than the expected value of 0.5; however, this appears to be true in other cases as well.[1,39]

On the basis of the above rationale, we propose that the electron transfer is proceeding through a ferrocyano nitrogen bridging axially to the square-planar Cu(III) complex in the transition state, as shown in Figure 5. As indicated in eq 1, Cu(III) has no coordinated water and must gain two waters on going to Cu(II). Judging from the small negative values of $\Delta S^{\ddagger}$ found, the gain of waters probably occurs after the transition state for the following reasons. We expect ~9 cal deg^{-1} mol^{-1} will be lost in bringing together the two metal centers, and perhaps slightly more in forming the inner-sphere bridge. A small gain in $\Delta S^{\ddagger}$ is possible due to delocalization of the Fe charge over the copper complex, which gives rise to a less organized solvent structure. Overall, this indicates a slightly negative $\Delta S^{\ddagger}$, and addition of H_2O to copper in the transition state (−7.6 cal deg^{-1} mol^{-1} contribution to $\Delta S^{\ddagger}$ [7,16]) would produce an entropy value too negative compared to the observed $\Delta S^{\ddagger}$ to be probable and suggests the mechanism in Figure 5.

Acknowledgment. The authors are extremely grateful to Arlene W. Hamburg for her synthesis of high-purity peptides containing the amino acid Aib. This investigation was supported by Public Health Service Grant Nos. GM-19775 and GM-12152 from the National Institute of General Medicinal Sciences.

Registry No. $Fe(CN)_6^{3-}$, 13408-62-3; $Cu^{III}(H_{-3}Aib_3a)$, 82495-22-5; $Cu^{III}(H_{-3}G_2AibG)^-$, 82495-23-6; $Cu^{III}(H_{-3}G_4)^-$, 57692-61-2; $Cu^{III}(H_{-2}Aib_3)$, 69990-31-4; $Cu^{III}(H_{-3}A_4)^-$, 68628-66-0; $Cu^{III}(H_{-3}V_4)^-$, 62959-93-7; $Cu^{III}(H_{-3}F_4)^-$, 82495-24-7; $Cu^{III}(H_{-3}A_3G)^-$, 82495-25-8; $Cu^{III}(H_{-3}AG_3)^-$, 69088-03-5; $Cu^{III}(H_{-3}VG_2a)$, 62801-40-5; $Cu^{III}(H_{-3}G_3a)$, 62801-36-9; $Cu^{III}(H_{-3}G_3A)^-$, 82495-26-9.

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Axial Coordination of Monodentate Ligands with Nickel(III) Peptide Complexes

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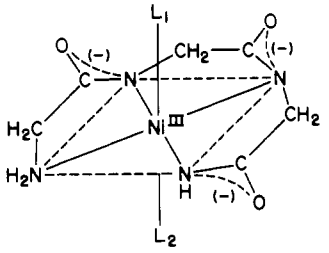
Stability constants are determined by an electrochemical method for axial coordination of monodentate nitrogen ligands to nickel(III) peptide complexes in aqueous solution. The stability constants at 25 °C vary from 1100 to 50 M^{-1} (in the order imidazole > $NH_3 \simeq N_3^-$ > pyridine) but are relatively independent of the nature of the peptide. The substitution is too fast to observe by stopped-flow methods, and a lower limit for the axial water exchange rate constant is estimated as $k_{H_2O} > 4 \times 10^6$ s^{-1}. There are no reactions observed with the corresponding nickel(II) peptides. Displacement of water from the second axial site of nickel(III) occurs in frozen aqueous solutions with ammonia but not at room temperature. The diglycylethylenediamine (DGEN) complex, $Ni^{III}(H_{-2}DGEN)^+$, adds H^+ and Cl^- to give one or two axially coordinated Cl^- in frozen aqueous solution (123 K), but the complexes are too weak to be detected at room temperature.

Introduction

Nickel(II) promotes ionization of peptide and amide hydrogens upon complexation by oligopeptides.[1] Coordination of deprotonated peptide nitrogens stabilizes the trivalent oxidation state of nickel, and the reduction potentials in aqueous solution for a variety of nickel(III, II) peptide couples have been determined.[2] Studies of the temperature dependence[3] of the electrode potentials indicate that the nickel(II) peptide complexes are not axially solvated, in contrast to the nickel(III) forms. Electron paramagnetic resonance studies[4,5] show that the nickel(III) peptides such as $Ni^{III}(H_{-3}G_3a)$[6] (**1**) have a tetragonally distorted octahedral geometry, with solvent molecules occupying the axial sites and an approximately square-planar arrangement of the peptide donors. The EPR studies presented evidence for axial substitution by ammonia in frozen aqueous glasses to form both mono- and diammine adducts. Even very low ammonia concentrations resulted in the formation of complexes such as $Ni^{III}(H_{-3}G_3a)NH_3$ in the frozen state, giving the appearance of a very strong complex in aqueous solution.[5] However, the present work shows that the ammonia complexes in aqueous solution are relatively weak and are many orders of magnitude less stable than estimated from the composition of the solutions before they are frozen.



1a, $L_1 = L_2 = H_2O$
b, $L_1 = NH_3$, $L_2 = H_2O$

Axial coordination of anionic ligands such as halides and sulfate to nickel(III) macrocyclic complexes has been recently reported.[7-10] Stability constants range from about 50 M^{-1} for Br^- to more than 10^3 M^{-1} for SO_4^{2-}. The rates of axial substitution have been examined as well. The corresponding complexes are not observed with the nickel(III) peptides.

Measurement of equilibrium constants for axial coordination of ammonia, imidazole, and other nitrogen ligands to nickel(III) peptides is complicated by protonation of the nitrogen

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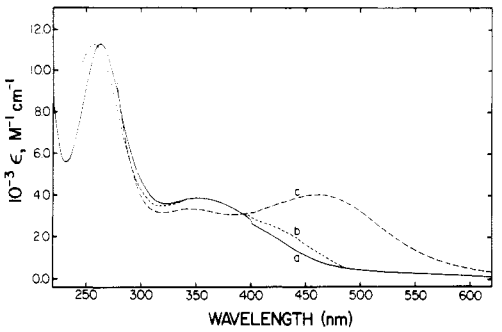

Figure 1. UV–visible spectrum of $Ni^{III}[H_{-2}(Aib)_3]$ in 1.0 M $NaClO_4$: (a) no added ligand; (b) [imidazole] = 0.15 M; (c) $[N_3^-]$ = 0.20 M.

bases in acidic media and by rapid decomposition of the nickel(III) complex in base. In most cases the UV–visible absorption spectra are similar for the complexed and uncomplexed species (Figure 1), so spectrophotometric determination is difficult. These problems have been overcome by use of an electrochemical method of determining binding constants.[11] Since nickel(II) peptides do not react with axial donors and nickel(III) peptides do, the trivalent oxidation state is stabilized relative to the divalent state by the presence of monodentate ligands. Thus, if substitution is rapid, the observed reduction potential of the couple decreases with increasing axial binding to nickel(III). This method has the great advantage of using only nickel(II) solutions, which are much more stable in mild base than the corresponding nickel(III) complexes.

In the present work, equilibrium constants ranging from 20 to 10^3 M^{-1} are measured for coordination of a variety of monodentate ligands to nickel(III) peptide complexes. The rate of substitution is too fast to observe by stopped-flow methods.

Experimental Section

Tetraglycine (G_4), tetraalanine (A_4), and trialanine (A_3) were obtained from Biosynthetika. Triglycinamide (G_3a) and glycylglycylalaninamide (G_2Aa) were obtained as the hydrochlorides from Vega-Fox Chemical Co. Peptides containing the amino acid residue α-aminoisobutyric acid (Aib) were synthesized by methods described elsewhere.[12] *N,N'*-Diglycylethylenediamine was prepared by the method of Cottrell and Gill[13] and isolated as the free base. The purity of all peptides was checked by liquid chromatography and elemental analysis. A stock solution of $Ni(ClO_4)_2$ was prepared by reaction of $NiCO_3$ and $HClO_4$ and standardized by EDTA titration using murexide as an indicator. Imidazole was recrystallized twice from toluene prior to use. Pyridine and 4-methylpyridine were purified by vacuum distillation.

Solutions of nickel(II) peptides (5×10^{-3} M) were prepared by the reaction of 10–30% excess peptide with $Ni(ClO_4)_2$. The pH was adjusted to 10.5 with NaOH to form the fully deprotonated complexes. Stock solutions of monodentate ligands were freshly prepared daily. Solutions for electrochemical measurements were prepared by mixing aliquots of the peptide complex and the monodentate ligand with a solution of background electrolyte (KNO_3) and adjusting the volume to 10 mL. The ionic strength was always maintained at 1.0, and the pH was held between 8 and 9 with either borate buffer (2.5 mM) or the ligand itself. In the latter case, the pH was measured and the concentration of unprotonated base calculated. This pH range is necessary because irreversible electrochemical behavior occurs at higher pH and the nickel(II) peptide complex is unstable in more acidic conditions. The temperature was controlled at 25.0 ± 0.1 °C unless otherwise noted. The relationship between observed pH values and −log $[H^+]$ was determined by titration of $HClO_4$ and NaOH (Sargent-Welch electrodes, saturated NaCl reference) and is given by −log $[H^+]$ = pH + 0.29 in 1 M KNO_3.

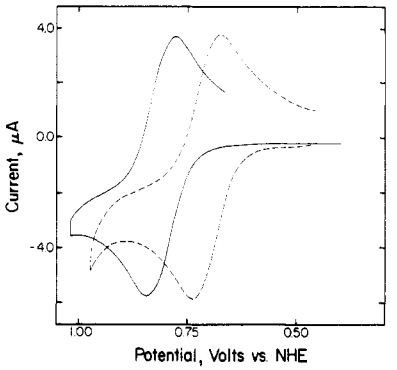

Figure 2. Cyclic voltammograms of $Ni^{II}[H_{-3}(Aib)_3a]^-$ in aqueous solution at a glassy-carbon electrode: (—) [imidazole] = 0; (---) [imidazole] = 0.010 M. $[Ni((Aib)_3a)]_T = 5 \times 10^{-4}$ M; μ = 1.0; scan rate = 40 mV/s; T = 25 °C.

Cyclic voltammetry was performed with a three-electrode system consisting of a saturated KCl calomel reference electrode, a platinum wire auxiliary electrode, and either a carbon-paste or glassy-carbon working electrode. Voltammograms were generated with a Bioanalytical Systems, Inc., CV-1 instrument and were recorded on a Hewlett-Packard HP 7035B X-Y recorder. Scan rates between 30 and 200 mV s^{-1} were used. Preconditioning of the carbon-paste electrode by cycling between the potential limits of the solvent was necessary to obtain quasi-reversible cyclic voltammograms. Potentials were measured from the midpoint of the peaks. Data from at least three cyclic voltammograms were averaged for each concentration of monodentate ligand, [L]. The concentration of the nickel–peptide complex was always ≤10% of the ligand concentration so that [L] remained essentially invariant during the scan. Formal reduction potentials at [L] = 0 were redetermined during each series of solutions to minimize errors from day to day. All potentials are reported in terms of formal reduction potentials vs. NHE.

Solutions of nickel(III) peptide complexes were prepared by electrochemical oxidation of the corresponding Ni(II) species using a flow electrolysis apparatus.[14–16] Yields of 50–90% nickel(III) were obtained, and the eluent was acidified to pH ~3 with a few drops of 0.1 M $HClO_4$ to minimize decomposition of the nickel(III) complex.

Ultraviolet and visible absorption measurements were obtained with either a Cary 14 or a HP 8450A spectrophotometer. Electron paramagnetic resonance (EPR) spectra were obtained with a Varian E-109 X-band EPR system modulated at 100 KHz and equipped with a Varian variable-temperature controller. Spectra at room temperature were obtained with an E-238 multipurpose cavity and a thin quartz cell, S-813, supplied by Scanco, Solvang, CA. Solutions were freeze-quenched in liquid nitrogen within 30 s of formation. Coupling constants and g values were determined by a spectrum-matching procedure,[17] which entailed generation of calculated curves from estimated values until the best fit with the experimental curve was obtained. The magnetic field was calibrated with DPPH in KCl embedded in paraffin.

Results

Determination of Equilibrium Constants. Equilibrium constants K^{III} (eq 1) for a variety of nickel(III) peptide com-

$$Ni^{III}(peptide)(H_2O)_2 + L \overset{K^{III}}{\rightleftharpoons} Ni^{III}(peptide)(H_2O)L + H_2O \quad (1)$$

$$Ni^{III}(peptide)(H_2O)_2 + e^- \rightleftharpoons Ni^{II}(peptide) + 2H_2O \quad (2)$$

plexes with monodentate donors in aqueous solution were

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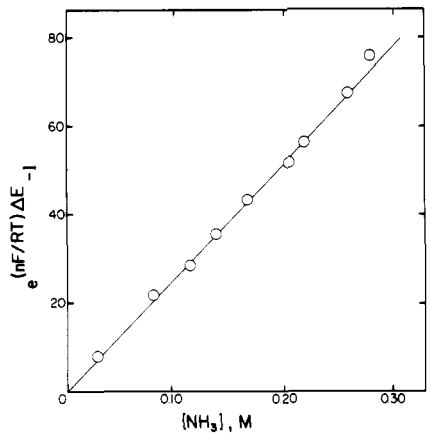

Figure 3. Plot of $\exp[\Delta E(nF/RT)] - 1$ vs. $[NH_3]$ for nine concentrations of NH_3 with $[Ni^{II}(H_{-3}G_3a)] = 5 \times 10^{-4}$ M. Slope = K = 262 ± 5 M^{-1}; intercept = −0.3 ± 0.8; r^2 = 0.998.

Table I. Equilibrium Constants for Coordination of NH_3 to Ni^{III}(peptide)[a]

peptide	K^{III}, M^{-1}	peptide	K^{III}, M^{-1}	peptide	K^{III}, M^{-1}
A_3	80 ± 10	GGAa	320 ± 40	A_4	180 ± 20
$(Aib)_3$	110 ± 14	$(Aib)_3a$	350 ± 40	GG(Aib)G	270 ± 30
G_3a	270 ± 30	G_4	160 ± 20		

[a] $[Ni^{II}] = 5 \times 10^{-4}$ M, μ = 1.0 KNO_3/NH_4NO_3, T = 25.0 °C, and $[NH_4^+]_T$ = 0–1.0 M.

determined by measuring the shift in formal potential ($E°'$) in the presence of the ligand (Figure 2). The formal potential is the measured reduction potential of the cell under specified conditions of ligand concentration, ionic strength, and pH. This technique has been treated in detail elsewhere.[11,18-21] Provided that eq 1 and 2 represent the only equilibria in solution and that relaxation of these equilibria is rapid on the time scale of the electrochemical measurement, the relationship in eq 3 holds, where ΔE is defined as in eq 4 and $E°'_L$ rep-

$$\exp[\Delta E(nF/RT)] - 1 = K^{III}[L] \quad (3)$$

$$\Delta E = E°' - E°'_L \quad (4)$$

resents the formal potential measured in the presence of L. Cyclic voltammograms of $Ni[H_{-3}(Aib)_3a]^-$ in the presence and absence of imidazole are shown in Figure 2. Other expressions describing binding of L to both oxidation states[11] or the binding of two molecules of L to nickel(III) have been derived. In all cases, plots of $\exp[\Delta E(nF/RT)] - 1$ vs. [L] were linear with ordinate intercepts statistically equal to zero. In no case were the data better fit by removal of the assumption that only one ligand molecule binds to the trivalent oxidation state exclusively. Therefore, values of K^{III} were determined by a weighted least-squares fit of the data to the function $y = ax$ with a forced zero intercept and the slope $a = K^{III}$. Good fits ($r^2 > 0.990$) were obtained in all cases. A typical plot is given in Figure 3.

Values of binding constants of NH_3 to a series of Ni(III)–peptide complexes are given in Table I. For $Ni^{III}(H_{-3}G_3a)$ the value of K^{III} for formation of the adduct was determined to be invariant over the −log $[H^+]$ range 8–9. This, along with EPR evidence,[5] shows that the substitution of monodentate ligands involves replacement of axial water rather than substitution of the peptide ligand. The latter reaction is expected to be pH dependent, since a displaced amide nitrogen would be protonated immediately.

Table II. Temperature Dependence of K^{III} for the Reaction of $Ni^{III}(H_{-3}G_3a)$ with NH_3[a]

T, °C	K^{III}, M^{-1}	T, °C	K^{III}, M^{-1}	T, °C	K^{III}, M^{-1}
20.1	291	30.0	245	34.0	219
25.0	270				

$\Delta H° = -3.6 \pm 0.4$ kcal mol^{-1}

$\Delta S° = 1.0 \pm 1.2$ cal deg^{-1} mol^{-1}

[a] $[Ni^{II}] = 5 \times 10^{-4}$ M, μ = 1.0 KNO_3/NH_4NO_3, and $[NH_4^+]_T$ = 0–1.0 M.

Table III. Equilibrium Constants for the Reaction $Ni^{III}(H_{-x}peptide) + L \rightleftarrows Ni^{III}(H_{-x}peptide)L$[a]

L	peptide		
	G_3a	$(Aib)_3a$	$(Aib)_3$
imidazole	650 ± 10	1130 ± 30	780 ± 15
1-methylimidazole	550 ± 10	1150 ± 20	570 ± 10
2-methylimidazole	38 ± 2	24 ± 1	19 ± 1
pyridine	55 ± 2	57± 2	40 ± 2
4-methylpyridine	93 ± 3	132 ± 6	83 ± 2
azide	*b*	*b*	137 ± 1

[a] $[Ni^{II}] = 5 \times 10^{-4}$ M, μ = 1.0 KNO_3, T = 25.0 °C, and $[L]_T$ = 0.0–0.05 M. [b] Not measured.

The thermodynamic constants $\Delta H°$ and $\Delta S°$ for the reaction of ammonia with $Ni^{III}(H_{-3}G_3a)$ were determined by measuring K^{III} over the temperature range 15–35 °C (Table II). Values of −3.6 ± 0.4 kcal mol^{-1} and 1.0 ± 1.2 cal deg^{-1} mol^{-1} were found for $\Delta H°$ and $\Delta S°$, respectively.

The equilibrium constants for reaction of several other monodentate ligands with the nickel(III) complexes of $(Aib)_3$, $(Aib)_3a$, and G_3a appear in Table III. In addition we checked for coordination of several anionic ligands including Cl^-, Br^-, HPO_4^{2-}, SO_4^{2-}, $CH_3CO_2^-$, and borate ion. With the exception of acetate, no evidence for coordination of these ions to nickel(III) peptides was found, and values of K^{III} are estimated to be less than 2 M^{-1}. In the case of acetate ion, concentrations of 0.5 M resulted in a small potential shift corresponding to $K^{III} \simeq 0.5$ M^{-1}, but this may be due to a medium effect since sodium acetate made up the bulk of the ionic background. Finally, the pK_a of coordinated water is estimated to be greater than 11, since the reduction potential is constant for −log $[H^+]$ values between 6.5 and 10.5.

In most cases, only small changes in the electronic spectra of nickel(III) peptides are observed upon axial substitution. Figure 1 shows the spectrum of $Ni^{III}[H_{-2}(Aib)_3]$ in 1 M $NaClO_4$ and in the presence of 0.15 M imidazole in pH 7.6, where the imidazole adduct is over 98% formed. A shift in the ultraviolet λ_{max} from 263 to 256 nm is observed. Additionally, a shoulder between 400 and 450 nm appears in the spectrum of the imidazole complex.

Addition of azide to a solution of $Ni^{III}[H_{-2}(Aib)_3]$ results in the appearance of a new maximum at 456 nm with only a small loss of absorbance at 352 nm. This band is probably an azide-to-metal charge-transfer transition. The stability constant for binding of azide was determined spectrophotometrically with use of curve-fitting software provided with the HP 8450A spectrophotometer and was found to be 130 ± 20 M^{-1}, in excellent agreement with the value of 137 M^{-1} found electrochemically.

Rate of Axial Substitution. Attempts were made to measure the rate of dissociation of the imidazole and azide adducts of $Ni^{III}[H_{-2}(Aib)_3]$ using a Durrum stopped-flow spectrometer. Solutions of the fully formed imidazole complex at pH 7 were mixed with acetate buffer at pH 5, and the absorbance at 450

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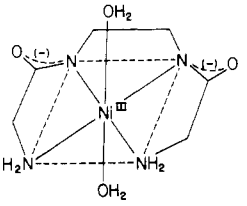
nm was followed. In the case of azide, a solution containing the adduct was rapidly mixed with 0.1 M $NaClO_4$ and the absorbance at 456 nm was followed. In both cases, a constant absorbance corresponding to that expected for the products was observed, indicating that the reaction was complete within the dead time (<5 ms) of the instrument. A lower limit of 500 s^{-1} can be estimated for the dissociation rate constant, and the formation rate constant $k_f = K^{III}k_d$ is therefore greater than 4×10^5 M^{-1} s^{-1} for imidazole and greater than 6.5×10^4 M^{-1} s^{-1} for azide.

EPR Studies. In an earlier report,[6] the value of the binding constant of NH_3 to $Ni^{III}(H_{-3}G_3a)$ was approximated by estimating the ratio of EPR signals from mixtures of nickel(III) species in frozen solutions at 123 K. The value found was on the order of 10^7 M^{-1} for coordination of one ammonia molecule. In solutions with higher concentrations of NH_3, a spectrum assignable to a diammine adduct was observed with an apparent stability constant of 60 M^{-1} for $Ni^{III}(H_{-3}G_3a)(NH_3)_2$. However, the assumption that the freezing process does not greatly shift the equilibria is highly erroneous. No evidence for coordination of a second ammonia at room temperature is found in the present study, and the stability constant for the first substitution is only about 2×10^2 M^{-1}. The relative amounts of species identified in the frozen EPR samples do not correspond to the concentrations of species in solution before freezing. Despite the fact that the freezing process takes only a few seconds, the ammonia appears to concentrate in the vicinity of the nickel peptides to give Ni(III) axial adducts. Once the frozen state is obtained, the EPR spectra do not change between 100 and 225 K, so there is no shift in equilibria due to relaxations in the frozen state between NH_4^+ in the outer sphere and NH_3 in the inner sphere of the nickel. The fact that the freezing process changes the amount of Ni^{III}–NH_3 bonding is not surprising, but the magnitude of the change (corresponding to a factor of 10^5 in the apparent stability constant) is far greater than expected. The composition of the frozen glass is very different from that of the room-temperature solution even though the quenching process is moderately rapid.

Another complex showing marked differences in behavior between room temperature and −150 °C is $Ni^{III}(H_{-2}DGEN)^+$ (structure **2**). In the absence of halide, the spectrum of this



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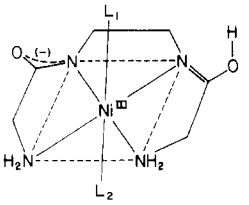
species at −150 °C undergoes a shift (Table IV) at $[H^+] \approx 0.1$ M. This is attributed to "outside" protonation of one of the peptide oxygens without loss of coordination of the peptide nitrogen to form $Ni^{III}(H_{-2}DGEN)H^{2+}$ (**3**). Outside proton-



3a, $L_1 = L_2 = H_2O$
b, $L_1 = Cl^-$, $L_2 = H_2O$
c, $L_1 = L_2 = Cl^-$

ation has been previously observed in kinetic studies of metal peptide complexes,[22-24] and the shift to lower values of $g_\perp$ is consistent with the weakening of the in-place donor strength expected.

Table IV. EPR Data for $Ni^{III}(H_{-2}DGEN)^+$ Complexes in Frozen Aqueous Solutions (123 K, Microwave Frequency 9.08 GHz

	$g_\perp$	$g_\parallel$	$a_\parallel$
$Ni(H_{-2}DGEN)^+$ [a]	2.256	2.011	
$Ni(H_{-2}DGEN)H^{2+}$ [b]	2.247	2.014	
$Ni(H_{-2}DGEN)HCl^+$ [c]	2.20	2.009	33.3[d]
$Ni(H_{-2}DGEN)HCl_2$ [c]	2.192	2.015	31.2[d]

[a] $[Ni^{III}] = 10^{-4}$ M, pH 5, unbuffered. [b] $[Ni^{III}] = 10^{-4}$ M, $[H^+] = 0.5$ M. [c] Conditions of Figure 4. [d] Values in gauss for ^{35}Cl. The hyperfine constant for ^{37}Cl was not resolved.

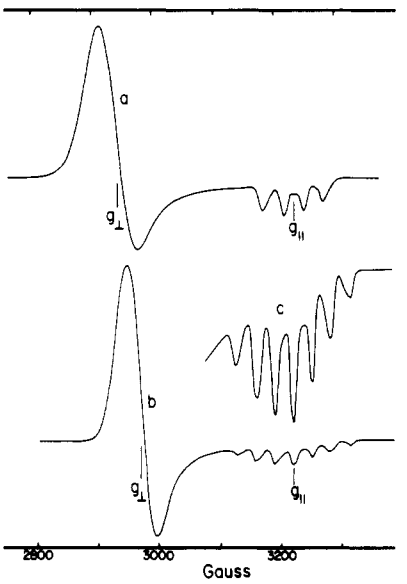


Figure 4. EPR spectra of chloride adducts of $Ni^{III}(DGEN)$ in frozen aqueous solutions at 123 K and microwave frequency 9.08 GHz: (a) $Ni^{III}(H_{-2}DGEN)HCl^+$ formed from 10^{-4} M $Ni^{III}(H_{-2}DGEN)^+$ at $[H^+] = 0.1$ M and $[Cl^-] = 10^{-3}$ M; (b) $Ni^{III}(H_{-2}DGEN)HCl_2$ formed from 10^{-4} M $Ni^{III}(H_{-2}DGEN)^+$ at [HCl] = 1.0 M; (c) expansion of $g_\parallel$ region of (b).

In the presence of 10^{-3} M chloride at $[H^+] > 0.1$ M, the low-temperature spectrum (Figure 4a) corresponds to axial coordination of chloride ion ($I = {}^3/_2$) to the protonated complex, and replacement of the second axial water is complete when $[Cl^-] > 0.1$ M. In contrast, at pH 4 and $[Cl^-] = 0.10$ M, the monochloro adduct is only about 75% formed. Nickel(III)–DGEN is the only nickel(III) peptide system that shows chloride coordination.

At 25 °C, however, no changes in the UV–visible spectrum of $Ni^{III}(H_{-2}DGEN)^+$ are seen between pH 7 and 1.0 M HCl. Also the shift in g_{av} obtained from room-temperature EPR spectra is less than half the calculated value for coordination of even one chloride ion. The difference in stability for this adduct between 25 °C and the frozen state is estimated to be at least a factor of 2×10^4. Hence, the freezing process shifts the nickel(III)–chloride equilibria to a similar extent as that observed with nickel(III)–ammonia.

Discussion

Nickel(III) peptides form moderately strong axial adducts with nitrogen bases, with values of K^{III} ranging from about 50 M^{-1} for pyridine donors to about 10^3 M^{-1} for imidazole

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donors (Table III). As seen in Table I, the magnitude of K^{III} is relatively insensitive to the nature of the peptide. Stability constants for binding of ammonia to the nickel(III) complexes of eight peptides differ by no more than a factor of 4. It may be noted that, within this narrow range, the binding constants are smallest for tripeptide complexes and largest for tripeptide amide complexes. Comparison of equilibrium constants for $Ni^{III}[H_{-2}(Aib)_3]$ and $Ni^{III}[H_{-3}(Aib)_3a]$ (Table III) confirms this trend.

The presence of alkyl groups on the α-carbons of the peptide also has little effect on the binding of axial donors. Even with the sterically hindered ligand 2-methylimidazole, the K^{III} value for $Ni^{III}[H_{-3}(Aib)_3a]$ is about the same as that for $Ni^{III}(H_{-3}G_3a)$, although both adducts are much less stable than the corresponding unsubstituted imidazole complexes. Thus, axial coordination to nickel(III) is unhindered, even when the α-carbons in the peptide chain are fully substituted.

The linearity of plots of $\exp[\Delta E(nF/RT)] - 1$ vs. [L] indicates that coordination of a second monodentate ligand is negligible over the concentration ranges used. This preference for four or five nitrogen donors may be compared with the case for low-spin cobalt(III) complexes. The stepwise constants for addition of the fifth and sixth ammonia molecules to give $Co(NH_3)_6^{3+}$ are 1.1×10^5 and 3.2×10^4 M^{-1}, respectively.[25,26] The low-spin d^6 cobalt(III) prefers an octahedral geometry, while low-spin d^7 nickel(III) prefers a square-planar or square-pyramidal arrangement of nitrogen donors. The isoelectronic low-spin cobalt(II) also commonly assumes a square-pyramidal geometry.[27,28]

Effect of L. The axial adducts of imidazole and 1-methylimidazole are about 10 times more stable than those of pyridine and 4-methylpyridine, reflecting the higher basicity of the imidazole nitrogen. The ammonia complexes are somewhat weaker than those of imidazole, which is typical for transition-metal complexes.[29,30]

Rate of Substitution. A lower limit for the rate constant for axial substitution is estimated to be 4×10^5 M^{-1} s^{-1}. Kinetic data for substitution in other low-spin d^7 complexes are scarce. Endicott et al.[31] reported axial aquation rate constants of $>10^3$ s^{-1} for several Co(II) macrocyclic species. The rate constants for formation of the sulfate adduct of a nickel(III) macrocyclic complex[8,9] has been reported as 1×10^6 M^{-1} s^{-1}, while halides have been found to replace axial water in $Ni^{III}(cyclam)^{3+}$ with rate constants of $2-12 \times 10^2$ M^{-1} s^{-1}.[7] A probable mechanism for Ni(III) substitution reactions is a dissociative-interchange process.[7,9] Substitution reactions of this type are considered to proceed via formation of an outer-sphere complex (eq 5) followed by dissociative

$$Ni^{III}(peptide)(H_2O)_2 + L \overset{K_{os}}{\rightleftharpoons} [Ni^{III}(peptide)(H_2O)_2,L] \xrightarrow{k_{ex}} Ni^{III}(peptide)(H_2O)(L) + H_2O \quad (5)$$

exchange of the incoming ligand and coordinated solvent. For $Ni^{III}[meso\text{-}Me_6[14]aneN_4](H_2O)_2^{3+}$, the value of k_{ex} was estimated as 1.1×10^4 s^{-1},[8] and for $Ni^{III}(cyclam)(H_2O)_2^{3+}$, $k_{ex} < 10^3$ s^{-1}.[7] If K_{os} for the formation of an outer-sphere complex between the neutral imidazole ligand and $Ni^{III}[H_{-2}(Aib)_3]$ is estimated as 0.1 M^{-1},[32] a water exchange rate constant in excess of 4×10^6 s^{-1} is obtained. This lower limit is over 2 orders of magnitude greater than the rates observed for nickel(III) macrocyclic systems. This may be explained by the relative tetragonal distortion of Ni(III) peptide and Ni(III) macrocycles. Deprotonated peptide nitrogens are stronger σ donors than amine nitrogens. Hence, the extent of axial elongation may be greater in the peptide complexes, resulting in greater lability in the axial positions.[31]

Coordination of Halides. Nickel(III) peptide complexes at 298 K show no evidence of binding halide ions axially, even in 1.0 M X^- concentrations. Solutions in the frozen state, which favors complex formation by many orders of magnitude, have EPR spectra corresponding to the unsubstituted species (except for the DGEN complex in acid). In contrast, nickel(III) macrocycles bind chloride, bromide, and other anionic ligands readily.[7-10] Haines and McAuley[7] reported the values of the binding constants of Cl^- and Br^- to $Ni^{III}(cyclam)^{3+}$ over the range 6–34 °C. Although the data are scattered, values of $\Delta H°$ and $\Delta S°$ for these reactions can be estimated from their data and are found to be 2–5 kcal mol^{-1} for $\Delta H°$ and 15–25 cal deg^{-1} mol^{-1} for $\Delta S°$. Hence, the driving force for halide substitution in this complex is the gain in entropy, which overcomes an unfavorable enthalpic contribution. This behavior is common for coordination of halides to metals in the +3 oxidation state[28] and may be explained by the charge neutralization which reduces the extent of solvation in the products.

In the present study, the nickel(III) complexes carry an overall charge of 0 or 1−, and the incoming axial ligands are neutral. Thus, there are no charge neutralization effects and the entropy change is small (1.0 ± 1.2 eu). The value of $\Delta H° = -3.6$ kcal mol^{-1} is not unusual for metal(III) ammine complex formation.[26] Coordination of an anionic ligand to a neutral or negative nickel(III) peptide complex would not lead to a large favorable entropic change as in the case of the tripositive nickel(III) macrocycles. We found no evidence for such coordination, even in frozen solutions.

However, as previously described, coordination of chloride to nickel(III) complexes of the pseudo-peptide DGEN is observed in frozen solutions. While EPR spectra of frozen solutions do not accurately reflect behavior at higher temperatures, comparisons between different nickel(III) complexes in frozen media are useful. Thus, while neutral and negative complexes show no coordination of chloride at 150 K, the adduct of the positively charged $Ni^{III}(H_{-2}DGEN)^+$ is about 80% formed at $[Cl^-] = 0.10$ M and the dipositive species $Ni^{III}(H_{-2}DGEN)H^{2+}$ is completely complexed by chloride at $[Cl^-] = 10^{-3}$ M. On the other hand, at 298 K, the chloride complex of $Ni^{III}DGEN$ is very weak (<1 M^{-1}), but the corresponding complex with $Ni^{III}(cyclam)^{3+}$ is moderately strong (250 M^{-1}).[6] These observations support the conclusion that the major thermodynamic differences between axial coordination in nickel(III) peptide complexes and nickel(III) macrocycle complexes can be attributed to differences in the overall charge.

Conclusions

Nickel(III) peptide complexes bind nitrogen donors with equilibrium constants ranging from about 50 M^{-1} for pyridine ligands to about 10^3 M^{-1} for imidazole ligands. The substitution rate is very rapid, with a water exchange rate estimated as $k_{ex} > 4 \times 10^6$ s^{-1}. For a given ligand, the strength of the axial adduct is relatively insensitive to the equatorial peptide. Substitution in the second axial site is not favored and was

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not detected at room temperature.

Formation of $Ni^{III}(H_{-3}G_3a)(NH_3)$ is exothermic and has a very small entropy charge, in contrast with axial substitutions of anions in nickel(III) macrocyclic complexes, where $\Delta H^\circ > 0$ and the reaction is driven by a favorable entropy change brought about by charge neutralization.

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Oxygenation of [Tris(2-pyridyl)amine](trifluoromethanesulfonato)copper(I) in Nonaqueous Solvents. Synthesis and Structural Characterization of the Cubane-like Cluster $[Cu_4(OH)_4(SO_3CF_3)_2[N(C_5H_4N)_3]_4][SO_3CF_3]_2 \cdot C_3H_6O$

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A product of the reaction of molecular oxygen with [tris(2-pyridyl)amine](trifluoromethanesulfonato)copper(I) has been characterized by a low-temperature X-ray diffraction analysis and found to be a cubane-like tetramer of formula $[Cu_4(OH)_4(SO_3CF_3)_2[N(C_5H_4N)_3]_4][SO_3CF_3]_2 \cdot C_3H_6O$, with cupric ions and hydroxyl oxygen atoms at alternating vertices of a cube. Each cupric ion is essentially octahedrally coordinated, being bound to three OH bridges, two pyridine N atoms, and one triflate O atom. The cube is of approximate D_{2d} symmetry, the elongation along one axis possibly arising as a consequence of Jahn-Teller distortion. In this complex the tris(2-pyridyl)amine acts as a *bidentate* rather than a tridentate ligand and each triflate ligand spans two vertices of the cluster. Magnetic susceptibility measurements reveal that the cupric ions in the cube are antiferromagnetically coupled, and this observation is readily rationalized on the basis of the structural data. Isotopic tracer experiments demonstrate that the hydroxyl oxygen atoms in the product originate largely in the molecular oxygen used in the reaction and that the hydrogen atoms originate largely in other tris(pyridyl)amine molecules. The material crystallizes with four formula units in space group C_{2h}^5-$P2_1/n$ of the monoclinic system in a cell of dimensions $a = 18.848$ (7) Å, $b = 13.804$ (5) Å, $c = 29.491$ (10) Å, and $\beta = 99.29$ (3)°. The structure has been refined isotropically to an R index of 0.098 on the basis of 337 variable parameters and 8904 unique observations obtained at −150 °C.

The importance of copper ions as catalysts in both enzymic[2] and nonenzymic[3,4] chemical systems is well-known. Many of the copper proteins activate molecular oxygen, and the functions of these proteins are varied; they serve as oxygen carriers (hemocyanin)[5] or, more often, as catalysts in oxygenation (oxygenases)[2,6] or oxidation (oxidases) reactions.[2,6] The high catalytic activity of both enzymic and nonenzymic copper ions has been attributed to, among other factors, the ease with which Cu(I) is oxidized by O_2 to Cu(II). It has been difficult in the past to study this oxidation reaction in model systems because of both the very rapid oxygenation of Cu(I) in aqueous solution ($k > 10^5$ M^{-1} s^{-1})[7] and the paucity of Cu(I) salts soluble in aprotic media. Early work was carried out with CuCl in dilute acidic solution,[8,9] followed by experiments in glacial acetic acid,[10] where CuCl is less soluble and hence oxidized less rapidly. In the aqueous solutions the rate of Cu(I) oxidation was found to be dependent on $[H^+]$ and first order with respect to both molecular oxygen and Cu(I) concentrations. In glacial acetic acid the oxidation reaction showed first-order dependency on O_2 and second-order dependency on Cu(I). More recently the oxidation of $[Cu^I(imidazole)_2]^+$ and $[Cu(NH_3)_2]^+$ has also been studied.[11] The oxidation of a cuprous 2,2′,2″-terpyridine complex in aqueous acetonitrile[12] and the reaction of O_2 with $[Cu(CH_3CN)_4][ClO_4]$ in perchloric acid–acetonitrile solutions[13] were also examined, as was the oxidation of $Cu(bpy)_2^+$ in buffered aqueous solution.[14] All of these reactions were found to be first order in $[Cu^+]$ and $[O_2]$. These latter studies with aromatic nitrogenous ligands may be more relevant to the biological systems because in many of the copper proteins histidine (imidazole) has been implicated as a ligand.[15-17] Also noteworthy are the series of kinetic studies[7,18,19] performed with $Cu(1,10\text{-phen})_2^+$ in the aprotic solvent nitromethane; not only is phenanthroline a heterocyclic nitrogenous base, as is imidazole, but the aprotic

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