be required to determine whether this type of variation with temperature is general or significant. This effect is not seen in the $\Delta H°$ values for the copper(II)–phenylalanine system; however, the $\Delta H°$ values are less certain for this system. The $\Delta S°$ data also appear to be similar to those for other copper(II)–amino acid systems.[2,3] The $\Delta H°$ values calculated from the temperature dependence of K for both copper(II)–amino acid systems are in good agreement with the calorimetrically determined $\Delta H°$ values.

Contribution from the Evans and McPherson Chemical Laboratories,
The Ohio State University, Columbus, Ohio

Flexidentate Chelation of α,ω-Diaminocarboxylic Acids with Copper(II) and Nickel(II)

By George R. Brubaker and Daryle H. Busch

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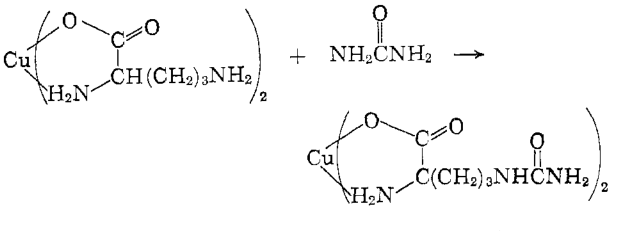
The functional groups used in chelation by α,ω-diaminocarboxylic acids in their nickel(II) and copper(II) complexes have been deduced. The numbers of coordinated oxygen and nitrogen donors are estimated from d–d band positions while the relative intensities of the first two triplet–triplet transitions are influenced by chelate ring size. The presence of uncoordinated amino groups is indicated by rapid reaction with benzoyl chloride. The ratio of metal to ligand is inferred from spectral measurements or obtained from earlier equilibrium studies. The bis copper(II) complexes of ornithine and lysine involve bidentate chelation by the carboxyl and α-amino groups in both acidic and basic media with the ω-amine groups remaining free. The species of maximum ligand to metal ratio formed by nickel(II) with ornithine in acidic media is $\mathrm{Ni(amac{\cdot}H^+)_3^{2+}}$, involving carboxyl and α-amino chelation. However, in basic media the ligand is tridentate and the highest complex is $\mathrm{Ni(amac)_2}$. With lysine, the ω-amine appears to bridge to a second metal ion while the carboxyl and α-amine chelate.

Introduction

In 1937, Kurtz[1] demonstrated the use of copper(II) as a masking agent to protect the α-amine when preparing citrulline (α-amino-δ-carbamidovaleric acid) from ornithine (α,δ-diaminovaleric acid).



His choice of the copper complex was dictated by prior knowledge of the stabilities of the α- and δ-amino acid chelates and the ease with which the copper ion can be removed from the organic products.

Further studies[2] indicated that the copper complexes of lysine, ornithine, and 2,4-diaminobutyric acid undergo a variety of reactions at the free ω-amine. Kurtz prepared carbamyl, phenylcarbamyl, benzoyl, *p*-nitrobenzoyl, and phenylsulfonyl derivatives, recovering near theoretical yields of the expected products in some cases.

Our interest in these reactions arises from the extremely specific exclusion of reactions at the donor atoms. We report here the properties and inferred structures of some copper(II) and nickel(II) complexes with α,ω-diaminocarboxylic acids.

The fact that α-amino acid complexes with first-row transition metal ions are vastly more stable in aqueous solution than the corresponding simple carboxylic acid anions suggests that complexation involves both the carboxyl oxygen and the α-amine in a five-member chelate ring.[3] It has been observed that the stability of amino acid complexes decreases with increased separation of the amino and carboxyl groups. The γ- and δ-amino acid complexes are quite unstable in aqueous solution relative to the α and β derivatives.[4] Cyclic complexes of ε-amino acids have not been reported in the literature, but Nakahara, Hidaka, and Tsuchida reported the isolation of tetrakis(ε-aminocaproate)copper(II) perchlorate, with four ligands bound to the metal ion solely through the amino groups.[5]

Albert[6] applied Bjerrum's technique to determine the stability constants of some copper and nickel complexes with α,ω-diaminocarboxylic acids. His evidence suggests that several of these ligands can coordinate with metal ions in more than one way. Such behavior may be conveniently called flexidentate chelation. It was reported that the copper(II) complexes of 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 2,5-diaminovaleric acid (ornithine), and 2,6-diaminocaproic acid (lysine) are similar to the copper complex with glycine (structure I). With nickel(II), 2,3-diaminopropionic acid and 2,4-diaminobutyric acid form either diamine or tridentate complexes (structures II and III).

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(1) A. C. Kurtz, *J. Biol. Chem.*, **122**, 477 (1937–38).

(2) A. C. Kurtz, *ibid.*, **180**, 1253 (1949).

(3) H. Ley, *Z. Elektrochem.*, **10**, 954 (1904).

(4) H. Ley, *Ber.*, **42**, 354 (1909).

(5) A. Nakahara, J. Hidaka, and R. Tsuchida, *Bull. Chem. Soc. Japan*, **29**, 925 (1956).

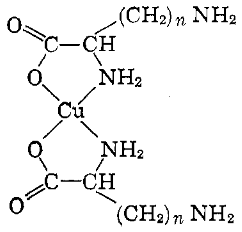
(6) A. Albert, *Biochem. J.*, **50**, 690 (1952).

TABLE I

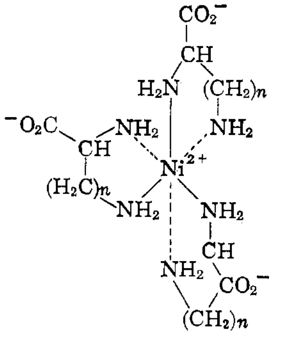
ELECTRONIC ABSORPTION SPECTRA OF SOLUTIONS CONTAINING COMPLEXES OF COPPER(II) AND NICKEL(II) WITH α,ω-DIAMINOCARBOXYLIC ACIDS

		$^3A_{2g} \rightarrow {}^3T_{2g}$		$^3A_{2g} \rightarrow {}^1E_g$		$^3A_{2g} \rightarrow {}^3T_{1g}(F)$		$^3A_{2g} \rightarrow {}^3T_{1g}(P)$				15B,[b]	
	Compound[a]	ν_1	ϵ_1	ν_2	ϵ_2	ν_3	ϵ_3	ν_4	ϵ_4	ϵ_3/ϵ_1	Δ, cm^{-1}	kK	β
1	$Cu(OrHCl)_2$	16.3	53.8										
2	$Cu(LyHCl)_2$	16.3	53.1										
3	$Ni(gly)(H_2O)_4^+$	9.2	6.0	13.9	2.4	15.6	4.1	26.2	8.5	0.69	9,200	14.2	0.84
4	$Ni(gly)_2(H_2O)_2$	9.9	9.2	13.4	2.1	16.2	6.8	27.0	12.5	0.74	9,870	13.5	0.80
5	$Ni(gly)_3^-$	10.0	10.2	13.1	2.2	16.7	9.1	27.6	15.8	0.92	10,000	14.3	0.84
6	$Ni(DabaHCl)_3^-$	9.7		13.4		16.3		27.2			9,700	14.4	0.85
7	$Ni(Daba)_2$	10.7	7.8	12.9	4.6	17.9	8.4	28.1	14.4	1.10	10,720	13.8	0.82
8	$Ni(OrHCl)_3^-$	10.0	8.8	13.2	3.1	16.5	7.8	27.6	13.2	0.89	10,000	14.1	0.83
9	$Ni(Or)_2$	10.8	9.2	12.9	4.7	17.6	11.3	27.8	15.8	1.23	10,820	12.9	0.76
10	$Ni(LyHCl)_2$	10.0	10.5	13.1	2.7	16.6	10.0	27.7	17.7	0.95	10,000	14.2	0.84
11[c]	$Ni(H_2O)_6^{2+}$	8.5		(13.5)		(15.4)		25.3			8,500	15.2	0.90
12	$Ni(ata)(H_2O)^-$	9.5	16.0	13.3	2.5	16.0	6.6	25.6	12.8	0.41	9,500	13.1	0.78
13	$Ni(en)(H_2O)_4^{2+}$	9.8		13.6		15.8		26.8			9,800	13.2	0.78
14	$Ni(ata)(gly)^{2-}$	9.9	9.8	13.0	2.9	17.1	7.0	27.2	11.1	0.71	9,900	14.6	0.86
15	$Ni(en)(gly)_2$	10.5	8.7	12.8	2.6	17.8	8.0	27.8	12.7	0.92	10,500	14.1	0.83
16	$Ni(tren)(H_2O)_2^{2+}$	10.5	15.5	13.0	6.3	17.3	9.3	28.1	12.0	0.60	10,500	13.9	0.83
17	$Ni(en)_2(gly)^+$	10.8	9.2	12.7	4.2	17.9	8.7	28.6	12.0	0.95	10,800	14.1	0.83
18	$Ni(tren)(gly)^+$	11.2	14.0	12.6	9.8	18.8	11.0	28.2	11.0	0.79	11,200	13.4	0.79
19	$Ni(tn)_3^{2+}$	10.9	5.9	12.5	2.7	17.8	7.7	28.2	10.8	1.31	10,900	13.3	0.79
20	$Ni(bdn)_3^{2+}$	10.95	6.5	12.7	3.0	18.0	7.0	28.6	10.0	1.08	10,950	13.8	0.81
21	$Ni(ptn)_3^{2+}$	11.2		12.4		18.3		29.0			11,200	15.1	0.89
22	$Ni(en)_3^{2+}$	11.2	4.7	12.5	3.8	19.0	4.5	29.7	4.6	0.96	11,200	13.8	0.81

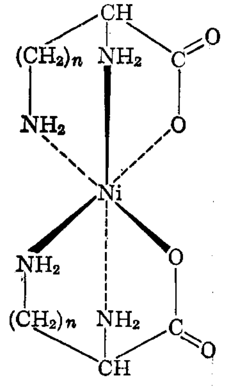
[a] Abbreviations; Or, ornithine; Ly, lysine; gly, glycine; Daba, 2,4-diaminobutyric acid; ata, ammonia triacetate; en, ethylenediamine; tren, β,β',β''-tris(ethylamino)amine; tn, 1,3-diaminopropane; bdn, 1,3-diaminobutane; ptn, 1,2,3-triaminopropane. [b] All absorption maxima given in kilokaysers (1 kK = 10^3 cm^{-1}). [c] The data in lines 11 to 22 from ref 7.



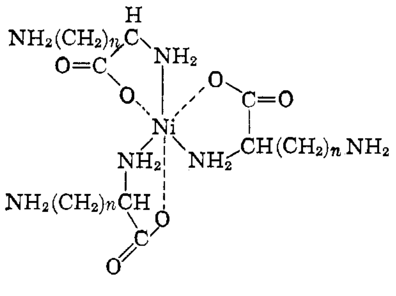
I



II



III



IV

Ornithine appears to form a glycine-like complex with nickel below pH 7.5, and a diamine or tridentate complex at higher pH. The lysine complex appears analogous to the glycine complex (structure IV) throughout the pH range. The observation that the α-amino acid chelates are more stable than the β, γ, and δ derivatives enhances the argument that the ligands are coordinated through the carboxyl oxygen and the α-amine in preference to the ω-amine, in those cases where one amine function appears to remain free.

Results and Discussion

The composition and manner of chelation of the complexes of 2,4-diaminobutyric acid, lysine, and ornithine with copper(II) and nickel(II) in aqueous solutions have been deduced from the electronic spectra, as compared with the results reported by Albert and from experiments bearing on the reactivity of the bound and free amines. Jørgensen[7] has observed that the spectra of nickel complexes are similar for any given combination of n amine and $6 - n$ oxygen donor atoms, an effect he has called the rule of average environment. From this rule, it is possible to estimate the number of each type of donor atom and, indirectly, the number of ligands bound to each metal ion. Spectral data are reported in Table I for the diamino acid complexes of principal interest and for some representative amine complexes.

Melson[8] observed that the ratio of the intensities of the visible (ϵ_3) and the near-infrared (ϵ_1) absorption bands of nickel diamine complexes varies with the size of the chelate ring. For chelate rings of five atoms, the ratio ϵ_3/ϵ_1 is less than 1, while the ratio is greater than 1 for rings of six atoms or more. It is therefore possible to distinguish between the coordination by α- and ω-amine donor atoms by this effect of ring size. Ratios calculated from the spectra of the diamino acid complexes and from data compiled by Jørgensen are given in Table I.

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[7] C. K. Jørgensen, *Acta Chem. Scand.*, **10**, 887 (1956).

[8] G. A. Melson, Ph.D. Thesis, University of Sheffield, 1962.

Complexes of Copper(II).—The electronic spectra of aqueous solutions of bis(ornithine monohydrochloride)-copper(II) and bis(lysine monohydrochloride)copper(II) show a single pH-independent band at 16.3 kK, having a molar extinction coefficient of 53. The energy of this transition is unchanged when the spectra are obtained from solid samples of CuL_2 dispersed in potassium bromide disks.

The complexes were treated with benzoyl chloride in alkaline aqueous solutions following the procedure given by Kurtz. The benzoylated complexes precipitated within 15 min at 0°. The infrared spectra of the products show a broadening of the carbonyl asymmetric stretching frequency (about 1600 cm^{-1}) corresponding to the appearance of the amide carbonyl group. The elemental analyses agree closely with the CuL_2 formulation, and reflectance spectra obtained from samples dispersed in potassium bromide disks are identical with those obtained from samples having terminal amine groups.

The absence of detectable amounts of disubstituted ligand in the reaction mixture indicates that coordination of the α-amine reduces the reactivity of that donor atom toward benzoyl chloride. The relative rapidity of the reaction at the ω-amine suggests that the terminal amine is free in solution as proposed by Albert[6] and by Kurtz.[1]

Complexes of Nickel(II).—Albert proposed that the structures of the nickel(II) complexes varied with the chain length between the amine functions and with the pH. We have obtained electronic spectra from solutions with ligand to metal ratios varying between 1:5 and 6:1. Absorption bands and structures were assigned by comparing the experimental data with spectral data from the literature for substances with the various possible structures.

The electronic spectrum of a solution of nickel(II) and ornithine monohydrochloride displays constant extinction coefficients and absorption maxima only after four or more equivalents of ligand has been added. The spectrum then has band maxima almost coincident with those of the tris(glycinato)nickelate(II) ion. The average deviation in the absorption frequencies is only ±30 cm^{-1}, or a few tenths of a per cent (Table I, lines 5 and 8). Moreover, the ratio of the intensities ϵ_3/ϵ_1 is consistent with the presence of five-membered chelate rings. The species existing in a solution containing an excess of ornithine monohydrochloride is the tris(ornithine monohydrochloride)nickel(II) ion; however, the only compound which was isolated from this solution was bis(ornithine monohydrochloride)-nickel(II), as confirmed by three-element analysis.

The addition of sufficient base to neutralize the hydrochloride results in a deepening of the blue color. The increasing intensity of the absorption bands is saturated at a ligand to metal ratio of 2:1. The electronic spectrum of this complex exhibits band maxima which correspond to those of $Ni(en)(gly)_2$, with four nitrogen and two oxygen donors, within 1.5% (Table I, lines 9 and 15). In addition, the ratio of the intensities, ϵ_3/ϵ_1, has changed from 0.89 to 1.23 upon addition of base. The latter value is characteristic of a large ring compound and quite similar to the ratio 1.31 calculated for $Ni(tn)_3^{2+}$ (Table I, line 19). Consequently it is concluded that both nitrogens of each ornithine are coordinated and that the remaining coordination positions of the nickel are either bound to the carboxyl groups or to water molecules.

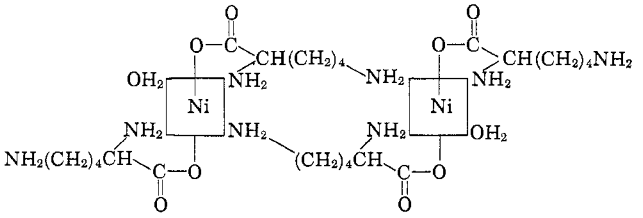
The reaction with benzoyl chloride takes place in alkaline solutions where the species involved is necessarily that described immediately above. In contrast with the copper system, where the reaction with benzoyl chloride occurs rapidly at 0°, the nickel complex reacts at a detectable rate only at room temperature or above. The inhibited reactivity of the ω-amine suggests that it is coordinated with the nickel ion, at least at temperatures substantially below room temperature. No dibenzoylated ornithine was detected in the reaction mixture, suggesting that the α-amine is firmly coordinated with the nickel ion at all times by participating in a five-atom chelate ring involving the carboxyl oxygen. Ornithine is therefore a tridentate ligand in cold alkaline aqueous solutions.

The behavior of the 2,4-diaminobutyric acid complexes in solution is similar to that of the ornithine system (Table I). The complete unreactivity of the diaminobutyric acid complex toward benzoyl chloride suggests that the diamine chelate ring is much more stable than the similar ring in the corresponding ornithine complex.

The spectrum of a solution containing nickel(II) and lysine (or lysine monohydrochloride) at any pH between 5.5 and 9.2 displays constant absorption frequencies after the addition of only two equivalents of ligand; however the molar extinction coefficients reach constant values after the addition of approximately three equivalents of ligand. The band maxima are almost coincident with those of the tris(glycinato)-nickelate(II), ion, as in the example of the ornithine complex (Table I, lines 5 and 10). The ratios of the intensities of the appropriate absorption bands do not indicate that large chelate rings have been formed; however, the data needed to show that eight-membered rings give the anticipated effect are not available. Indeed, eight-membered chelate rings are uncommon. Binding to three nitrogen and three oxygen donor atoms can only be achieved for a ligand-to-metal ratio of 2:1 if all of the donor atoms of half the diamino acid ligands are coordinated. In the absence of evidence either confirming or eliminating the possible presence of large chelate rings, two possible structures must be considered further. The most obvious structure involves one bidentate and one tridentate lysinate ligand. The other is the dimeric structure V.

At 25°, the addition of sufficient base to neutralize the hydrochloride does not change the electronic spectrum. At 0°, neutralization results in the precipitation of a blue gum, which dissolves when the solution is heated. The reactivity of these complexes toward benzoyl chloride parallels that of the ornithine complexes, indicating that the terminal amine is coordinated in cold alkaline aqueous solutions.

Dimeric structure V with the ligands bound to one nickel ion through the α-amine and the carboxyl group, as in the glycinato complexes, and the terminal amine coordinated with an adjacent nickel ion, as in the copper complexes of ε-aminocaproic acid,[5] satisfies the requirements of the spectra, the reduced reactivity of the terminal amine, and the precipitation at higher pH. If all of the amines are coordinated at low temperatures (including those shown free here), a high polymer may result. In this polynuclear form, the low reactivity of the lysine complex may be correlated with the appearance of a gummy precipitate in cold solutions. Though spectra alone cannot distinguish between the proposed dimer and a trisglycine-like complex, the proposed polynuclear structure seems best suited to the explanation of all the properties of the system.



V

The series of ligands studied provides an interesting illustration of the influence of size on the stability of chelate rings. It is useful to learn that the seven-membered rings form while the system that might produce an eight-membered ring appears to bridge to a second metal ion rather than form an additional chelate ring. It is suggested that the application of both physical measurements and ligand reactions should provide powerful techniques for the demonstration of the manner of chelation of complicated ligands, especially in solution.

Experimental Section

Starting Materials.—L-Lysine monohydrochloride (99+% purity), L-ornithine monohydrochloride (*Anal.* Calcd: N, 16.6. Found: N, 16.7), and 2,4-diaminobutyric acid dihydrochloride were purchased from Nutritional Biochemicals, Cleveland, Ohio. Benzoyl chloride was distilled (bp 195 ± 2°) before use. All solvents and metal salts were of reagent grade or the equivalent. All standard solutions were prepared by the Ohio State University Reagent Laboratory.

Synthesis of the Complexes of Copper(II). Bis(L-lysine monohydrochloride)copper(II).—L-Lysine monohydrochloride (0.1 mole, 18.7 g) was dissolved in 50 ml of water. This solution was added to a slurry of 0.025 mole (5.18 g) of $CuCO_3 \cdot Cu(OH)_2$ in 50 ml of water, and the mixture was stirred with heating until the evolution of CO_2 stopped. The deep blue solution was filtered to remove any insoluble salts, and absolute ethanol was added to precipitate the blue-violet complex. The product was extracted overnight with 95% ethanol in a Soxhlet extractor, then dried for 8 hr *in vacuo* over P_4O_{10} at 80°. The yields ranged from 65 to 75%. *Anal.* Calcd for $Cu(C_6H_{14}N_2O_2Cl)_2$: C, 33.60; H, 6.88; N, 13.06; Cl, 16.30. Found: C, 33.42; H, 6.58; N, 13.08; Cl, 16.52.

Bis(N^6-benzoyllysine)copper(II).—A solution of bis(lysine monohydrochloride)copper(II) was prepared as described above and cooled to 0°. One equivalent of benzoyl chloride (plus a 20% excess) was added for each equivalent of the ligand simultaneously with 2 equiv of 5 *N* sodium hydroxide. The solution was stirred vigorously for 15 min, which was sufficient time essentially to complete the precipitation of the pale blue complex. The precipitate was washed with 50 ml of water and 50 ml of acetone, then dried *in vacuo* over P_4O_{10} overnight. *Anal.* Calcd for $Cu(C_{13}H_{17}N_2O_3)_2$: C, 55.54; H, 6.10; N, 9.97. Found: C, 55.29; H, 6.15; N, 9.91.

Bis(ornithine monohydrochloride)copper(II).—The synthesis of this compound was identical with that of bis(lysine monohydrochloride)copper(II), except for the substitution of 0.10 mole (16.8 g) of L-ornithine monohydrochloride for the L-lysine monohydrochloride. *Anal.* Calcd for $Cu(C_5H_{12}N_2O_2Cl)_2$: C, 30.11; H, 6.07; N, 14.05; Cl, 17.79. Found: C, 30.40; H, 6.07; N, 14.25; Cl, 17.99.

Bis(N^5-benzoylornithine)copper(II).—The synthesis of this compound was identical with that of bis(N^6-benzoyllysine)copper(II) except for the substitution of an aqueous solution of bis(ornithine monohydrochloride)copper(II) for the solution of bis(lysine monohydrochloride)copper(II). *Anal.* Calcd for $Cu(C_{12}H_{15}N_2O_3)_2 \cdot {}^1/_2H_2O$: C, 53.06; H, 5.75; N, 10.31. Found: C, 52.67; H, 5.77; N, 10.14.

Bis(2,4-diaminobutyric acid monohydrochloride)copper(II).—Two grams (0.01 mole) of 2,4-diaminobutyric acid dihydrochloride was dissolved in 50 ml of water, and the resulting solution was added to a slurry of an excess (2 g) of $CuCO_3$–$Cu(OH)_2$ in 50 ml of water. The mixture was stirred with heating until the evolution of CO_2 ceased, then filtered to remove any insoluble material. Several volumes of absolute ethanol were added to precipitate the complex, which was extracted overnight with 95% ethanol. The insoluble fraction was dried *in vacuo* over P_4O_{10}. The soluble fraction was precipitated with ether, then dried *in vacuo* over P_4O_{10} at 80°. *Anal.* Calcd for $Cu(C_4H_{10}N_2O_2Cl)_2$: N, 15.02. Found: N, 14.54, 14.68, 15.62.

Synthesis of the Complexes of Nickel(II). Bis(L-lysine monohydrochloride)nickel(II).—L-Lysine monohydrochloride (0.1 mole, 18.7 g) was dissolved in 50 ml of water. This solution was added to a slurry of 0.05 mole (5.94 g) of $NiCO_3$ in 50 ml of water, and the mixture was stirred with heating until the evolution of CO_2 ceased. The blue-green solution was filtered to remove any insoluble material, then evaporated to dryness with a rotary evaporator. The solid product was extracted overnight with 95% ethanol in a Soxhlet extractor and the pale green powder dried *in vacuo* over P_4O_{10} at 80°. *Anal.* Calcd for $Ni(C_6H_{14}N_2O_2Cl)_2$: C, 33.98; H, 6.65; N, 13.21; Cl, 16.72. Found: C, 33.96; H, 6.90; N, 13.13; Cl, 16.55.

Bis(N^6-benzoyllysine)nickel(II).—A solution of bis(L-lysine monohydrochloride)nickel(II) was prepared as described above. One equivalent of benzoyl chloride (plus at least a 20% excess) was added for each equivalent of ligand simultaneously with 2 equiv of 5 *N* sodium hydroxide. Precipitation of the benzoylated complex is essentially complete within 15 min at room temperature. The product was filtered, then decomposed with 50 ml of 1 *N* hydrochloric acid. This solution was filtered and the complex reprecipitated with the addition of 1 *N* sodium hydroxide. The precipitate was washed with 50 ml of 1 *N* aqueous ammonia and 50 ml of acetone, then dried *in vacuo* over P_4O_{10}. *Anal.* Calcd for $Ni(C_{13}H_{17}N_2O_3)_2 \cdot 3H_2O$: C, 51.07; H, 6.59; N, 9.17. Found: C, 50.90; H, 6.28; N, 9.09.

Bis(L-ornithine monohydrochloride)nickel(II).—The synthesis of this compound was identical with that of bis(L-lysine monohydrochloride)nickel(II) except for the substitution of 0.10 mole (16.8 g) of L-ornithine monohydrochloride for the L-lysine monohydrochloride. *Anal.* Calcd for $Ni(C_5H_{12}N_2O_2Cl)_2$: C, 30.48; H, 6.14; N, 14.22; Cl, 17.63. Found: C, 30.49; H, 6.27; N, 14.21; Cl, 18.00.

Bis(N^5-benzoylornithine)nickel(II).—The synthesis of this compound was identical with that of bis(N^6-benzoyllysine)nickel(II) except for the substitution of an aqueous solution of bis(ornithine monohydrochloride)nickel(II) for the solution of bis(L-