large part to entropy effects.[28] If it were not for sizable negative entropies of activation, the cobaloximes would in fact be very labile compared to many "normal" aquocobalt(III) complexes.[2,3] In view of the striking differences in activation entropies, it seems worthwhile to ask whether the cobaloximes and cobalamins might react *via* different mechanisms. Large negative activation entropies and rather small activation enthalpies can be indicative of significant bond formation in the activated complex.[3] Obviously, however, the meaning of the present observations will become clear only after more experimental data are available.

The fast OD changes observed under conditions where essentially all of the cobalamin is saturated with ligand clearly do not arise from the perturbation of equilibrium 1. Furthermore, the ligand-, pH-, and supporting-electrolyte-independent amplitudes observed for $L = SCN^-$, the ligand- and pH-independent difference spectrum for $L = N_3^-$, and the known stoichiometry of the systems under consideration[6-8,11] argue against ion-pair formation, proton-transfer reactions, or displacement of the benzimidazole group by a second mole of ligand.

Because of its intramolecular nature and very high rate, it is tempting to attribute the phenomenon to a subtle structural change in the corrin ring. It is of interest that porphyrins and corrinoids are known to be flexible and to possess regions of nonplanarity.[4,5,29,30] The difficulties inherent in terming a temperature-dependent structural change in the corrin ring as (1) a change in conformation, (2) a change in the distribution over vibrational states, or (3) an electronic effect have recently been discussed by Firth, *et al.*,[31] who have also observed changes in cobalamin spectra on varying the temperature. Although it is not certain that the process in question can be described by a single category, the temperature-difference spectra would seem to favor the second classification;[31] a comparison of the overall features of Figures 6 and 7 with the absorption spectra of the individual complexes indicates that a lowering of temperature results for the most part only in an increase in the sharpness and intensity of the main absorption bands.[32]

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(28) At least two DMG aquation reactions also exhibit large negative entropies relative to many "normal" cobalt(III) complexes. Using rate data from ref 24 activation parameters for the aquation of *trans*-$Co(DH)_2(NO_2)Cl^-$ and *trans*-$Co(DH)_2(NO_2)Br^-$ have been calculated. For the chloro complex, $\Delta H^{\ddagger} = 16.7$ kcal/mol, $\Delta S^{\ddagger} = -21$ eu; and for the bromo complex, $\Delta H^{\ddagger} = 18.3$ kcal/mol, $\Delta S^{\ddagger} = -16$ eu.

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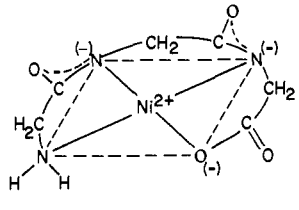
Kinetics of Ligand Exchange with Nickel(II) Triglycine

E. J. Billo, Gregory F. Smith, and Dale W. Margerum*

Contribution from the Department of Chemistry, Purdue University, Lafayette, Indiana 47907. *Received September 10, 1970*

Abstract: Steric hindrance, chelation, and donor ability are important factors in the reactivity of ligands with $NiH_{-2}L^-$ (where L^- is the triglycinate ion and protons are ionized from the two peptide nitrogens coordinated to nickel). Ligands can react by a nucleophilic mechanism similar to that proposed for the analogous copper complex, $CuH_{-2}L^-$. Ethylenediamine and polyamine ligands have second-order rate constants of $(1.2\text{–}1.7) \times 10^4\ M^{-1}\ sec^{-1}$ at 25° and are most effective in breaking up the square-planar $NiH_{-2}L$ complex. The diamines and polyamines are (2–3) $\times 10^3$ times more reactive than ammonia. Addition of *N*-methyl groups to ethylenediamine has relatively little kinetic effect until both nitrogens are tertiary and then the reactivity decreases sharply. Glycinate ion and *N,N*-dimethylglycinate ion have comparable reactivities but are much slower than the sterically unhindered diamines. In order for a ligand to be an effective nucleophile one donor group must be able to coordinate to nickel in the plane of the nickel–N (peptide) bonds. The order of reactivity is: diamines ≫ aminocarboxylates ≫ monodentate ligands ($NH_3 \gg CH_3COO^-$). Trimethylamine is unreactive.

Triglycine (glycylglycylglycine) forms a yellow, square-planar complex with nickel(II) in which two protons are ionized from the peptide nitrogens and the nitrogen atoms are coordinated to nickel.[1-3] This complex, $NiH_{-2}L^-$ (depicted in structure I), reacts with



I

acids[4] or with ligands to give blue, octahedral nickel(II)

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Table I. Ligands and Protonation Constants at 25° Used for Resolution of the Kinetic Data

Ligand	Log K_H	Ref
NH_3	9.24	*a*
en, $H_2NCH_2CH_2NH_2$	9.83, 7.05	*b*
dien, $(H_2NCH_2CH_2)_2NH$	9.80, 9.00, (4.24)	*c*
trien, $(H_2NCH_2CH_2NHCH_2\cdot)_2$	9.80, 9.08, 6.55, (3.25)	*d*
$(CH_3)_3N$	9.91	*e*
N,N-diMeen, $(CH_3)_2NCH_2CH_2NH_2$	9.60, 6.32	*b*
N,N'-diMeen, $CH_3NHCH_2CH_2NHCH_3$	10.29, 7.47	*f*
Me_4en, $(CH_3)_2NCH_2CH_2N(CH_3)_2$	9.34, 6.26	*g*
$C_2O_4^{2-}$	(3.85, 1.14)	*h*
$H_2NCH_2COO^-$	9.59, (2.38)	*i*
$(CH_3)_2NCH_2COO^-$	9.88, (2.06)	*j*
IDA^{2-}, $HN(CH_2COO)_2^{2-}$	9.33, (2.65)	*k*
$MeIDA^{2-}$, $CH_3N(CH_2COO)_2^{2-}$	9.57, (2.12)	*l*
NTA^{3-}, $N(CH_2COO)_3^{3-}$	9.68, (2.49)	*m*
$EDTA^{4-}$, $[\cdot CH_2N(CH_2COO)_2]_2^{4-}$	10.26, 6.16, (2.67)	*n*
L^-, $H_2NCH_2CONHCH_2CONHCH_2COO^-$	7.88, (3.30)	*o*

[a] D. H. Everett and D. A. Landsman, *Trans. Faraday Soc.*, **50**, 1221 (1954). [b] This work. [c] J. E. Prue and G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 985 (1950). Temperature correction from G. H. McIntyre, B. P. Block, and W. C. Fernelius, *J. Amer. Chem. Soc.*, **81**, 529 (1959). [d] G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 974 (1950). Temperature correction from H. B. Jonassen, R. B. LeBlanc, A. W. Meibohm, and R. M. Rogan, *J. Amer. Chem. Soc.*, **72**, 2430 (1950). [e] H. T. S. Britton and W. G. Williams, *J. Chem. Soc.*, 796 (1935); 15°, 0.10 μ. [f] F. Basolo, R. K. Murmann, and Y. T. Chen, *J. Amer. Chem. Soc.*, **75**, 1478 (1953). [g] D. L. Leussing, *Inorg. Chem.*, **2**, 77 (1963). [h] R. K. Cannan and A. Kibrick, *J. Amer. Chem. Soc.*, **60**, 2314 (1938). [i] E. J. King, *ibid.*, **73**, 155 (1951). [j] A. L. Remizov. *Zh. Obshch. Khim.*, **34**, 3192 (1964). [k] G. Schwarzenbach and H. Senn, unpublished results in L. G. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes," 2nd ed, The Chemical Society, London, 1964; corrected to 25° using the temperature effect for NTA. [l] G. Schwarzenbach, G. Anderegg, W. Schneider, and H. Senn. *Helv. Chim. Acta*, **38**, 1147 (1955). Temperature correction from N. E. Ockerbloom and A. E. Martell, *J. Amer. Chem. Soc.*, **78**, 267 (1956). [m] G. Schwarzenbach and R. Gut, *Helv. Chim. Acta*, **39**, 1589 (1956). Temperature correction from T. Moeller and R. Ferrus, *Inorg. Chem.*, **1**, 49 (1962). [n] G. Schwarzenbach and H. Ackerman, *Helv. Chim. Acta*, **30**, 1798 (1947); 20°, 0.10 μ. [o] Reference 4; also W. L. Koltun, R. H. Roth, and F. R. N. Gurd, *J. Biol. Chem.*, **238**, 124 (1963).

complexes. In the reaction of EDTA with $NiH_{-2}L^-$ and with the corresponding copper(II) complex, the EDTA is a very poor nucleophile and acts primarily as an acid and as a scavenger after one proton has been added to a peptide nitrogen.[4-6] However, some ligands do react directly with $CuH_{-2}L^-$ in a nucleophilic mechanism in which the displacing ligand coordinates to copper and speeds the breaking of the copper–peptide bonds.[6] Steric factors are very important in governing the ligand reactivity with copper triglycine.

In the present work a nucleophilic mechanism is found also for substitution reactions with $NiH_{-2}L^-$. The effects of chelation, steric hindrance, and donor ability of the ligands are examined. The rate of disappearance of the yellow $NiH_{-2}L^-$ complex is observed in all cases. In some reactions the added ligand itself displaces the triglycine as is the case with triethylenetetramine (trien) in eq 1. The reactions of $NiH_{-2}L^-$

$$NiH_{-2}L^- + \text{trien} + 2H_2O \longrightarrow Ni(\text{trien})^{2+} + L^- + 2OH^- \quad (1)$$

with en, *N,N'*-diMeen, *N,N*-diMeen, dien, and $MeIDA^{2-}$ (see Table I) are studied by direct displacement.

In other reactions EDTA is used as a scavenger and the added ligand acts as a catalyst. This is the case with NH_3 for the reaction in eq 2, and for reactions with $C_2O_4^{2-}$, $H_2NCH_2COO^-$, $(CH_3)_2NCH_2COO^-$, IDA^{2-}, NTA^{3-}, and Me_4en.

$$NiH_{-2}L^- + EDTA^{4-} + 2H_2O \xrightarrow{NH_3} NiEDTA^{2-} + L^- + 2OH^- \quad (2)$$

Once the peptide nitrogens of the triglycine are removed from their coordination to nickel they rapidly pick up protons from the solvent to give the triglycinate ion, L^-, or the zwitterion, HL ($pK_a = 7.88$). The complex with only one peptide hydrogen ionized, $NiH_{-1}L$, is not stable thermodynamically[4] compared to NiL^+ or $NiH_{-2}L^-$. The $NiH_{-1}L$ complex appears to be kinetically very reactive with acids, EDTA, and other ligands. Therefore, the reactions under comparison in the present study are the attack of various ligands on $NiH_{-2}L^-$ in which the square-planar complex is destroyed.

Experimental Section

The ligands used and their protonation constants are given in Table I. The constants are corrected to 25.0° using values as close as possible to the ionic strength of the kinetic experiments. The ionic strength was controlled with $NaClO_4$ and was 0.16 *M* for all reactions except those with Me_4en and $(CH_3)_3N$, where it was 0.25 *M*. Boric acid or 2,6-lutidine was used as buffer when needed. Hydrogen ion concentrations were calculated using the relationship $-\log [H^+] = pH - 0.13$, where the pH was standardized with NBS buffers.

Ammonia, en, the *N*-CH_3 derivatives of en (Aldrich Chemical Co., Inc.), dien, trien, and 2,6-lutidine were purified by distillation. The disodium salt of IDA and *N,N*-dimethylglycine hydrochloride were recrystallized twice from ethanol–water; boric acid and NTA were recrystallized twice from water. Oxalic acid, glycine, disodium EDTA, $(CH_3)_3N$ (Eastman Kodak Organic Chemicals), and *N*-methyliminodiacetic acid (Aldrich Chemical Co., Inc.) were used without purification. Solutions of the ligands were standardized by pH titration or prepared from reagent grade chemicals.

Nickel(II) perchlorate was prepared from $NiCO_3$ and $HClO_4$ and was recrystallized from water. Solutions of triglycine were freshly prepared from the chromatographically pure solid (Mann Research Laboratories, New York, N. Y.). The $NiH_{-2}L^-$ solutions were prepared by the addition of NaOH to solutions containing 100% excess triglycine (to prevent $Ni(OH)_2$ precipitation) and the solutions were filtered through a 1.2-μ Millipore filter.

Kinetic measurements used stopped-flow spectrophotometers described previously.[4] In these experiments the $NiH_{-2}L^-$ solution (pH 9.5–10.0) was mixed with an equal volume of a solution containing the displacing ligand and EDTA if needed and maintained at the appropriate pH by buffer. The rates of the reactions were not affected by the EDTA concentration when it was present as a scavenger. The reaction rates were measured over a range of

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Table II. Observed Rate Constants[a] for the Reaction of Ligands (Z) with $NiH_{-2}L^-$ in the Presence of EDTA; 25.0°, 430 nm

$10^3[Z]_{tot}$, M	$-\log [H^+]$	k_{obsd}, sec^{-1}
Z = NH_3, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.03 × 10^{-3} M, [EDTA] = 3.0 × 10^{-3} M		
10.7	8.79	0.097 ± 0.001
10.7	9.09	0.106 ± 0.003
21.4	9.19	0.134 ± 0.002
42.8	9.26	0.200[b]
107.0	9.28	0.409 ± 0.001
107.0	9.79	0.514 ± 0.006
214.0	9.73	1.00 ± 0.01
Z = $C_2O_4^{2-}$, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.03 × 10^{-3} M, [EDTA] = 3.0 × 10^{-3} M		
4.1	9.09	0.086 ± 0.002
10.2	9.10	0.098 ± 0.001
20.4	9.11	0.121 ± 0.001
30.6	9.11	0.147 ± 0.002
Z = $H_2NCH_2COO^-$, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.03 × 10^{-3} M, [EDTA] = 3.0 × 10^{-3} M		
1.2	9.00	0.187 ± 0.003
2.4	9.00	0.284 ± 0.008
3.6	9.00	0.432 ± 0.006
4.8	8.97	0.576 ± 0.004
6.0	8.96	0.691 ± 0.009
12.0	9.20	1.34 ± 0.01
12.0	9.60	2.14 ± 0.01
12.0	9.95	2.74 ± 0.06
24.0	9.61	4.71 ± 0.05
24.0	9.64	4.99 ± 0.01[c]
Z = $(CH_3)_2NCH_2COO^-$, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.5 × 10^{-4} M, [EDTA] = 2.5 × 10^{-3} M		
5.06	7.99	0.068 ± 0.001
5.06	8.34	0.088 ± 0.001
5.06	8.77	0.146 ± 0.002
5.06	9.22	0.256 ± 0.002
5.06	9.74	0.356 ± 0.001
15.2	8.88	0.381 ± 0.004
50.6	8.95	1.34 ± 0.01
Z = IDA^{2-}, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.03 × 10^{-3} M, [EDTA] = 3.0 × 10^{-3} M		
3.7	8.47	0.34 ± 0.01
3.7	8.71	0.42 ± 0.01
3.7	9.04	0.55[b]
3.7	9.50	1.00 ± 0.03
7.4	9.13	1.14 ± 0.05
11.0	9.21	1.78[b]
14.7	9.31	2.73 ± 0.03
Z = NTA^{3-}, μ = 0.16, $[NiH_{-2}L^-]_{init}$ = 2.03 × 10^{-3} M, [EDTA] = 3.0 × 10^{-3} M		
5.04	7.90	0.100 ± 0.01
5.04	8.34	0.107 ± 0.001
5.04	8.79	0.128[b]
5.04	8.81	0.131 ± 0.001
5.04	9.19	0.145 ± 0.005
5.04	9.21	0.153 ± 0.003
10.08	8.84	0.192 ± 0.002
10.08	9.14	0.228[b]
10.08	9.17	0.240[b]
Z = $(CH_3)_3N$, μ = 0.25, $[NiH_{-2}L^-]_{init}$ = 2.5 × 10^{-4} M, [EDTA] = 2.5 × 10^{-3} M		
3.01	8.21	0.0577 ± 0.0005
3.01	8.60	0.0568 ± 0.0003
3.01	9.12	0.0529 ± 0.0007
3.01	9.64	0.0440 ± 0.0004
3.01	10.27	0.0335 ± 0.0004
6.02	8.19	0.0622 ± 0.0007
6.02	8.65	0.0605 ± 0.0006
6.02	9.24	0.0561 ± 0.0005
6.02	9.57	0.0447 ± 0.0005
6.02	10.22	0.0359 ± 0.0004
9.04	8.19	0.0606 ± 0.0009
9.04	8.66	0.0583 ± 0.0006
9.04	9.15	0.0613 ± 0.0003
9.04	9.76	0.0460 ± 0.0002
9.04	10.21	0.0356 ± 0.0003
Z = Me_4en, μ = 0.25, $[NiH_{-2}L^-]_{init}$ = 2.5 × 10^{-4} M, [EDTA] = 2.5 × 10^{-3} M		
2.05	8.03	0.066 ± 0.005
2.05	8.41	0.073 ± 0.001
2.05	8.88	0.100 ± 0.001
2.05	9.33	0.127 ± 0.001
6.14	7.92	0.086 ± 0.001
6.14	8.44	0.138 ± 0.001
10.2	7.98	0.122 ± 0.005
10.2	8.43	0.195 ± 0.001

[a] Average of two or more experiments, except as noted. Error limits are average deviations. [b] Single determination. [c] [EDTA] = 0.0.

ligand concentrations and with the exception of oxalate, over a range of hydrogen ion concentration.

The rate of disappearance of $NiH_{-2}L^-$ was followed at its visible absorption maximum (430 nm, ϵ 260 M^{-1} cm^{-1}). Similar experiments were performed in a few cases in the absence of buffer and with phenolphthalein indicator at 552 nm to determine the rate of gain or loss of protons.

Rate constants are calculated from an average of two to four experiments except where noted. Data were obtained from Polaroid photographs of an oscilloscope trace (Tektronix Model 564) except for the work with $(CH_3)_3N$, $(CH_3)_2NCH_2COO^-$, $MeIDA^{2-}$, *N,N'*-diMeen, and Me_4en, where a computer interfaced unit was used.[7]

Most of the reactions were studied under pseudo-first-order conditions because the added ligand was either in excess or was not consumed during the reaction, and $-d[NiH_{-2}L^-]/dt = k_{obsd}[NiH_{-2}L^-]$. The reactions of dien and trien were studied under second-order conditions (unequal concentrations).

Results

The rate of $NiH_{-2}L^-$ disappearance varied greatly with the nature of the ligands added, but in every case the reaction was first order in the $NiH_{-2}L^-$ concentration. When EDTA was present at low concentrations or below pH 10, the reaction rate was EDTA independent. Under these conditions moderately high concentrations of NH_3 and $C_2O_4^{2-}$ were needed to catalyze the reaction (eq 2). The glycinate, iminodiacetate, and nitrilotriacetate ions were one to two orders of magnitude more effective as catalysts than ammonia or oxalate ion. Table II gives the observed first-order rate constants with these ligands present. The value of k_{obsd} increases with pH, indicating that the added ligands are reactive as nucleophiles rather than as acids. The reaction observed is the attack of the nucleophile (Z) on $NiH_{-2}L^-$. This reaction is followed by a more rapid breakup of the mixed complex and the formation of $NiEDTA^{2-}$.

Above pH 10 and at higher EDTA concentrations there is an EDTA-dependent path, as reported earlier.[4] It is interesting that $EDTA^{4-}$ is slightly reactive, $H(EDTA)^{3-}$ shows no detectable reactivity and $H_2(EDTA)^{2-}$ should be reactive. The doubly protonated EDTA is expected to act as a general acid catalyst

(7) B. G. Willis, J. A. Bittikofer, H. L. Pardue, and D. W. Margerum, *Anal. Chem.*, 42, 1340 (1970).

with a predicted rate constant of 10^2 M^{-1} sec^{-1}. The singly protonated EDTA is too weak an acid to be effective as a general acid catalyst, and the proton appears to lower its nucleophilic activity with $NiH_{-2}L^-$ when compared to the unprotonated EDTA.

Triglycine itself can catalyze the EDTA displacement of triglycine from Ni(II) at high pH. The contribution from this path to the dissociation of $NiH_{-2}L^-$ is almost negligible for the k_{obsd} values in Table II and did not affect the first-order kinetics. However, an approximate value of 15 M^{-1} sec^{-1} can be given for the triglycinate ion reaction with $NiH_{-2}L^-$. A similar catalysis has been studied in detail for copper(II) triglycine,[8] and the kinetics are moderately complex, so the triglycine catalysis was not explored further in the present work.

Data for one ligand which had no catalytic effect are included in Table II. Trimethylamine shows no catalysis even with concentrations as high as 0.09 M. The k_{obsd} values are all approximately 0.05 sec^{-1} at pH 8–9, which is the value found[4] for the uncatalyzed dissociation rate constant for $NiH_{-2}L^-$. The free triglycine concentration under the conditions used is initially only 2.5×10^{-4} M, and hence its catalytic contribution to the observed first-order rate constant is about 0.004 sec^{-1}. (The free triglycine concentration is higher in the oxalate and NH_3 studies, and therefore the minimum k_{obsd} values for these systems are about 0.09 sec^{-1}.) Above pH 9 the $(CH_3)_3N$ data show a suppression of the reaction rate as the hydroxide ion concentration increases. This is consistent with earlier observations of a dissociation sequence

$$NiH_{-2}L^- + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} NiH_{-1}L + OH^- \quad (3)$$

$$NiH_{-1}L + H(EDTA)^{3-} \xrightarrow{k_2} NiEDTA^{2-} + L^- \quad (4)$$

in which a steady-state approximation applies to $NiH_{-1}L$ so that

$$\text{rate} = \frac{k_1 k_2 [NiH_{-2}L^-][EDTA]}{k_{-1}[OH^-] + k_2[EDTA]} \quad (5)$$

At low hydroxide ion concentration the rate becomes equal to $k_1[NiH_{-2}L^-]$, and k_1 is 0.06 sec^{-1} from the present data. The ratio of k_{-1}/k_2 is about 17, but it appears to be a function of pH owing to the form of the EDTA (*i.e.*, $EDTA^{4-}$ or $H(EDTA)^{3-}$) and to catalysis by triglycine, so it was not evaluated further.

The ligand Me_4en had only a small catalytic effect even in 0.1 M concentrations. In this case, unlike any of the other systems in Table II, high concentrations and higher pH caused some deviation from simple first-order kinetic behavior. This deviation was not negligible, but the cause of this behavior was not established and hence data with this effect have been omitted.

Table III gives the results for reactions where EDTA was not needed to assist the breakup of the $NiH_{-2}L^-$ complex. The reactions of en, *N*,*N*-diMeen, and *N*,*N*′-diMeen were run under pseudo-first-order conditions and the reaction rates depended on the diamine concentrations. Mixed complexes of nickel triglycine and en were not observed under the conditions used, al-

(8) G. R. Dukes, G. K. Pagenkopf, and D. W. Margerum, manuscript in preparation.

Table III. Observed Rate Constants[a] for the Reaction of Ligands (Z) with $NiH_{-2}L^-$; 25.0, μ = 0.16, 430 nm

$10^3[Z]_{tot}$, M	$-\text{Log}\,[H^+]$	k_{obsd}, sec^{-1}	
Z = en, $[NiH_{-2}L^-]_{init} = 2.54 \times 10^{-4}$ M			
5.31	8.31	3.55 ± 0.06	
5.31	8.41	4.78 ± 0.05	
5.31	8.66	7.27 ± 0.10	
5.31	9.11	13.3 ± 0.1	
5.31	9.60	27.8 ± 0.5	
5.31	10.11	42 ± 2	
7.45	9.26	22.5 ± 0.5	
10.6	9.30	34.5 ± 2	
Z = *N*,*N*′-diMeen, $[NiH_{-2}L^-]_{init} = 2.5 \times 10^{-4}$ M			
7.63	9.15	3.07 ± 0.02	
7.63	9.31	3.72 ± 0.07	
7.63	9.52	5.00 ± 0.09	
7.63	9.67	6.27 ± 0.08	
7.63	9.85	7.94 ± 0.07	
7.63	10.03	9.61 ± 0.06	
7.63	10.23	11.3 ± 0.4	
7.63	10.35	12.2 ± 0.3	
15.3	10.04	19.6 ± 0.1	
Z = *N*,*N*-diMeen, $[NiH_{-2}L^-]_{init} = 2.5 \times 10^{-4}$ M		First reaction	Second reaction
5.39	8.97	5.3 ± 0.1	0.85 ± 0.02
5.39	9.12	7.2 ± 0.1	0.86 ± 0.04
5.39	9.30	9.0 ± 0.1	0.85 ± 0.01
5.39	9.46	11.6 ± 0.3	0.89 ± 0.01
5.39	9.64	14.4 ± 0.3	0.86 ± 0.02
5.39	9.85	18.6 ± 0.3	0.82 ± 0.02
5.39	10.03	22.7 ± 0.2	0.77 ± 0.01
5.39	10.22	31.2 ± 0.1	0.76 ± 0.01
7.38	9.86	24.0 ± 0.4	0.67 ± 0.01
11.1	9.87	30.0 ± 0.7	0.63 ± 0.01
Z = dien, $[NiH_{-2}L^-]_{init} = 2.03 \times 10^{-3}$ M			
4.04	7.15	0.11 ± 0.01	
4.04	8.28	1.62 ± 0.02	
4.04	8.50	2.65 ± 0.15	
4.04	8.92	4.75 ± 0.25	
4.04	9.41	7.5 ± 0.3	
4.04	9.83	10.1 ± 0.6	
4.04	11.02	12.4 ± 0.1	
5.05	8.47	2.2 ± 0.1	
5.05	8.63	2.50 ± 0.05[c]	
5.05	8.67	2.95 ± 0.07	
5.05	8.79	3.66 ± 0.01[c]	
5.05	8.93	3.94 ± 0.06	
5.05	8.98	4.93 ± 0.03[c]	
5.05	9.22	6.50 ± 0.01[c]	
5.05	9.55	9.19[b,c]	
5.05	9.81	9.99[b]	
5.05	9.93	10.72 ± 0.02[c]	
10.1	8.64	3.55 ± 0.25	
10.1	9.33	7.03[b]	
20.2	9.06	5.7 ± 0.3	
Z = trien, $[NiH_{-2}L^-]_{init} = 5.07 \times 10^{-4}$ M			
1.18	7.84	2.00 ± 0.02	
1.18	8.18	2.85 ± 0.1	
1.18	8.70	5.45 ± 0.05	
1.18	9.07	9.80 ± 0.05	
1.18	9.50	13.5 ± 0.4	
1.18	10.11	17.5[b]	
2.94	8.63	6.7 ± 0.1[d]	
2.94	9.02	11.1 ± 0.1[d]	
2.94	9.04	8.10 ± 0.10	
5.88	6.64	0.63 ± 0.03[d]	
5.88	6.78	0.53 ± 0.01	
5.88	7.03	0.80 ± 0.01	
5.88	7.05	0.97 ± 0.03[d]	
Z = $MeIDA^{2-}$, $[NiH_{-2}L^-]_{init} = 2.5 \times 10^{-4}$ M			
5.02	7.86	0.064 ± 0.001	
5.02	8.22	0.081 ± 0.001	
5.02	8.70	0.121 ± 0.001	
5.02	9.24	0.199 ± 0.001	
5.02	9.72	0.285 ± 0.005	
15.1	8.79	0.310 ± 0.001	
30.2	8.88	0.627 ± 0.007	

Table III (*Footnotes*)

[a] Average of two or more experiments, except as noted. Error limits are average deviations. [b] Single determination. [c] [EDTA] = 3.0×10^{-3} *M*. [d] $[NiH_{-2}L^-]_{init} = 2.03 \times 10^{-3}$ *M*.

though such a complex has been suggested.[9] Excellent first-order plots were obtained with all three reactions. However, with *N,N*-diMeen a much slower second reaction also was observed. The faster reaction with *N,N*-diMeen is first order in the polyamine concentration. It is dependent on the pH and it accounts for 80–90% of the total absorbance change. The second reaction has a rate constant of 0.8 ± 0.1 sec^{-1} and is independent of polyamine concentration and of pH. The second reaction must be due to the formation of small concentrations of another square-planar complex which then decays. It may be the rearrangement of an intermediate nickel–triglycine–*N,N*-diMeen complex.

The reactions of dien and trien were studied under second-order conditions because of the speed of the reactions. Excellent second-order plots were obtained for the trien reaction. The reaction of $NiH_{-2}L^-$ with $Htrien^+$ also was followed by observing the uptake or release of protons using an indicator. A single reaction was observed, first order in each reactant, which consumed protons and had approximately the same rate constant as that measured for the rate of disappearance of $NiH_{-2}L^-$ at 430 nm. Thus, there is no evidence of stable reaction intermediates with trien.

On the other hand the reaction of $Hdien^+$ and $NiH_{-2}L^-$ when followed by the indicator method gave two reactions. The first reaction consumed protons and the second reaction released protons. The dien reactions in which the disappearance of $NiH_{-2}L^-$ was followed (Table III) gave a second-order fit for the uptake of one dien. Therefore, the final product, $Ni(dien)_2^{2+}$, is slow to form by comparison. The reaction sequence may be that given in eq 6 and 7. Other spectral

$$NiH_{-2}L^- + Hdien^+ + H_2O \longrightarrow Ni(dien)\cdot L^+ + OH^- \quad (6)$$

$$Ni(dien)\cdot L^+ + Hdien^+ \longrightarrow Ni(dien)_2^{2+} + H^+ + L^- \quad (7)$$

evidence indicates that small amounts of a mixed complex exist in solutions of nickel, dien, and triglycine.

Figure 1 plots the second-order rate constants for the reactions of the polyamines with $NiH_{-2}L^-$ as a function of pH. The plots indicate the nucleophilic nature of the reactions, because the rate constants increase with pH even though the overall reaction consumes acid. The relative contributions of the individual polyamine species (such as trien, $Htrien^+$, and H_2trien^{2+}) were evaluated from a weighted regression analysis program, WRAP.[6] In the diamine reactions graphical methods were sufficient to resolve the individual rate constants.

The resolved second-order rate constants for all the ligands are given in Table IV. Acetate ion was not used in the present study, but the limit for its rate constant is the result of studies using acetic acid–acetate ion mixtures.[4]

(9) N. W. H. Ma, D. A. White, and R. B. Martin, *Inorg. Chem.*, 6, 1632 (1967).

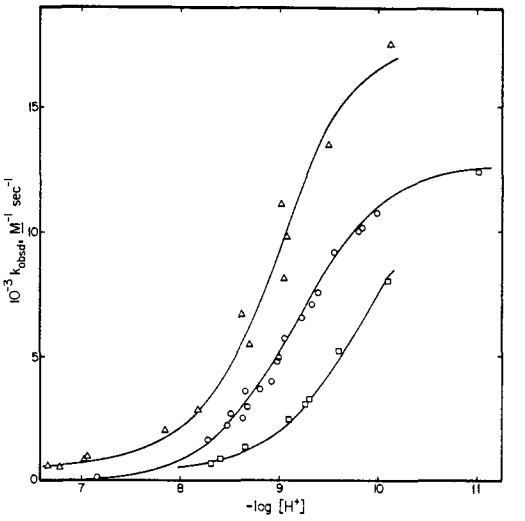


Figure 1. Rate constant–pH profile for the reactions of polyamines with $NiH_{-2}L^-$, 25.0°, μ = 0.16 *M*. Experimental points are given and the curves are plotted from the resolved rate constants in Table IV: Δ, trien; ○, dien; □, en.

Discussion

At least three important kinetic factors can be seen from a comparison of the reactivities of the ligands in Table IV: (1) pronounced steric effects, (2) a large chelate effect, and (3) amine groups being much more effective than carboxylate groups.

Table IV. Rate Constants for Ligand Reaction with $NiH_{-2}L^-$ Leading to Loss of the Nickel–Triglycine Square-Planar Complex

Ligand, Z	k, M^{-1} sec^{-1}
CH_3COO^-	Negligible (<1)
$C_2O_4^{2-}$	2.31 ± 0.01
Pyridine	~0.3
NH_3	5.6 ± 0.1
$(CH_3)_3N$	Negligible (<0.1)
$H_2NCH_2COO^-$	365 ± 14
$(CH_3)_2NCH_2COO^-$	213 ± 6
IDA^{2-}	361 ± 8
$MeIDA^{2-}$	76 ± 2
NTA^{3-}	62 ± 5
$EDTA^{4-}$	~6
$H(EDTA)^{3-}$	Negligible
$Triglycinate^-$	~15
en	$(1.19 \pm 0.02) \times 10^4$
Hen^+	$(7 \pm 1) \times 10^2$
N,N-diMeen	$(5.0 \pm 0.1) \times 10^3$
$H(N,N\text{-diMeen})^+$	<100
N,N'-diMeen	$(2.85 \pm 0.16) \times 10^3$
$H(N,N'\text{-diMeen})^+$	$(0.33 \pm 0.03) \times 10^3$
Me_4en	7.4 ± 0.9
$H(Me_4en)^+$	0.5 ± 0.1
dien	$(1.28 \pm 0.08) \times 10^4$
$Hdien^+$	$(9 \pm 2) \times 10^3$
H_2dien^{2+}	Negligible
trien	$(1.7 \pm 0.4) \times 10^4$
$Htrien^+$	$(1.8 \pm 0.1) \times 10^4$
H_2trien^{2+}	$(9.0 \pm 0.7) \times 10^2$

The steric effect has been pointed out in the reactions of nucleophiles with $CuH_{-2}L^-$, where ligands with primary or secondary amine nitrogens acted as nucleophiles but those with tertiary amine nitrogens did not. A similar effect is seen with $NiH_{-2}L^-$ in the comparison of the behavior of NH_3 and $(CH_3)_3N$ and in the be-

havior of en and Me_4en. In the latter case steric interference reduces the ligand reactivity by a factor of 1600. The methyl groups in $(CH_3)_3N$ and in Me_4en would not appreciably hinder coordination in the axial positions (above or below the plane of the nickel–triglycinate complex). However, models show[6] that the methyl groups could block coordination in the equatorial position initially occupied by the carboxylate group of the coordinated triglycinate ion. On the other hand, the secondary amine *N,N'*-diMeen is quite an effective nucleophilic agent which also is consistent with models which show that coordination in the equatorial position is possible.

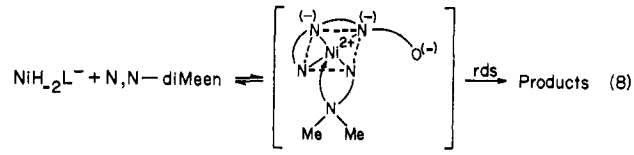
Chelates show a very large increase in nucleophilic reactivity compared to monodentate ligands. The rate constant for en is 2100 times that of NH_3, and oxalate, despite electrostatic repulsion from $NiH_{-2}L^-$, is much more reactive than acetate ion. Similarly glycinate ion is much more reactive than NH_3 or acetate ion. Steric factors are important in chelating ligands when both groups are blocked as in Me_4en, but the effect is not large when only one group is hindered, as in *N,N*-diMeen. In fact, a simple statistical factor can account for the difference in reactivity of en and *N,N*-diMeen. The data with en, dien, and trien show that one chelate group is sufficient to cause rapid nucleophilic reaction with $NiH_{-2}L^-$, and the relative reactivities of the unprotonated polyamine ligands are nearly the same.

Amine nitrogens are much more effective than carboxylate groups in their attack on $NiH_{-2}L^-$. Comparison can be made for NH_3 and acetate, for en and oxalate, and for en and glycinate.

The steric selectivity, chelate, and pH effects suggest some microscopic details of the reaction mechanism. The importance of chelation indicates that there is coordination of the ligand before the rate-determining step. One position of coordination of the reacting chelate is sterically sensitive while the other position is not. The pH effects indicate that there is no release of a peptide-nitrogen group until the decomposition of the square-planar complex. The location of the rate-determining step in these reactions must be before or during the cleavage of the first peptide-nitrogen–nickel bond, because once the peptide group is free of the nickel it will add a proton rapidly. If the rate-determining step were subsequent to this reaction then hydrogen ion would assist rather than suppress the kinetics.

Only the equatorial positions occupied initially by the amine terminal or carboxylate terminal of triglycine qualify for the steric sensitivity. The carboxylate terminal is kinetically and thermodynamically much easier to replace from its nickel coordination than the amine terminal. The site vacated by the carboxylate terminal position also is more sterically hindered than the amine terminal position (the amine hydrogens reduce the volume available at its adjacent position).

The greater reactivity of the stronger nucleophiles indicates that an associative type reaction is involved. Therefore, the proposed mechanism with a chelate such as *N,N*-diMeen is given in eq 8. The observed second-order rate constant is a product of the equilibrium constant leading to a reaction intermediate such as II and the rate constant for the rate-determining step. The reaction intermediate II is not present in appreciable concentrations. The rate-determining step can be considered



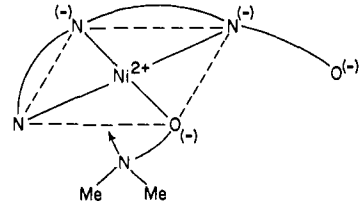
II

to have some similarities with the associative-type mechanism of Pt(II) and Pd(II) complexes.[10] Associative mechanisms have been found with other square-planar nickel complexes.[11,12] Chelation also is an important factor in the reactions of $Ni(CN)_4^{2-}$ with amines.[11]

Since the reactions of $NiH_{-2}L^-$ were, in general, followed by the disappearance of the square-planar species, it is not possible to state in all cases whether the observed rate constants correspond to the complete displacement of triglycine or to the formation of an octahedral mixed complex, $NiH_{-n}L \cdot Z$, which then decomposes more slowly. However, in the reaction of trien there is no appreciable intermediate formation, as shown by the fact that a single reaction is observed in the indicator experiments. With dien, the first reaction consumed protons so there is a cleavage of one or more of the peptide-nitrogen bonds to nickel occurring at the same rate as the loss of the square-planar complex. In the reactions of en with $CuH_{-2}L^-$ a stable reaction intermediate is observed[13] in which one peptide nitrogen is released and $Cu(H_{-1}L)en$ is formed. Hence, the existing evidence indicates that one or more of the peptide nitrogens are readily displaced in the reaction with polyamine chelates.

The relative kinetic reactivities of en and $H_2NCH_2COO^-$ and of *N,N*-diMeen and $(CH_3)_2NCH_2COO^-$ are roughly proportional to the ratio of their nickel stability constants in accord with the suggested reaction pathway.

In the reaction of glycinate ion, it may be noted that either the amine or carboxylate end of the glycinate ion could attack the site vacated by the carboxylate terminal of triglycine. Molecular models show that for *N,N*-dimethylglycinate ion, the carboxylate end is able to coordinate to the site vacated by the carboxylate terminal of triglycine, but the amine end coordinates to this site only with difficulty. At the same time that the carboxylate end is coordinated in the plane, the amine end may coordinate axially. The similarity of the rate constants for glycinate ion and its *N,N*-dimethyl derivative suggests a reaction intermediate of the type in structure III for both. On the other hand addition of



III

(10) C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, New York, N. Y., 1965, Chapter 2.
(11) G. B. Kolski and D. W. Margerum, *Inorg. Chem.*, 8, 1125 (1969).
(12) R. G. Pearson and D. A. Sweigart, *ibid.*, 9, 1167 (1970).
(13) H. Hauer, E. J. Billo, and D. W. Margerum, *J. Amer. Chem. Soc.*, in press.

an *N*-methyl group to IDA^{2-} reduces its reactivity by a factor of 5. Hence the amine end of an aminocarboxylate chelate can react axially, but it is not clear whether its preferred position (without steric hindrance) is equatorial or axial.

With NTA steric factors would prevent the tertiary nitrogen from coordinating in the plane defined by the metal and the N(peptide) groups, but a carboxylate group of NTA^{3-} could coordinate in the plane.[14] The nitrogen of NTA^{3-} provides the chelating amine group to assist the nucleophilic reaction. The reactions of $(CH_3)_2NCH_2COO^-$, $CH_3N(CH_2COO)_2^{2-}$, and $N(CH_2COO)_3^{3-}$ can proceed by the same mechanism with diminishing reactivity as charge repulsion and steric hindrance increase. Even $EDTA^{4-}$ shows a small but noticeable reactivity at higher pH. The lack of reactivity of $H(EDTA)^{3-}$ suggests that a proton adjacent to the nitrogen diminishes its nucleophilic reactivity much as in the case with H_2trien^{2+}.

In Table IV it may be noted that the rate constant for Hen^+ is 700 M^{-1} sec^{-1} compared to a value of only 5.6 M^{-1} sec^{-1} for NH_3. Yet Hen^+ cannot be acting as a chelate, and its slight advantage in electrostatic attraction to $NiH_{-2}L^-$ ought to be offset by a weaker nickel–amine bond due to the nearby proton. The fact that Hen^+ is so reactive suggests it is acting as a coordinating acid rather than as a monodentate nucleophile. Enhanced reactivity by acids which can coordinate to $MH_{-2}L^-$ complexes has been observed[4,5] with $H_2PO_4^-$ and with $H_2(EDTA)^{2-}$. Similarly, the monoprotonated form of *N*,*N*′-diMeen is moderately reactive.

Table V compares the rate constants for ammonia and polyamine reactions with $NiH_{-2}L^-$, $Ni(CN)_4^{2-}$, and $CuH_{-2}L^-$. In each case there is a large effect (2×10^3–4×10^5) in the relative reactivity of ammonia and the polyamines, and there is relatively little difference in the reactivity of en, dien, and trien. In each case a square-planar complex reacts much faster with chelating ligands and one chelate ring is sufficient to accelerate the reaction rate.

(14) A nucleophilic pathway was not observed in the reaction of NTA^{3-} with copper triglycine (ref 6), but in the present work the NTA^{3-} concentrations were 200 times greater and an appreciable effect was observed.

Table V. Rate Constants for Amine and Polyamine Reactions with Square-Planar Complexes

Ligand	Second-order rate constant, M^{-1} sec^{-1}, at 25°		
	$NiH_{-2}L^-$	$Ni(CN)_4^{2-}$ [a]	$CuH_{-2}L^-$ [b]
NH_3	5.6	$\sim 9 \times 10^{-4}$	29
en	1.2×10^4	50	4.8×10^6
dien	1.3×10^4		$\sim 4 \times 10^6$
trien	1.7×10^4	310	1.1×10^7
$Htrien^+$	1.8×10^4	295	5.1×10^6
H_2trien^{2+}	9.0×10^2	14	1.2×10^5

[a] Reference 11. [b] Reference 6.

Conclusions

The nickel–triglycine complex, like $CuH_{-2}L^-$, undergoes nucleophilic reactions with ligands. These reactions greatly speed the dissociation of the metal–peptide bonds. The peptide nitrogens add protons rapidly after the rate-determining reaction of the triglycine complex with ligands. Chelating amine ligands are particularly effective reactants if at least one primary or secondary amine group is present. Aminocarboxylates are less effective and dicarboxylates least effective. The steric requirements of the reaction support the earlier conclusion that ligand coordination in the equatorial plane of the metal complex—replacing a carboxylate group—is important. Relatively little has been known about the nature of substitution reactions in square-planar complexes which undergo easy conversion to octahedral complexes. It is of interest to note similar and important effects due to chelation for $NiH_{-2}L^-$, $CuH_{-2}L^-$, and $Ni(CN)_4^{2-}$.

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