance change *vs.* time, were used to calculate the observed rate constant. Normally six to eight runs were done at each set of concentration conditions and the results averaged to give the reported value. During the reaction the buffer (2,6-lutidine) limited the pH change to $\lesssim 0.1$ pH unit; therefore the pH is reported as an average value. As in the previous study blank experiments indicated a small absorbance change when buffer and indicator were mixed with ligand. This change was less than 1% of that normally observed and was too slow ($t_{1/2} \approx 2$ sec) to interfere with the analyses of the major reaction.

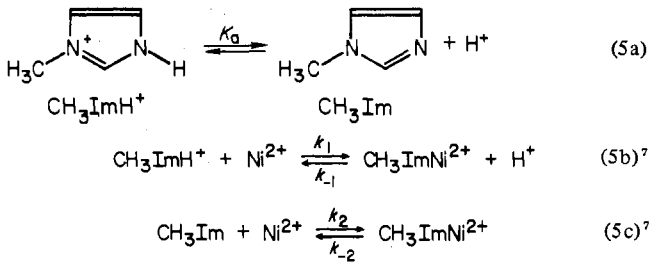
The acid dissociation constants of 3-methylhistidine were determined at 24.0 ± 0.2° in 0.1 *M* KNO_3 by titration of 10^{-3} *M* amino acid with 0.100 *M* sodium hydroxide. The pH was recorded on a Beckman Expandomatic pH meter with a 2 pH unit full-scale expansion. The dissociation constants given are the average determined from three titration curves.[6] The acid dissociation constants of the ligands used and of some other histidine derivatives are given in Table I.

Results and Discussion

All kinetic runs were carried out with a large molar excess of nickel(II) over ligand, and the observed rate constant was calculated from the equation

$$k_{obsd} = 0.693/[Ni^{2+}]t_{1/2} \qquad (4)$$

***N*-Methylimidazole.** The kinetic plots for this system were linear for at least 90% of the reaction. The variation of k_{obsd} with hydrogen ion (Table II) is consistent with the reaction scheme



(5) W. F. Reynolds, I. R. Peat, M. H. Freedman, and J. R. Lyerla, Jr., *J. Amer. Chem. Soc.*, 95, 328 (1973). Note that this paper uses the IUPAC numbering system for histidine which is opposite to the common biochemical system used in the present work.

(6) J. E. Letter, Jr., and J. E. Bauman, Jr., *J. Amer. Chem. Soc.*, 92, 437 (1970).

(7) R. G. Wilkins (private communication) has pointed out that we incorrectly neglected the reverse reaction in our earlier work[1] on imidazole. More extensive work (J. E. Letter, Jr., unpublished data) and inclusion of the reverse reactions give rate constants for the imidazole system of $k_1 = 2 \times 10^2\ M^{-1}\ sec^{-1}$ and $k_2 = 2.8 \times 10^3\ M^{-1}\ sec^{-1}$. Only the k_1 value is significantly altered from ref 1.

If the first reaction is a rapid equilibrium, then the rate of disappearance of free methylimidazole is given by

$$-d([CH_3ImH] + [CH_3Im])/dt = (k_1[CH_3ImH] + k_2[CH_3Im])[Ni] - (k_{-1}[H] + k_{-2})[NiCH_3Im] \quad (6)$$

Then since the initial concentration

$$([CH_3ImH] + [CH_3Im])_0 = [NiCH_3Im] + [CH_3ImH] + [CH_3Im] \quad (7)$$

and at equilibrium

$$[CH_3ImH]_e + [CH_3Im]_e + [NiCH_3Im]_e = ([CH_3IH] + [CH_3Im])_0 \quad (8)$$

and from the general relationships

$$([CH_3ImH] + [CH_3Im])_0 = \frac{K_a + [H]}{[H]}[CH_3ImH] = \frac{K_a + [H]}{K_a}[CH_3Im] \quad (9)$$

and

$$k_1/k_{-1} = k_2K_a/k_{-2} \quad (10)$$

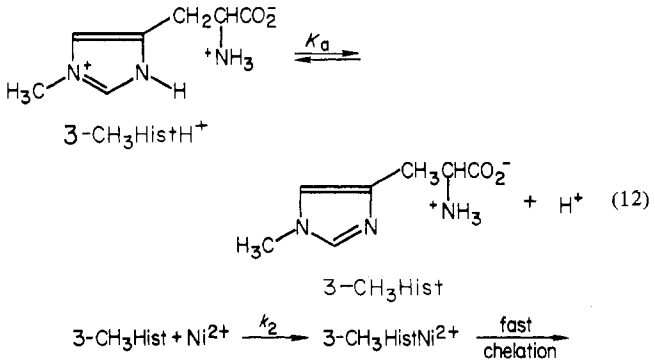
it can be shown that

$$k_{obsd}[Ni^{2+}] = \left(\frac{k_1[H^+] + k_2K_a}{K_a + [H^+]}\right)[Ni^{2+}] + k_{-2} + k_{-1}[H^+] \quad (11)$$

where k_{obsd} is defined by eq 4.

A preliminary analysis indicated that $k_{-1}[H^+] \ll k_{obsd}$ $[Ni^{2+}]$[8] under our experimental conditions (pH $\gtrsim$6), in which case eq 11 can be rearranged to a form in which, at constant $[Ni^{2+}]$, a plot of $k_{obsd}(K_a + [H^+])$ *vs.* $[H^+]$ should be linear with slope $(k_1[Ni^{2+}] + k_{-2})$ and intercept $(k_2K_a[Ni^{2+}] + k_{-2}K_a)$. The values of $k_2 = 4.45 \times 10^3\ M^{-1}\ sec^{-1}$, $k_{-2} = \sim 2.5$, and $k_1 = 2.3 \times 10^2\ M^{-1}\ sec^{-1}$ yield the calculated k_{obsd} values given in parentheses in Table II.

3-Methylhistidine. The kinetic plots for this system were linear for at least 90% reaction. The experimental results of the study of the pH dependence of k_{obsd} are given in Table II. These results are consistent with the reaction scheme



(12)

For this scheme a plot of $k_{obsd}(K_a + [H^+])[H^+]^{-1}$ *vs.* $[H^+]^{-1}$, where $K_a = 1.62 \times 10^{-6}\ M$,[9] should be linear with a zero intercept as shown in Figure 1. From the slope of this line a value for k_2 of $2.1 \times 10^3\ M^{-1}\ sec^{-1}$ can be calculated.

(8) The final results confirm this approximation since k_{-1} calculated through eq 10 is $\sim 2 \times 10^6\ M^{-1}\ sec^{-1}$.

(9) The value measured in this work at 25° in 0.10 *M* KNO_3 agrees with that of R. W. Cowgill given in Table I.

Table I. Summary of Acid Dissociation Constants

Ligand	pK_a Imidazole	pK_a Amino	Ref
N-Methylimidazole	7.20		*a*
Histidine	6.17	9.21	*b*
3-Methylhistidine	5.79	9.30	*c*
1-Methylhistidine	6.58	8.60	*c*
1,3-Dimethylhistidine		7.95	*c*

[a] N. C. Li, J. M. White, and E. Doody, *J. Amer. Chem. Soc.*, 76, 6219 (1954); at 25° in 0.12 *M* KNO_3. [b] J. L. Meyer and J. E. Bauman, Jr., *ibid.*, 92, 4210 (1970); at 25° in 0.16 *M* KNO_3. [c] R. W. Cowgill, *ibid.*, 79, 2249 (1957); at an unspecified temperature in 0.1 *M* KCl.

Table II. Kinetic Results for Complexation of Nickel(II) by 1-Methylimidazole and 3-Methylhistidine (0.10 *M* KNO_3, 23.7°)[a]

10^3·[ligand], *M*	10^2·$[Ni^{2+}]$, *M*	Av pH	$10^{-3}k_{obsd}$,[b] $M^{-1}\ sec^{-1}$
	N-Methylimidazole Ligand		
2.51	2.76	5.98	0.65 (0.56)
1.26	1.04	6.19	0.98 (0.85)
1.10	1.49	6.20	0.78 (0.71)
1.10	1.49	6.25	0.82 (0.81)
2.51	2.76	6.43	1.05 (0.93)
1.10	1.49	6.46	1.05 (1.00)
1.26	1.04	6.58	1.21 (1.29)
1.26	1.04	6.69	1.33 (1.46)
2.51	2.76	6.69	1.22 (1.31)
2.51	2.76	6.82	1.64 (1.56)
	3-Methylhistidine Ligand		
0.97	2.76	5.95	1.05
1.34	1.04	5.99	1.29
0.97	2.76	6.20	1.40
1.34	1.04	6.22	1.60
0.97	2.76	6.36	1.60
1.34	1.04	6.61	1.96

[a] The buffer was 0.015 *M* 2,6-lutidine in all cases. [b] Values given are the average from six to eight runs for each set of concentration conditions.

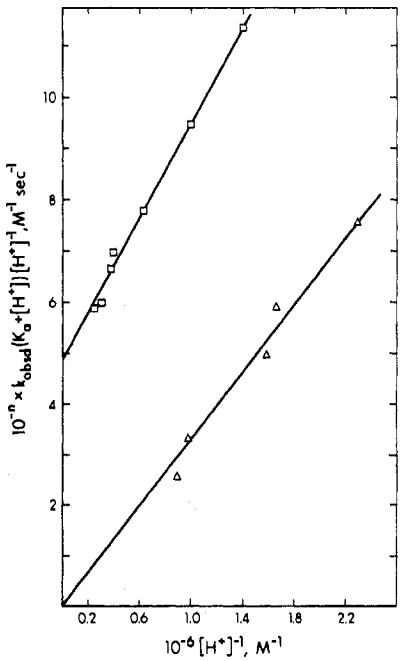


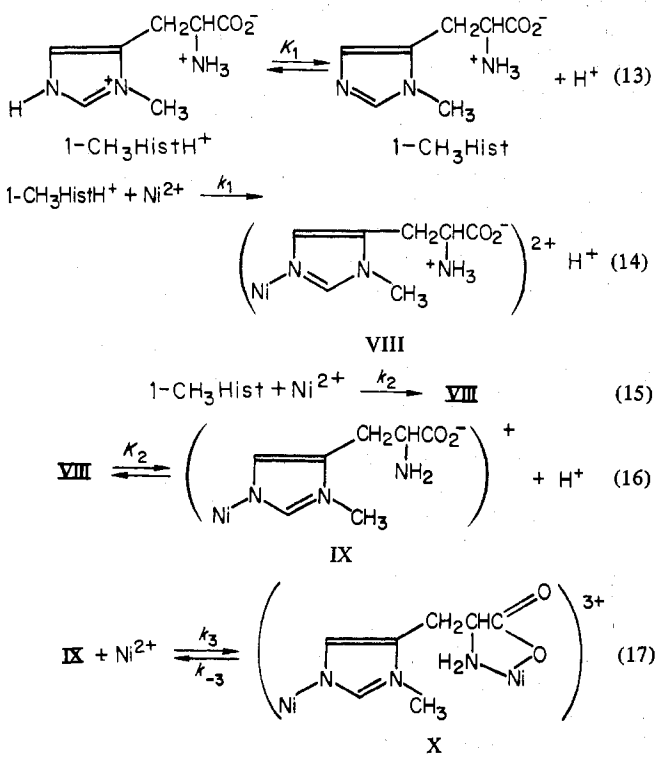
Figure 1. Variation of $10^{-n}k_{obsd}(K_a + [H^+])[H^+]^{-1}$ with $[H^+]^{-1}$ at 23.7° in 0.1 *M* KNO_3; for 3-methylhistidine (Δ), $n = 3$, $K_a = 1.62 \times 10^{-6}\ M$; for 1-methylhistidine (□), $n = 2$, $K_a = 2.63 \times 10^{-7}\ M$.

If initial complexing is assumed to occur at the glycine part of 3-methylhistidine, then a similar plot with $K_a = 5 \times 10^{-10}$

M should be made. This plot appears definitely nonlinear but can be roughly approximated by a line with a slope of 1.7×10^{-3} sec^{-1} and an intercept of 1.1×10^{3} M^{-1} sec^{-1}. The intercept would be without precedent for metal binding to a glycine type ligand, and the predicted value for k_2, for the neutral ligand, of 3×10^{5} M^{-1} sec^{-1} is 10 times greater than the analogous value for the glycinate anion.[2] Therefore it is concluded that eq 12 with initial complexing at imidazole represents the correct reaction scheme. It is important to note that no evidence could be found for a second reaction with 3-methylhistidine despite the fact that it was studied at a 50% higher nickel concentration than was used for histidine.[1] This result is consistent with our previous proposal that the second reaction which was observed with histidine involves coordination of a second nickel(II) at the pyrrole nitrogen.[10]

1-Methylhistidine. This system is more complex than the two considered above because two distinct reaction steps are observed with half-times of about 0.1 and 1 sec, respectively, in the region of pH ~6. The fraction of the total absorbance change associated with the faster reaction decreases as the pH increases, while that for the second reaction shows the opposite trend. Thus it has been necessary to study the first reaction in the pH range 5.4–6.15 and the second reaction at pH 5.8–7.14. It should also be noted that molecular models indicate that 1-methylhistidine cannot form a chelate with the imidazole and amino nitrogens simultaneously bound to nickel(II). The 1-methylhistidine differs from histidine and the 3-methyl derivative in this respect.

Although several reaction sequences have been considered the results have been found to be most consistent with the scheme (13)–(17). The faster reaction is attributed to the



formation of VIII by the k_1 and k_2 paths. Since $pK_1 = 6.58$, then as the pH increases above 6 there will be less of the protonated species 1-CH_3HistH$^+$, and the relative amount of hydrogen ion produced in the first step will decrease as observed. The slower reaction is associated with the production of X and the fact that relatively little of this reaction is observed at the lower pH values is consistent with the equilibrium proposed for eq 17.

The kinetic results for the slower reaction were analyzed in the usual way since the first step does not interfere significantly. The results are summarized in Table III. The reaction scheme outlined above predicts that the apparent rate constant for the second reaction should be given by

$$k_3' = \frac{k_3 K_2}{K_2 + [H^+]}[Ni^{2+}] + k_{-3} \qquad (18)$$

A least-squares fit[11] of the results to eq 10 gave the values $k_3K_2 = (2.60 \pm 0.60) \times 10^{-5}$ sec^{-1}, $K_2 = (4.7 \pm 3) \times 10^{-8}$ M, and $k_{-3} = 0.149 \pm 0.07$ sec^{-1}, respectively. The calculated and observed values are compared in Table III and a plot of the results is shown in Figure 2. It can be seen from this figure that the slope of the line is well defined but the intercept (k_{-3}) is small and therefore has a large uncertainty.

Before continuing, some consideration may be given to whether the least-squares parameters are reasonable. From k_3K_2 and K_2 a value for k_3 of 5.5×10^{2} M^{-1} sec^{-1} is obtained. Then the equilibrium constant k_3/k_{-3} is 3.7×10^{3} M^{-1}. The value for k_3 seems reasonable when compared to rate constants for other unipositive ligands reacting with nickel(II) (see below). The equilibrium constant k_3/k_{-3} is about 10^2 smaller than values for an α-amino acid such as glycine, but the histidine species VIII is a much stronger acid than a normal amino acid and this may account for the lower formation constant. The value of K_2, 4.7×10^{-8}, may be compared to the K_a of 1.12×10^{-8} for 1,3-dimethylhistidine. The latter has a methyl group in place of nickel(II) in species IV, and it seems reasonable that the dipositive metal ion would increase the acidity more than the methyl group. Therefore the parameters obtained in fitting the kinetic data for the second reaction are consistent with the qualitatively predicted values.

It was not possible to determine the observed rate constants for the first reaction from the usual semilogarithmic plots of absorbance change *vs.* time because interference from the second reaction leads to uncertainty in the proper infinite-time absorbance for the first reaction. Therefore the results from each kinetic trace were fitted by least squares[11] to the appropriate kinetic expression, noting that the change in hydrogen ion concentration is given by

$$[H^+] = \left(\frac{[H^+]}{K_1 + [H^+]}\right)[VIII] + [IX] + [X] \qquad (19)$$

Expressions for the concentrations of VIII and X were obtained from Rodiguin and Rodiguina.[12] The factor $[H^+]/(K_1 + [H^+])$ takes account of the ionization of 1-methylhistidine which will be too fast to be observed. No account was made for the deprotonation of species VIII, since this reaction was only studied to pH 6.15 and very little depro-

(10) A referee has suggested that the first and second reactions might have similar rates with 3-methylhistidine and therefore may not be resolvable. However, in view of the very similar k_2 and pK_a values for histidine and 3-methylhistidine, it does not seem reasonable to expect the second reaction to be 10 times faster with 3-methylhistidine than it is with histidine.

(11) L. L. Rines, J. A. Plambeck, and D. J. Francis, "ENLLSQ, Reprogrammed," Program Library, Department of Chemistry, University of Alberta, 1970. The kinetic data used covered a time of at least 0.2 and generally 0.5 sec.

(12) N. M. Rodiguin and E. N. Rodiguina, "Consecutive Chemical Reactions," Van Nostrand, New York, N. Y., 1964, pp 42–43.

Table III. Kinetic Results for the Second Step of the Reaction of Nickel(II) with 1-Methylhistidine (0.10 *M* KNO_3, 23.7°)[a]

10^3·[ligand], *M*	10^2·[Ni^{2+}], *M*	Av pH	k_2', sec^{-1} Obsd	k_2', sec^{-1} Calcd[b]
1.05	1.04	5.82	0.311	0.321
1.05	1.04	5.88	0.352	0.345
1.11	2.76	6.38	1.68	1.69
1.28	1.04	6.40	0.797	0.753
1.11	2.76	6.50	2.10	2.12
1.15	2.07	6.62	2.19	2.02
1.18	1.73	6.70	2.09	1.97
1.28	1.04	6.80	1.38	1.46
1.11	2.76	6.86	3.70	4.02
1.15	2.07	6.91	3.37	3.58
1.10	1.73	6.97	3.09	3.05
1.18	1.73	7.18	4.49	4.11

[a] The buffer is 0.015 *M* 2,6-lutidine in all cases. [b] Calculated from eq 10 and the least-squares best fit parameters given in the text.

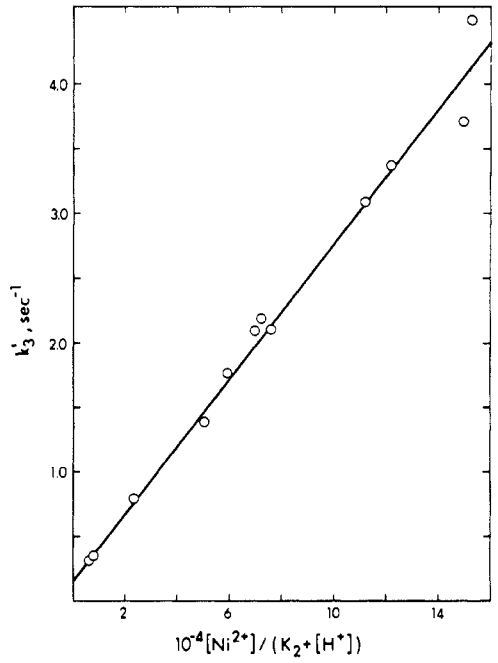


Figure 2. Variation of the apparent rate constant k_3' for the second reaction of 1-methylhistidine with $[Ni^{2+}]/(K_2 + [H^+])$, $K_2 = 4.7 \times 10^{-8}$ *M* (23.7°, 0.10 *M* KNO_3).

tonation will occur if pK_2 is 7.3, as indicated from the fit of the kinetics of the second reaction. The absorbance decay curves were initially fitted with k_3, K_2, and k_{-3} fixed at the values given above, with the initial absorbance and apparent rate constant for the first reaction (k_1') allowed to vary. It was found that the k_1' values did not show any rational trend with pH but were rather random. In addition the calculated best fit curves always fell below the observed curve after about 60% of the first reaction with the deviations increasing at longer times. The latter observation indicates that either k_3K_2 or k_{-3} are too large. Changing the value of k_3K_2 within its error limits did not improve the fits significantly, but changing k_{-3} to 0.090 sec^{-1} produced generally satisfactory fits of the absorbance decay curves. This value for k_{-3} is within the error limits obtained from the study of the second reaction and may be closer to the true value since it is obtained from kinetic runs at higher acidities where the k_{-3} term is more important in eq 18. It may be noted that changing the intercept in Figure 2 from 0.149 to 0.09 will not significantly affect the fit.

The apparent k_{obsd} values for the first reaction are given in Table IV. Reactions 13-15 predict that k_{obsd} should have the same hydrogen ion dependence as that given by eq 11 with $K_a = 2.63 \times 10^{-7}$. The appropriate plot of $k_{obsd}(K_a + [H^+])/[H^+]$ *vs.* $[H^+]^{-1}$ is linear as shown in Figure 1. The slope and intercept of this line give $k_1 = 480\ M^{-1}\ sec^{-1}$ and $k_2 = 1.77 \times 10^3\ M^{-1}\ sec^{-1}$.[13]

The possibility that the glycine end of 1-methylhistidine complexes first may also be considered. The rate law is the same with the appropriate interchange of acid dissociation constants. However, there are several difficulties with this proposal. First, it is not possible to account for the fact that the first reaction becomes less apparent as the pH increases above 6. With a p*K* of 8.6 the amino group will still be fully protonated in the pH 6-7 region. Second, it would be difficult to rationalize why K_2 would be smaller than the K_a of 2.63×10^{-7} *M* for the ionization of the imidazole proton in 1-methylhistidine. Third, if initial glycine complexing is assumed, the rate constant for the first reaction is $9.5 \times 10^4\ M^{-1}\ sec^{-1}$. This value for the neutral ligand is over 4 times larger than that for the negative glycinate ion[2] and therefore seems quite unreasonable. All of these factors argue very strongly against initial complexing at the glycine end of 1-methylhistidine.

Comparison with Related Systems. The rate constants obtained in this study and related work are summarized in Table V.

The imidazole and *N*-methylimidazole systems show very similar kinetic behavior. The rate constant obtained in the previous study[1] is not in particularly good agreement with the recent value given by Cassatt, *et al.*[14] We have since repeated our earlier work on this system and have shown that the ionic strength difference is not a significant factor. In a separate study we have found substantial agreement with the values of Cassatt, *et al.*, for pennicillamine and cysteine, so that the difference does not seem to be due to an instrumental problem. Our earlier value for imidazole also appears low when compared to the analogous rate constant for *N*-methylimidazole obtained in the present work.

In the case of histidine the rate constants for the neutral ligand are not in very good agreement. This results in large part because Cassatt, *et al.*, found evidence for reaction of the unprotonated anion of histidine. A comparison of the two studies shows that they are in good agreement at two of the three pH values studied by Cassatt, *et al.*, but at the highest pH of 6.9 our data give an observed rate constant of $1.9 \times 10^3\ M^{-1}\ sec^{-1}$ while Cassatt, *et al.*, found $2.6 \times 10^3\ M^{-1}\ sec^{-1}$. It is only this larger rate constant at high pH which causes the curvature in the appropriate plot which Cassatt, *et al.*, attributed to reaction of the anion. Since our study covered eight pH values in the range 5.6-6.9, it is felt that the evidence for reaction of the anion should be considered tenuous.

The histidine and 3-methylhistidine systems also are kinetically very similar. The rate constants for complexation of the neutral ligands are essentially identical. It should be noted that no rate term for the protonated cation form of these ligands has been observed. This seems unusual considering that the protonated imidazole and methylimidazole do

(13) The results with imidazole[7] and *N*-methylimidazole indicate that a k_{-2} term should be included in this analysis. However, there are so many parameters already that k_{-2} could not be realistically evaluated from the data. Our experience with imidazole and *N*-methylimidazole shows that inclusion of k_{-2} could reduce k_1 by ~2 times but would not significantly affect k_2.

(14) J. C. Cassatt, W. A. Johnson, L. M. Smith, and R. G. Wilkins, *J. Amer. Chem. Soc.*, 94, 8399 (1972).

Table IV. Kinetic Results for the First Step of the Reaction of Nickel(II) with 1-Methylhistidine (0.10 *M* KNO_3, 23.7°)[a]

10^2·[Ni^{2+}], *M*	Av pH	k_{obsd},[b,d] M^{-1} sec^{-1}	10^2·[Ni^{2+}], *M*	Av pH	k_{obsd},[b,d] M^{-1} sec^{-1}
1.73	5.39	553 (±25)[c]	1.73	5.80	667 (±40)[c]
1.73	5.48	554 (±15)[c]	1.04	6.00	749 (±80)[c]
1.04	5.57	607 (±80)[c]	1.04	6.15	828 (±50)[c]
1.04	5.60	632 (±60)[c]			

[a] The buffer is 0.015 *M* 2,6-lutidine in all cases. [b] Average of four to six values obtained from least-squares fits of the absorbance decay curves, with $k_{-3} = 0.090$ sec^{-1}. [c] Errors cover the range of the four to six values used to obtain the average. [d] Ligand concentration was 1.1×10^{-3} *M* in all cases.

Table V. Summary of Rate Constants for Complexation of Nickel(II)

Ligand	Rate const, M^{-1} sec^{-1}	Ref
Imidazole H_2L^+	2.0×10^2	*a, b*
	$\lesssim 2.0 \times 10^2$	*c*
HL	2.8×10^3	*a, b*
	6.4×10^3	*c*
	5.0×10^3	*d*
N-Methylimidazole CH_3HL^+	2.3×10^2	*e*
CH_3L	4.5×10^3	*e*
Histidine HL	2.2×10^3	*a*
	1.2×10^3	*c*
L^-	3.8×10^5	*c*
Histidine methyl ester HL^+	6.0×10^2	*a*
L	2.6×10^3	*a*
3-Methylhistidine CH_3HL	2.1×10^3	*e*
1-Methylhistidine $CH_3H_2L^+$	$\sim 4.8 \times 10^2$	*e*
CH_3HL	1.8×10^3	*e*
CH_3LNi^+	5.5×10^2	*e*

[a] Reference 1; at 23.7° and ionic strength 0.10 *M*. [b] Corrected values as described in ref 7. [c] Reference 14; at 25° and ionic strength 0.30 *M*. [d] G. G. Hammes and J. I. Steinfeld, *J. Amer. Chem. Soc.*, 84, 4639 (1962); at 25° and ionic strength 0.15 *M*. [e] This work at 23.7° and ionic strength 0.10 *M*.

react. However, as can be seen in Figure 1 the larger K_a of the histidine derivative makes the slope of the $k_{obsd}(K_a + [H^+])[H^+]^{-1}$ curve much larger and the uncertainty in the intercept is increased. Thus a positive intercept could exist but it is too small, even if it is 4×10^2, to be positively identified. This is further illustrated by the 1-methylhistidine system for which the pK_a is between those of imidazole and 3-methylhistidine. In the 1-methyl system the positive intercept in Figure 1 can be identified with reasonable certainty but not with great accuracy.

The histidine and 3-methylhistidine systems differ, however, in that only the former shows a second reaction. This observation strongly supports the previous proposal[1] that this second reaction involves coordination of nickel(II) at the uncoordinated imidazole nitrogen and does not involve bis complex formation hydrolysis nor reaction at another site on the ligand, since then it should have been observed with both histidine and 3-methylhistidine. It seems unlikely, for steric reasons, that a dinickel(II) species would form with 3-methylhistidine, but this cannot be established by the present work since such a reaction would not produce hydrogen ions.

The 1-methylhistidine system behaves differently from any of the other histidine systems studied, apparently because of its inability to chelate with the two nitrogen atoms. The ligand acts essentially as two independent units, the imidazole part and the glycine part. Complexing occurs first at the imidazole part, and the kinetic behavior and rate constants (Table IV) seem quite typical for nickel(II) complexing to imidazole. This reaction is followed by the complexing of a second nickel(II) to the glycine end of 1-methylhistidine. This second reaction reaches equilibrium in the pH range 5.4–6.0. The rate constant for complexation, 5.5×10^2, is rather similar to values for other 1+ ions such as ImH^+ and CH_3ImH^+. The insensitivity of the rate to the separation of positive charge and reaction site has been noted previously in studies of various amino-substituted α-amino acids.[2,10]

Finally it should be noted that the parallel between ligand charge and rate constant[1,2] is found also in the systems studied here. The rate constants for the cations of 1-methylhistidine are somewhat larger than the others but are still a factor of 4 smaller than the rate constants for the neutral ligand.

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Registry No. Ni^{2+}, 14701-22-5; *N*-methylimidazole, 616-47-7; 3-methylhistidine, 368-16-1; 1-methylhistidine, 332-80-9; *N*-methylimidazole-H^+, 17009-89-1; 1-methylhistidine-H^+, 50599-61-6.