Carboxymethylated Cage Amines: Coordination and Lactamization

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Depending upon the position and degree of substitution, carboxymethyl derivatives of cage amines of the "sarcophagine" (3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane) type vary considerably in the stability of their lactamized forms. For 1,8-diamino-3-carboxymethylsarcophagine, $\mathbf{L^1}$, only indirect evidence for some involvement of a lactamized form of its Ni(II) complex has been obtained. Crystal structure determinations for $[Cu(H_2\mathbf{L^1})](NO_3)_{3.5}Cl_{0.5}\cdot 2.5H_2O$ and $[Ni(H\mathbf{L^1})]Cl_3\cdot 3H_2O$ show distorted octahedral coordination of all six endocyclic N-donor atoms in both cases. For related diaminosarcophagine derivatives with either two (1,8; $\mathbf{L^2}$) or three (1,1,8; $\mathbf{L^3}$) carboxymethyl substituents on the exocyclic N atoms, crystallographic studies have shown a dilactam form for the ligands in their Ni(II) and Cu(II) complexes which is of almost identical conformation to that of the diprotonated "free" ligand in $[H_2\mathbf{L^3}][ZnCl_4]\cdot 6H_2O$. The lactamized ligands appear to strongly favor square planar four-coordination, and the Co(II) complex of $\mathbf{L^2}$ shows a remarkable lack of reactivity toward oxygen. Kinetic studies indicate that the hydrolytic stability of the lactam rings is comparable to that of uncoordinated analogues.

Introduction

The incorporation of a kinetically inert and thermodynamically stable molecular unit with particular desired properties into a higher, "supramolecular" structure commonly requires the introduction of functional groups to that unit.[1,2] We have recently provided an illustration of this approach in the carboxymethylation of the 1,8-diamino derivative of the macrobicyclic polyamine known as "sarcophagine" (3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane)[3] and the use of one of the products to form coordination polymers.[4] Desirably, the functionalization of a ligand does not deleteriously alter its properties, nor does the method of synthesis hinder the use of the derivative. In some circumstances, these disadvantages do attach to carboxymethylation of sarcophagines, as illustrated by (i) significant changes in complex ion properties when alkylation occurs at a secondary N-donor; (ii) intramolecular reactions of the carboxymethylated amines to give lactams acting as quadridentate rather than sexidentate ligands; and (iii) difficulty in removing the substituted ligand from a Co(III) template.[3] We show presently, however, in analyzing some chemistry of mono-, di-, and tricarboxymethyl derivatives of 1,8-diaminosarcophagine, that these difficulties either are not of practical importance or can be readily circumvented.

Results and Discussion

1. Complexes of 1,8-Diamino-3-carboxymethylsarcophagine, $\mathbf{L^1}$. A crystal structure determination of the Co(III) complex of this ligand ($\mathbf{L^1}$, Figure 1) has shown that the carboxymethyl substituent on the donor nitrogen produces a significant distortion of the primary coordination sphere of the metal, reflected most obviously in the reddish color of the complex.[3] Whether this may be a significant disadvantage in any possible applications of the ligand requiring tenacious binding of a metal ion is difficult to say, however, since the complex retains the kinetic inertness which may be considered typical of Co(III) hexamine complexes. Hence, it was of interest to determine the properties of its complexes with metals normally giving more labile species.

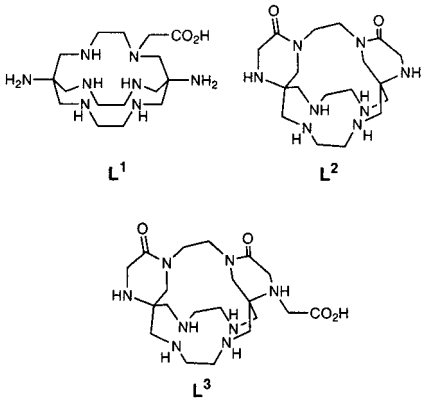

Figure 1. The ligands, $\mathbf{L^1}$, $\mathbf{L^2}$, and $\mathbf{L^3}$.

Representations of the cationic species present in the crystals of the Ni(II) and Cu(II) complexes of $\mathbf{L^1}$ in its 1,8-N-diprotonated-carboxyl-deprotonated and 1,8-N-diprotonated forms, respectively, are shown in Figure 2a and Figure 2b. As with the Co(III) complex, it is possible to describe the ligand conformation as *lel*$_3$ about an approximately octahedral, N_6-coordinated metal ion, although the distortions of the primary coordination sphere about both metals from a regular geometry are quite marked, especially for the Cu(II) species. As with the Co(III) complex, the longest M−N bond is that to the tertiary donor (bearing the carboxymethyl substituent), with these

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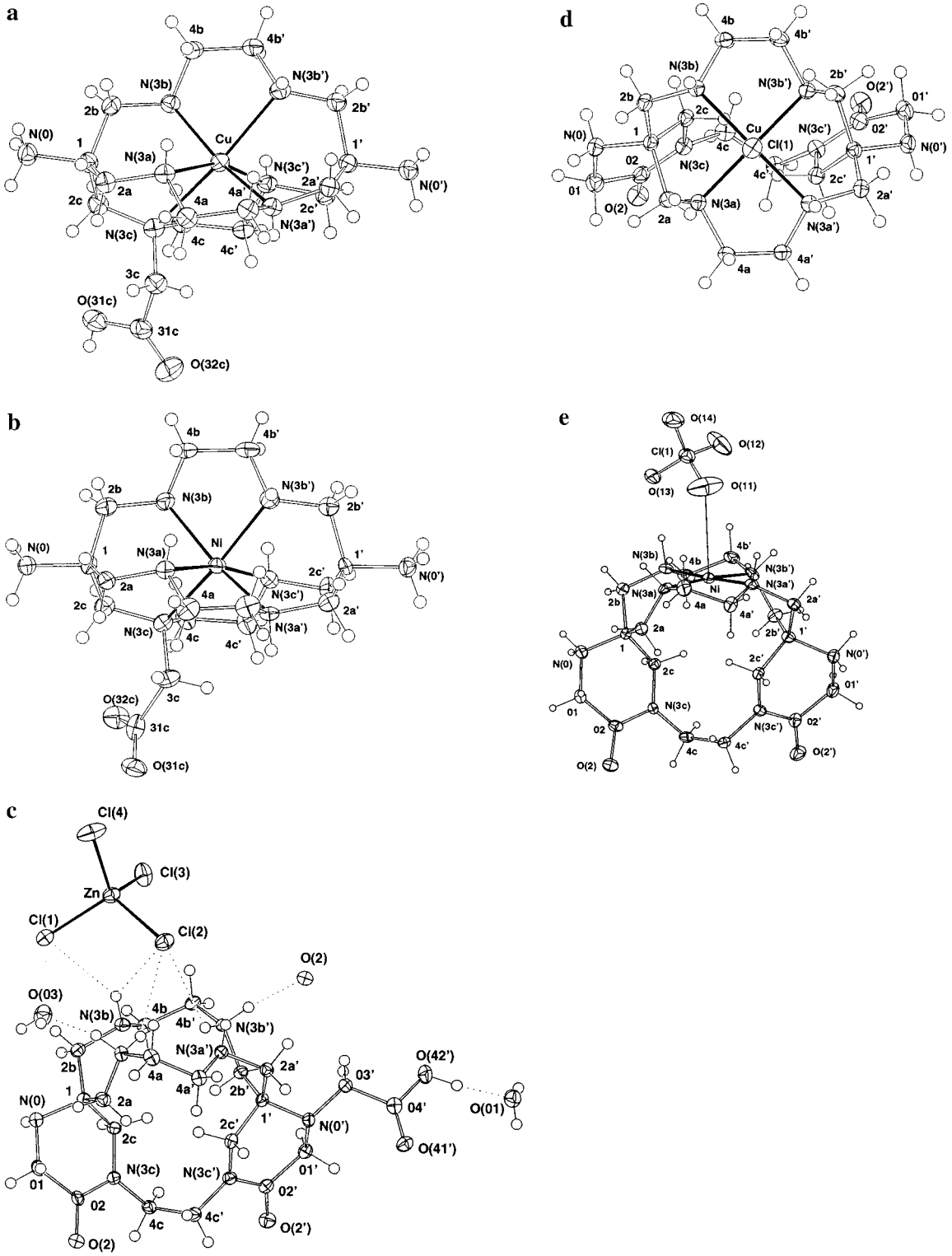

Figure 2. Projection of the cationic moieties (a) $[Cu(H_2\mathbf{L^1})]^{4+}$ and (b) $[Ni(H\mathbf{L^1})]^{3+}$ in a similar orientation; (c) $[H_2\mathbf{L^3}]^{2+}$; (d) $[Cu(H\mathbf{L^2})Cl]^{2+}$; (e) $[Ni(H_2\mathbf{L^2})OClO_3]^{3+}$; (d) being down Cl−Cu, (e) normal to Ni−O, with (c) in similar, "prepared" orientation (see text), with neighboring anion and solvent molecules. Atom numbering is shown throughout, carbon atoms being denoted by number only.

distances being 2.224(5) Å (Ni) and 2.633(3) Å (Cu). The shortest Ni−N distance of 2.101(6) Å, however, means that the range in that complex is very similar to that about Co(III) (∼0.09 Å)[3] and quite unlike that for Cu(II). For this metal, there is a pronounced distortion of the primary coordination sphere toward a square planar geometry: the M−N(3b′) bond trans to the longest, M−N(3c), bond is also relatively long (2.318(3) Å), and the remaining four bonds range from 2.024(3) to 2.109(3) Å. Deprotonation of the carboxyl substituent on the Ni complex may have some effect on the ligand conformation (note that the carboxyl group is protonated in the Co(III) complex[3]), though the carboxylate oxygen atoms are primarily involved in H-bonding interactions with protons on the 1,8-amino centers and not the donor NH groups (O(31c)···N(0′) ($^3/_4 - x$, $y - {}^1/_4$, $^1/_4 + z$), ($x - {}^1/_4$, $^3/_4 - y$, $^1/_4 + z$) 2.805(8), 2.772(8); O(32c)···N(0) ($^1/_4 - x$, $y - {}^1/_4$, $z - {}^1/_4$) 2.665(8) Å). In the Cu complex, the carboxylic acid group environment comprises anions and water molecules as well (O(05)···O(31c,32c) (x, $y + 1$, z)

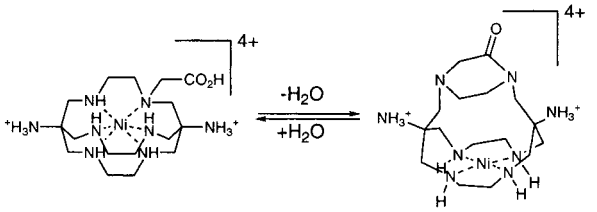

Figure 3. Possible lactam formation and square planar/octahedral equilibrium.

2.589(6), 2.859(6); O(31c)···Cl (x, $y - 1$, z) 3.003(9); O(32c)···N(0′) ($1 - x$, $y - 1/2$, $1 1/2 - z$) 2.835(4) Å).

Although isolated as a violet, pseudooctahedral species, the visible spectrum showing maxima at 338 nm ($^3A_{2g} \rightarrow {}^3T_{1g}(P)$), $\epsilon = 15$ M^{-1} cm^{-1}, 518 nm ($^3A_{2g} \rightarrow {}^3T_{1g}(F)$), $\epsilon = 9$ M^{-1} cm^{-1}, and 820 nm ($^3A_{2g} \rightarrow {}^3T_{2g}$), $\epsilon = 13$ M^{-1} cm^{-1}, very like $[Ni((NH_3)_2sar)]^{4+}$ [7] and $[Ni(NH_3)_6]^{2+}$,[8] a yellow, presumably square planar[9] complex, is also present in the preparative reaction mixture from Ni(II) and **L1**, and conversion between the two forms is relatively slow. Somewhat similar behavior is observed for $[Ni((NH_3)_2sar)]^{4+}$,[7] though the interconversion rates are faster, suggesting the possibility that, with **L1**, a square planar/octahedral equilibrium may be associated with lactam formation (and some N-inversion), as shown in Figure 3. The ligands **L2** and **L3** (Figure 1) also involved in the present study are formed in lactamization reactions of this type, though to give constitutional isomers of what is suggested for **L1**, and it does appear that the stability of the lactamized forms of carboxymethylated cages increases with the number of carboxymethyl substituents.[3] A 3,6-bridged oxamide of sarcophagine is known,[10] showing that such linking within the cage is possible, though it is noteworthy that there is no apparent evidence that the complex $[Cu(H_2\mathbf{L^1})]^{4+}$ undergoes lactamization even after extended times in acid solution.

Despite the considerable coordination sphere distortions seen in all complexes of **L1**, it is apparent from the preparative procedures used herein that the complexes of Ni(II) and Cu(II), at least, retain a considerable kinetic robustness, indicating that this readily prepared, functionalized cage ligand could have useful application in, for example, radiopharmaceutical agents.[11] We show in a related paper that the Co(III) complex can, for example, be grafted to polyamines.[12]

2.1. Lactam Derivatives of Carboxymethylated 1,8-Diaminosarcophagine, L2: Structural Studies. The utility of $[Cu((NH_2)_2sar)]^{2+}$ as a reagent for production of selectively carboxymethylated cage amines[3] is illustrated presently by the ease of conversion of the product Cu(II) complexes to their Zn(II) analogues and the ease of ligand release from these. Previous work has shown that the dilactamization reactions occurring during isolation of the Cu complexes from acidic media involve a single arm of the original cage amine, presumably as a result of stereochemical preferences of the metal and a ready adoption of a square planar array of four nitrogen atoms by two unacylated arms. The structure determination for $[H_2\mathbf{L^3}][ZnCl_4]\cdot 6H_2O$ (Figure 2c) shows that the processes involved in ligand release do not result in any rearrangement, the conformation of this diprotonated species corresponding remarkably closely to that of various related complexes (see ref 3 and below). Such ligand "preorganization" is, however, seen also to some degree with the parent cages, too.[13]

The structure of the Cu(II) chloride complex of the dilactam derivative of 1,8-bis(carboxymethylamino)sarcophagine, $[Cu(H\mathbf{L^2})Cl]Cl_2\cdot 2H_2O\cdot EtOH$ (Figure 2d), is isomorphous with that of $[CuCl(\mathbf{L^3})]Cl\cdot\sim 3.9H_2O$,[3] as noted in the Experimental Section. In both, the geometries of the five-coordinate metal are very similar, the only significant difference being in Cu−Cl distances, that in the **L3** complex being 2.472(2) Å and that in the present **L2** species 2.5036(8) Å (Table 1). In the former, Cl−Cu−N(3a,3a′,3b,3b′) are 101.4(1)°, 98.7(1)°, 91.3(1)°, 95.1(1)°, slightly differing from those of the latter, perhaps because of a better-defined water molecule approach here with Cl···O 3.140(3) Å, rather than 3.17(2) Å in the **L3** complex, where the water site is modeled as half-occupied. Cl(2) in both compounds interacts most strongly with N(0) and O(01), (Cl(2)···N(0) ($x - 1$, y, z), O(01) 3.147(3), 3.178(2) Å (**L2** species), 3.372(5), 3.173(4) Å (**L3** species)) despite the difference in the degree of protonation of N(0).

The structure (Figure 2e) of the Ni(II) perchlorate complex of **L2**, $[Ni(H_2\mathbf{L^2})OClO_3](ClO_4)_3\cdot 6H_2O$, is closely similar to those of other lactamized cage ligand complexes, the most obvious difference from that of $[Cu(H\mathbf{L^2})Cl]Cl_2\cdot 2H_2O\cdot EtOH$ being that the Ni environment might reasonably be described as square pyramidal (see trans N−M−N angles in Table 1), with the perchlorate approach really rather distant, while that of the Cu is clearly square-pyramidal. Transfer of the ligand from Cu(II) to Zn(II) to H^+ and then to Ni(II) seems otherwise to have had almost negligible effect. Torsion angles, as descriptors of ligand conformation, are given in Table 2. These quantify the close similarities for the present Ni and Cu complexes (and for related species[3]), but more remarkable is the close similarity to the conformation of the ligand in $[H_2\mathbf{L^3}][ZnCl_4]\cdot 6H_2O$. Here, the diprotonated ligand, with *quasi-2* symmetry, can be considered "preorganized" for metal binding, despite the fact that repulsion between the protonated macrocyclic-N donors, N(3a,3b′), might be expected to have some effect on the conformation. Any such effects appear to have been counterbalanced by *trans*-annular N(3b)···H(3aA) (2.06(4) Å) and N(3a′)···H(3b′A) (1.98(4) Å) interactions, resulting in N···N distances very similar to those in the complexes (Table 1a). This may be further assisted by interactions with the anion and solvent molecules (N(3b)···Cl(1,2) (x, $1/2 - y$, $z + 1/2$), N(3a)···Cl(2) (x, $1/2 - y$, $z + 1/2$) 3.437(3), 3.524(3), 3.464(3) Å, N(3a)···O(03) (x, $1/2 - y$, $z + 1/2$) 2.720(4) Å , N(3b′)···O(2) ($x - 1$, y, z) 2.709(3) Å). The carboxylic acid moiety interacts with a nearby water molecule (H,O(42′)···O(01) ($\bar{x}$, $1/2 + y$, $\bar{z} - 1/2$) 1.66(4), 2.605(4) Å).

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Table 1. Metal Atom Environments

(a) The Five-Coordinate [$\mathbf{L^2}$MX] Species (X = *O*ClO$_3$ (Ni); Cl (Cu))[a,b]

atom	*r*	N(3a)	N(3a′)	N(3b)	N(3b′)
X	2.85(1)	95.4(5)	94.2(5)	83.0(5)	90.4(6)
	2.5036(8)	97.15(7)	94.49(7)	95.54(7)	98.95(7)
N(3a)	1.892(9)		89.0(4)	91.4(5)	174.2(4)
	1.981(2)		87.68(9)	91.54(9)	163.90(9)
N(3a′)	1.92(1)			177.2(4)	91.3(5)
	2.024(2)			169.96(9)	90.9(1)
N(3b)	1.90(1)				88.6(5)
	2.031(2)				87.1(1)
N(3b′)	1.904(9)				
	1.972(2)				

(b) The Six-Coordinate [M(H$_x$$\mathbf{L^1}$)]$^{(x+2)+}$ Arrays

atom	*r*	N(3a′)	N(3b)	N(3b′)	N(3c)	N(3c′)
N(3a)	2.102(7)	82.1(2)	86.2(3)	101.7(2)	90.8(2)	167.9(2)
	2.041(3)	86.1(1)	89.8(1)	118.7(1)	(82.7(1))	156.2(1)
N(3a′)	2.141(6)		161.1(2)	85.5(2)	107.0(2)	90.1(2)
	2.024(3)		166.4(1)	88.8(1)	(108.87(9))	87.6(1)
N(3b)	2.126(5)			82.3(2)	87.9(2)	103.6(3)
	2.048(2)			81.8(1)	(83.37(9))	101.1(1)
N(3b′)	2.142(6)				163.5(2)	86.9(2)
	2.318(3)				(153.76(9))	84.0(1)
N(3c)	2.224(5)					82.5(2)
	(2.633(3))					(77.73(9))
N(3c′)	2.101(6)					
	2.109(3)					

[a] *r*/Å is the metal ligand distance; other entries are the angles/deg subtended at the metal atom by the relevant atom at the head of the row and column. Values for the Ni complex are given above those for its Cu counterpart. [b] Ni−O(11)−Cl(1) is 131(1)°. For the ligand cation [H$_2$$\mathbf{L^3}$]$^{2+}$, copper and nickel species, N(3a)···N(3a′,3b) are 2.859(4), 2.764(4); 2.774(3), 2.875(4); 2.67(1), 2.71(2); and N(3b′)···N(3a′,3b) are 2.754(4), 2.866(4); 2.847(4), 2.759(2); 2.74(1), 2.66(2) Å.

2.2. Lactam Derivatives of Carboxymethylated 1,8-Diaminosarcophagine: Solution Studies. The replacement of Cu(II) in complexes of the lactamized cage ligands is very facile through the reductive route using Zn, and, although ESMS measurements show that the Zn(II) complexes are present in solution, removal of Zn (presumably involving halide assistance)[14] to provide the "free" ligand also occurs readily. Detailed studies have not yet been made of the kinetics of metal ion binding to the ligands presently studied, but the incorporation of Co(II) (and Cu(II)) in neutral media is fast (the preparative procedure given for the Ni(II) complex of $\mathbf{L^2}$ was based on the reaction periods described as necessary for binding permethylated cage ligands,[15] and visual observation suggested that it was unnecessarily long), so that radioisotopes such as ^{60}Co and ^{64}Cu, for example, could be expected to be readily bound to any reagents based on the ligands.

Although many Ni(II) complexes of quadridentate macrocycles are known to exist in solution as a mixture of octahedral and square planar forms,[9,16] no evidence was obtained that [Ni($H_2\mathbf{L^2}$)]$^{4+}$ behaved in this way. The visible spectrum (λ_{max} 416 nm, ϵ 64 M^{-1} cm^{-1} in water) was inappreciably affected by change in pH, addition of coordinating anions or amines, or increase in temperature, and both ^{1}H and ^{13}C NMR spectra (see ahead) showed sharp resonances under all conditions. The ligand field is strong for an NiN_4 system[16] and perhaps explains why there is no apparent tendency to add a fifth or sixth ligand, even if this might be facilitated by additional interactions with the "superstructure" created by the dilactam bridge.

The ligand conformation found in the crystal is analogous to that described as "*trans*-I" for the simple macrocycle cyclam,[17] with the bound N configurations *R*,*S*,*S*,*R*, meaning that the five-membered chelate rings might be considered formally as eclipsed, though the structure shows that distortions occur to avoid this situation, as in related systems.[18,19] Although it might still be anticipated that rapid interconversion between two enantiomeric conformations would occur, NMR spectra (Figure 4) show that in aqueous solution the diastereotopicity of methylene protons expected from the solid-state structure is maintained, meaning that the conformational inversion must at least be slow on the NMR time scale.

Assuming that, because of the ligand rigidity, the Co(II) complex of $\mathbf{L^2}$ would have a structure similar to that of the Ni(II) compound, some chemistry akin to that of "cyclidene" systems[20] was expected to be detectable and thus to possibly complicate any practical application of the ligand with Co. The complex, precipitated as the perchlorate salt from ethanol, is unusual for a cobalt cage species[3] in that it is not readily oxidized by air to the Co(III) form.[21] The complex is orange/brown but has an electronic spectrum quite unlike those of Co(III)−N_6 compounds[3] with λ_{max} = 422 nm ϵ = 122 M^{-1} cm^{-1} in a DMSO solution. The mass spectrum shows a peak at

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(21) The NMR spectra are very broad and unresolved over normal field widths, and remain so even with prolonged exposure of the solution to the normal atmosphere. The cyclic voltammogram of the complex in water shows a highly irreversible wave near potentials associated with the Co(II)/Co(III) couple in hexamine cage species, but, since a similar wave is seen in the Zn(II) complex of the dilactam ligand, we tentatively associate this with reduction of the lactam ring.

Table 2. Ligand Conformations[a]

(a) The (M)sar Core

atoms	$[H_2\mathbf{L^3}]^{2+}$	$[Ni(H_2\mathbf{L^2})OClO_3]^{3+}$	$[Cu(\mathbf{L^2})Cl]^{+}$	$[Cu(H_2\mathbf{L^1})]^{4+}$	$[Ni(H\mathbf{L^1})]^{3+}$
2b−1−2a−*3a*	−12.2(4)	−22(1)	−25.8(3)	−46.7(3)	−50.7(8)
2c−1−2b−*3b*	−63.5(3)	−60(1)	−60.8(3)	−54.5(4)	−57.0(8)
2a−1−2c−*3c*	65.5(3)	66(1)	64.1(3)	−49.8(4)	−52.2(8)
2c−1−2a−*3a*	112.1(3)	102(1)	101.4(3)	85.6(3)	79.6(7)
2a−1−2b−*3b*	62.7(3)	67(1)	68.9(3)	76.9(3)	74.9(8)
2b−1−2c−*3c*	−167.8(2)	−168(1)	−165.8(2)	80.1(3)	78.7(8)
2b′−1′−2a′−*3a*′	61.2(3)	67(1)	69.5(3)	90.4(3)	73.9(8)
2c′−1′−2b′−*3b*′	111.1(3)	102(1)	99.6(3)	79.6(3)	77.6(8)
2a′−1′−2c′−*3c*′	−169.6(2)	−167(1)	−166.2(2)	76.6(3)	79.5(8)
2c′−1′−2a′−*3a*′	−60.8(3)	−62(1)	−57.8(3)	−38.1(3)	−56.1(8)
2a′−1′−2b′−*3b*′	−8.3(4)	−25(1)	−24.9(3)	−48.1(3)	−52.4(8)
2b′−1′−2c′−*3c*′	67.2(3)	64(1)	67.3(3)	−50.9(4)	−50.6(8)
1−2a−*3a*−4a	−163.5(3)	−172(1)	−164.1(2)	−145.8(3)	−148.8(6)
1−2b−*3b*−4b	97.6(3)	97(1)	93.5(3)	−151.9(3)	−137.6(7)
1−2c−*3c*−4c	−167.3(2)	−166(1)	−167.7(2)	−126.6(3)	−130.8(6)
1′−2a′−*3a*′−4a′	98.1(3)	98(1)	91.3(3)	−157.9(3)	−134.3(6)
1′−2b′−*3b*′−4b′	−166.7(2)	−168(1)	−166.2(2)	−141.8(3)	−143.5(6)
1′−2c′−*3c*′−4c′	−168.3(2)	−166(1)	−170.5(2)	−157.8(3)	−150.6(6)
1−2a−*3a*−M		−48(1)	−40.9(3)	−20.1(3)	−22.7(7)
1−2b−*3b*−M		−34(1)	−36.4(3)	−29.8(4)	−16.4(8)
1−2c−*3c*−M				(−21.5(3))	−18.2(7)
1′−2a′−*3a*′−M		−30(1)	−37.6(3)	−36.1(3)	−13.4(7)
1′−2b′−*3b*′−M		−46(1)	−43.1(3)	−22.2(3)	−20.9(7)
1′−2c′−*3c*′−M				−29.5(3)	−23.3(8)
2a−*3a*−4a−4a′	73.6(3)	94(1)	89.1(3)	173.7(3)	165.7(6)
2b−*3b*−4b−4b′	−173.4(3)	−173(1)	−171.0(2)	177.3(3)	170.5(7)
2c−*3c*−4c−4c′	93.9(3)	96(1)	93.0(3)	160.5(3)	167.2(6)
2a′−*3a*′−4a′−4a	−175.3(3)	−168(1)	−168.9(2)	167.9(3)	170.5(6)
2b′−*3b*′−4b′−4b	72.9(3)	88(1)	85.7(3)	164.8(3)	167.4(7)
2c′−*3c*′−4c′−4c	97.3(3)	97(1)	96.1(3)	172.2(3)	166.6(6)
M−*3a*−4a−4a′		−31(1)	−39.0(2)	40.4(3)	36.4(7)
M−*3b*−4b−4b′		−38(1)	−36.3(2)	49.5(3)	43.4(9)
M−*3c*−4c−4c′				(47.1(2))	47.4(6)
M−*3a*′−4a′−4a		−34(1)	−35.4(2)	41.1(3)	43.1(7)
M−*3b*′−4b′−4b		−35(1)	−41.9(3)	38.6(3)	40.6(8)
M−*3c*′−4c′−4c				42.9(3)	35.5(7)
3a−4a−4a′−*3a*′	53.0(3)	43(1)	50.5(3)	−55.5(3)	−54.1(8)
3b−4b−4b′−*3b*′	54.7(3)	47(1)	52.7(3)	−61.4(3)	−57.1(10)
3c−4c−4c′−*3c*′	−86.5(3)	−89(1)	−86.0(3)	−66.6(3)	−58.2(7)

(b) The Lactam Torsion Angles (Primed Values Follow Unprimed)

atoms	$[H_2\mathbf{L^3}]^{2+}$	$[Ni(H_2\mathbf{L^2})OClO_3]^{3+}$	$[Cu(\mathbf{L^{2)}})Cl]^{+}$
01−*0*−1−2c	59.8(3), 62.5(3)	58(1), 60(1)	61.7(3), 58.9(3)
0−1−2c−*3c*	−52.5(3), −53.4(3)	−54(1), −53(1)	−52.4(3), −50.7(3)
1−2c−*3c*−02	26.3(4), 28.8(4)	35(1), 35(2)	26.8(4), 26.5(3)
2c−*3c*−02−01	−6.2(4), −10.3(4)	−16(2), −8(2)	−5.9(4), −9.0(4)
3c−02−01−*0*	13.9(4), 19.6(4)	19(2), 16(2)	14.1(4), 17.6(4)
02−01−*0*−1	−41.5(4), −47.8(3)	−43(1), −43(1)	−43.9(3), −43.9(3)
1−2c−*3c*−4c	−167.3(2), −168.3(2)	−166(1), −166(1)	−167.7(2), −170.5(2)
01−02−*3c*−4c	−172.3(3), −173.2(3)	−175(1), −173(1)	−171.2(3), −171.5(2)
01−*0*−1−2a	−61.8(3), 176.7(2)	−65(1), 178(1)	−60.0(3), 175.7(2)
01−*0*−1−2b	176.7(3), −57.9(3)	174(1), −62(1)	177.3(2), −64.0(3)

[a] Torsion angles/deg are given, defined by (carbon) atom numbers only, *N* italicized.

m/z 552 which corresponds to the 2+ cation with one perchlorate anion, $[(CoC_{18}H_{34}N_8O_2)ClO_4]^{+}$. Efforts to crystallize the complex in a form suitable for an X-ray structure determination have to date been unsuccessful. Co(II) complexes with quadridentate ligands in solution are known as either four-, five-, or six-coordinate species, where the additional sites are occupied by anions or solvent molecules.[22] There is no evidence, however, that $[Co(\mathbf{L^2})]^{2+}$ binds any additional ligands, and indeed efforts to force chloride ion binding in dimethyl sulfoxide solvent resulted in partial displacement of the metal as $[CoCl_4]^{2-}$. (Similarly, addition of a large excess of NCS^- to a solution of the complex in aqueous acetone results in the distinctive blue color of $[Co(NCS)_4]^{2-}$.) It is perhaps surprising that chloride can displace a macrocyclic ligand, but this has been observed even in Cu(II) systems.[23] Thus, although the Co complex may not have the kinetic inertness of its Ni(II) analogue, it is nonetheless a rather unreactive repository of the metal ion.

3. Regaining Hexamine Forms: Hydrolysis of Lactamized Ligands. Preparative observations[3] indicated that lactamization of carboxymethylated sarcophagine complexes occurred over the period of hours required for product isolation and that, once formed in acid, the lactams were very stable. For many purposes, however, it would be useful to regain the ring-opened forms,

(22) Rybak-Akimova, E. V.; Kuczera, K. *Inorg. Chem.* **2000**, *39*, 2462.

(23) Comba, P.; Curtis, N. F.; Lawrance, G. A.; O'Leary, M. A.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 497, 2145.

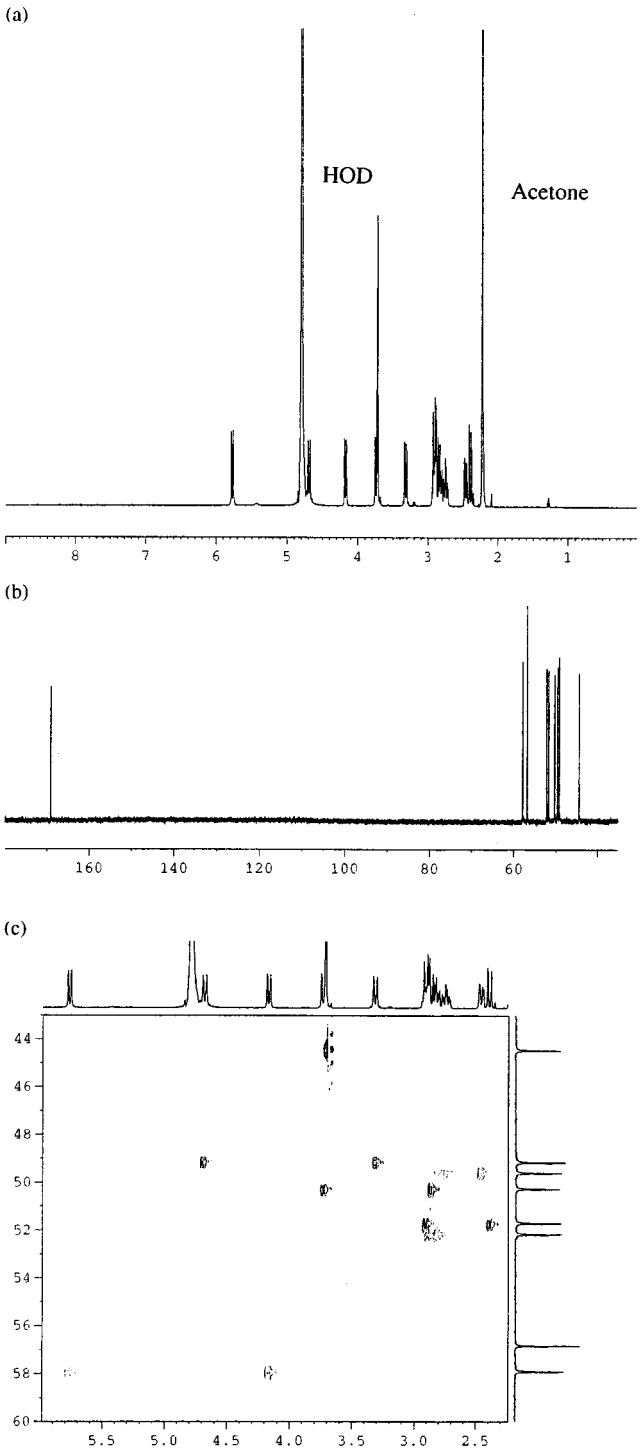

Figure 4. NMR spectra of $[Ni(H_2\mathbf{L^2})]^{4+}$: (a) ^1H NMR, (b) ^{13}C NMR, and (c) HSQC.

and in fact lactam hydrolysis occurs quite readily in basic media, resulting in MN_6 species replacing MN_4. For $[Cu(\mathbf{L^2})]^{2+}$ in 1 mol L^{-1} NaOH at room temperature, for example, hydrolysis is effectively complete within 1 h, an initially violet solution turning to a clear blue. More detailed kinetic measurements (by spectrophotometry; see Figure 5) were made on $[Ni(\mathbf{L^2})]^{2+}$ in 0.50−0.15 mol L^{-1} NaOH solutions (Table 3). Since at least two ring-opening and several N-inversion steps must be involved in the reaction, the kinetic analysis was surprisingly simple in being consistent with an A → B → C process. Assignment of the derived rate constants to the first and second steps of the reaction was difficult since neither spectrum calculated for the

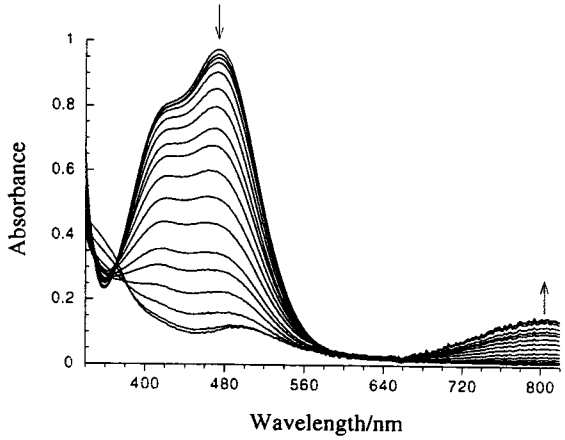

Figure 5. Visible spectra showing the hydrolysis of the lactam rings in $[Ni(H_2\mathbf{L^2})]^{4+}$.

Table 3. Rate Constants for the Hydrolysis of $[Ni(H_2\mathbf{L^2})]^{4+}$

NaOH (mol L^{-1})	k_{AB} (s^{-1})	k_{BC} (s^{-1})
0.50	$(4.9 \pm 0.6) \times 10^{-4}$	$(1.85 \pm 0.07) \times 10^{-4}$
0.25	$(3.6 \pm 0.4) \times 10^{-4}$	$(6.2 \pm 0.2) \times 10^{-5}$
0.15	$(2.7 \pm 0.3) \times 10^{-4}$	$(3.17 \pm 0.09) \times 10^{-5}$

intermediate on the two possibilities differed significantly.[24] If is assumed that the two steps are both those of ring opening, so that the first might statistically be expected to be faster than the second, and that both steps might show a first-order dependence on $[OH^-]$, then the assignments tabulated in Table 3 can be made. If these are indeed the rates for lactam hydrolysis, it appears that the metal has little effect upon the rates, perhaps unsurprisingly, since the metal is relatively remote from the carbonyl carbon and is not involved in coordination to the amide oxygen.[25]

Conclusions

This work builds upon our earlier report[3] of regioselective carboxymethylations of the cage amine 1,8-diaminosarcophagine. The most useful reaction with regard to many of the potential applications of these ligands is the reaction involving the copper complex of the ligand. This reaction provides a pathway to obtain the alkylated ligands in which the introduced functional groups are all on the external amine sites. The copper can be removed to obtain the free alkylated ligand, which can be used to form complexes with several other metals. Interestingly, at least two of these functional groups undergo intramolecular reaction to form lactam rings during the isolation procedure. This process converts the ligand to a tetraaza macrocycle with quite unique properties, and these ligands may be of interest in their own right. The amide rings can be hydrolyzed, and this process returns the macrocycle to a sexidentate ligand which retains the properties of the parent ligand. The introduced carboxymethyl pendent arms can then be used to form formally "charge neutral" complexes. It is possible to use these pendent arms as a site of further functionalization to enable the attachment of biomolecules that might provide a molecular agent with specificity in vivo, and this is the focus of a future paper.[12]

Experimental Section

General. Nuclear magnetic resonance (NMR) spectra were acquired using either a Varian Gemini 200 (^1H at 200 MHz and ^{13}C at 50.3

(24) Harrowfield, J. M.; Jackson, W. G.; Vowles, P. D. *Int. J. Kinet.* **1977**, *9*, 535.
(25) Buckingham, D. A.; Harrowfield, J. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1974**, *96*, 1726 and references therein.

MHz) spectrometer, a Bruker AM 300 (^{1}H at 300 MHz and ^{13}C at 75.5 MHz) spectrometer, or a Bruker ARX 500 (^{1}H at 500.13 MHz and ^{13}C at 125.8 MHz) spectrometer. Chemical shifts for samples measured in D_2O are expressed in parts per million relative to an internal standard of acetone which was taken as being δ 2.22 for ^{1}H NMR and δ 30.89 for ^{13}C NMR spectra. All spectra were acquired in D_2O unless stated otherwise. Assignments were made with the aid of either the DEPT or HSQC techniques.

Microanalyses for carbon, nitrogen, and hydrogen were carried out by The Australian National University Microanalytical Service. All samples were thoroughly dried under vacuum (0.1 mmHg) at 50 °C for 4 h prior to their analysis.

Mass spectra were recorded using the electrospray technique (positive ion trap) on a VG Autospec instrument using a 1:1 mix of acetonitrile/water as a solvent.

Ion exchange chromatography was performed under gravity flow using H^+ form Dowex 50Wx2 (200−400 mesh) or Na^+ form SP Sephadex C25 (200−400 mesh) cation-exchange resin.

The Schlenk technique using high-purity argon or high-purity nitrogen was employed wherever it was necessary to exclude oxygen or moisture from preparative mixtures. Deionized water was used in all preparations. All evaporations were performed at 50 °C under reduced pressure (∼20 mmHg) using a Büchi rotary evaporator and a water aspirator. All organic solvents (Aldrich Chemical Co.) were distilled prior to use. Acetonitrile was dried by distillation over CaH_2 and stored over 3 Å molecular sieves. Chloroacetic acid (Ajax Chemicals) was used as received.

Spectrophotometry was carried out using a Hewlett-Packard 8452A diode array instrument. Kinetic measurements were performed at 50 °C on stirred solutions prepared using water purified through a Milli-Q Ultra-Pure water system. Sodium hydroxide (1.000 ± 0.005 mol L^{-1}) was supplied by Ajax chemicals. Rate constants were determined using the program SPECFIT.[5]

Synthesis. Samples of the (crude) free ligand 1,8-diamino-3-carboxymethylsarcophagine, here designated **L^1**, and of the Cu(II) complexes of dilactamized forms, **L^2** and **L^3**, respectively, of the 1,8-di(carboxymethylamino)- and 1-(di-carboxymethyl)amino-8-carboxymethylamino-sarcophagine ligands were available from our previous work.[3] (Note that there is an error in the Experimental Section of ref 3, where the Cu complexes are all said to be derivatives of the 3,6-dicarboxymethyl cage ligand, whereas in fact they are derivatives of the 1,8-dicarboxymethylamino cage where lactamization has involved acylation/cyclization onto the 3,6-N atoms, as shown in the structures given. There is also an error in the formula for **Cu1b**, where two surplus perchlorate anions are included.)

[Cu(H$_2$L^1)]Cl$_4$·3H$_2$O. $Cu(CH_3CO_2)_2$·H_2O (0.41 g, 2.0 mmol) was added to a solution (in water, 10 mL) of the crude ligand (**L^1**) obtained[3] from 0.5 g of 1,8-$(NH_2)_2$sar. The deep blue solution formed was diluted with water and then applied to a column of SP Sephadex C25. Excess Cu(II) was removed by elution with 0.025 mol L^{-1} sodium citrate. Elution with 0.05 mol L^{-1} sodium citrate revealed four deep blue bands, followed by one light blue band which proved to be $[Cu((NH_2)_2sar)]^{2+}$. The third deep blue band was by far the major component. Its eluate was collected and applied to a column of H^+ form Dowex 50Wx2. The column was washed with water and then with 1 mol L^{-1} HCl (removing Na^+) before the complex was eluted with 3 mol L^{-1} HCl. The eluate was evaporated to dryness and the residue crystallized from water/acetone to give $[Cu(H_2\mathbf{L^1})]Cl_4$·$3H_2O$ as deep blue crystals. Yield: 1.04 g (80%). (Found: C, 30.2; H, 6.4; N,17.5. Calcd for $CuC_{16}H_{38}N_8Cl_4O_2$·$3H_2O$: C, 30.31; H, 7.00; N, 17.68.) MS: *m*/*z* 470 = $[CuC_{16}H_{36}N_8O_2Cl]^+$. Visible spectrum: λ_{max} = 582 nm, ϵ = 123 M^{-1} cm^{-1}.

Crystals suitable for X-ray studies were grown by dissolving the solid in the minimum volume of water and adding an equal volume of 2 mol L^{-1} HNO_3. Slow evaporation of the solvent led to the formation of deep blue, prismatic crystals, the composition $[Cu(H_2\mathbf{L^1})](NO_3)_{3.5}$-$Cl_{0.5}$·$2.5H_2O$ being assigned from the structural model.

[Ni(H$_2$L^1)]Cl$_4$·4H$_2$O and [Ni(HL^1)]Cl$_3$·3H$_2$O. Crude ligand (**L^1**) from 1,8-$(NH_2)_2$sar (0.5 g) and $Ni(CH_3CO_2)_2$·$4H_2O$ (0.47 g, 1.9 mmol) were dissolved in water, and the brown solution formed was heated at reflux under an atmosphere of nitrogen for 20 h. The red/brown final solution was cooled, diluted to a total volume of 500 mL, and applied to a column of SP Sephadex C25 (Na^+ form). Elution with 0.025 mol L^{-1} sodium citrate removed excess Ni(II) (green), and subsequent elution with 0.05 mol L^{-1} sodium citrate revealed three bands. The first band was pink, the second was yellow, and the third, which proved to be $[Ni((NH_2)_2sar)]^{2+}$, was pink. Band 1 was collected and applied to a column of Dowex 50Wx2. The column was washed with water (200 mL) and 1 mol L^{-1} HCl before being eluted with 3 mol L^{-1} HCl. The eluate was then evaporated to dryness under reduced pressure and then crystallized from water/ethanol/diethyl ether to give $[Ni(H_2\mathbf{L^1})]$-Cl_4·$4H_2O$ as pink crystals. Yield: 0.91 g (70%). (Found: C, 29.4; H, 6.9; N, 17.0. Calcd for $NiC_{16}H_{46}N_8Cl_4O_6$: C, 29.70; H, 7.17; N, 17.32.) MS: *m*/*z* 465 = $[NiC_{16}H_{36}N_8O_2Cl]^+$; 429 = $[NiC_{16}H_{38}N_8O_2]^+$; 256 = $[NiC_{16}H_{36}N_8O_2(CH_3CN)_2]^{2+}$. Visible spectrum: λ_{max} = 338 nm, ϵ = 15 M^{-1} cm^{-1}; λ_{max} = 518 nm, ϵ = 9 M^{-1} cm^{-1}; λ_{max} = 820 nm, ϵ = 13 M^{-1} cm^{-1}.

Vapor diffusion of ethanol into an aqueous solution of the complex gave pink/mauve spearlike crystals suitable for X-ray diffraction studies, from which composition was assigned as $[Ni(H\mathbf{L^1})]Cl_3$·$2.5H_2O$.

Band 2 was collected and desalted in the same way as band 1. The yellow/orange eluate from the Dowex column was evaporated to dryness under reduced pressure to give an orange/red residue. The ^{1}H NMR of this material showed broad resonances from 2.3 to 4.2 ppm. The ^{13}C NMR also exhibited broadening indicative of some paramagnetic character, but 9 major signals were observed (δ (75 MHz): 50.0, 52.4, 52.9, 54.7, 55.9, 60.2, 60.9, 62.0, and 166.8). This material inevitably turned mauve/pink on crystallization or after time, the final pink/mauve product having the same characteristics as the solid isolated in band 1.

[Zn(H$_2$L^2)][ZnCl$_4$]Cl$_2$·H$_2$O. Excess Zn dust was added to a purple aqueous solution of $[Cu(H_2\mathbf{L^2})]Cl_4$·$5H_2O$ (0.3 g) in water (3 mL). The mixture was stirred for 30 min and then filtered. The colorless filtrate was taken to dryness by evaporation under reduced pressure to give a white residue, which was crystallized from water/ethanol to give colorless crystals of $[Zn(H_2\mathbf{L^2})][ZnCl_4]Cl_2$·$H_2O$. Yield: 0.38 g (100%). (Found: C, 28.9; H, 5.1; N, 14.3. Calcd for $Zn_2C_{18}H_{30}N_8Cl_6O_2$·$H_2O$: C, 28.52; H, 5.05; N,14.78.) ^{1}H NMR (300 MHz): δ 2.5−3.8, complex m, 28H, CH_2. ^{13}C NMR (125 MHz): δ 44.6, 44.7, 46.8, 49.2, 51.6, 52.6, 53.2 CH_2, 59.1 C quaternary, and 170.8 amide. MS: *m*/*z* 493 = $[ZnC_{34}N_8O_2Cl]^+$.

[H$_6$L^2]Cl$_6$·3H$_2$O. $[Zn(H_2\mathbf{L^2})][ZnCl_4]Cl_2$·$H_2O$ (0.38 g) was dissolved in water and applied to a column of H^+ Dowex 50Wx2 (4 cm × 4 cm diameter). The column was washed with water (200 mL) and 1 mol L^{-1} HCl (to remove Zn(II)) and then eluted with 5 mol L^{-1} HCl. The eluate was evaporated to dryness to give a white solid. This was dissolved in 5 mol L^{-1} HCl, and addition of ethanol caused the precipitation of $[H_6\mathbf{L^2}]Cl_6$·$3H_2O$ as a white powder (0.25 g, 76%). (Found: C, 32.6; H, 6.7; N, 16.8. Calcd for $C_{18}H_{40}N_8Cl_6O_2$·$3H_2O$: C, 32.40; H, 6.95; N, 16.79.) ^{1}H NMR (300 MHz): δ 2.9−4.4, complex m, 28 H, methylene protons. ^{13}C NMR (125 MHz): δ 42.2, 44.6, 45.3, 46.4, 48.5, 49.3, 54.8, 54.9, and 163.9 (amide). MS: *m*/*z* 395 = $[C_{18}H_{35}N_8O_2]^+$.

[Ni(H$_2$L^2)](ClO$_4$)$_4$·5H$_2$O. $[H_6\mathbf{L^2}]Cl_6$·$3H_2O$ (0.100 g) was dissolved in water (5 mL). Excess $Ni(CH_3CO_2)_2$ (0.075 g) was added, and the green mixture was heated at reflux under an atmosphere of nitrogen for 8 h. The mixture was then diluted with water and applied to a column of Na^+ form SP Sephadex C25 (20 cm × 2 cm diameter). The column was eluted with 0.05 mol L^{-1} sodium citrate to give a green band of excess Ni^{2+} which eluted very quickly followed by a slower moving yellow band. The eluate of the latter was applied to a column of H^+ Dowex 50Wx2 (4 cm × 4 cm). The column was washed with water and 1 mol L^{-1} HCl before the yellow complex was eluted with 3 mol L^{-1} HCl. The yellow eluate was evaporated to dryness to give a yellow residue, which was dissolved in water and precipitated by the addition of ethanol, to give $[Ni(H_2\mathbf{L^2})]^{4+}$ as its chloride salt. ^{1}H NMR (500 MHz): δ 2.40, 4H, m, CH_2; 2.85, 10H, m, CH_2; 3.32, d of AB quartet, $^2J_{HH}$ = 14 Hz, CH_2; 3.70, 6H, m, CH_2; 4.15, 2H, d of AB quartet, $^2J_{HH}$ = 13 Hz, CH_2; 4.68, 2H, d of AB quartet, $^2J_{HH}$ = 14 Hz, CH_2; 5.75, d of AB quartet, $^2J_{HH}$ = 13 Hz, CH_2. ^{13}C NMR (500 MHz): δ 42.98, 47.94, 48.94, 49.60, 49.70, 52.74 methylene, 55.71 quaternary C, 58.15 CH_2CO, and 164.25 amide carbonyl. MS: *m*/*z* 487 =

$[NiC_{18}H_{34}N_8O_2Cl]^+$; *m*/*z* 451 = $[NiC_{18}H_{33}N_8O_2]^+$. Visible spectrum: λ_{max} = 416 nm, ϵ = 64 $M^{-1}cm^{-1}$.

Crystals of the perchlorate salt suitable for an X-ray structure determination were grown by slow evaporation of a solution of the chloride in 1 mol L^{-1} $HClO_4$. The bulk was converted to the perchlorate as follows: A solution of the chloride salt in water was passed through a column of acetate form Dowex 1 × 8 anion-exchange resin. The effluent was taken to dryness to give a yellow residue. This was dissolved in ethanol, and an excess of concentrated perchloric acid (**CAUTION!**) was added. Cooling in ice resulted in the precipitation of yellow crystals of $[Ni(H_2\mathbf{L^2})](ClO_4)_4\cdot 5H_2O$, which were collected by filtration and washed with ice cold ethanol and diethyl ether. (Found: C, 22.9; H, 4.5; N, 11.7. Calcd for $NiC_{18}H_{36}N_8O_2(ClO_4)_4\cdot 5H_2O$: C, 22.92; H, 4.92; N, 11.88.)

$[Co(HL^2)](ClO_4)_3\cdot 2H_2O$. $[H_6\mathbf{L^2}]Cl_6\cdot 3H_2O$ (0.089 g) was dissolved in water (5 mL). Excess $Co(CH_3CO_2)_2\cdot 4H_2O$ (0.083 g) was added, and the mixture was heated on a steam bath for 30 min. The solution formed was passed through a column of Dowex 1 × 8 anion-exchange resin (acetate form). The effluent was evaporated to dryness, the residue dissolved in ethanol, and concentrated $HClO_4$ (**CAUTION!**) added to afford a brown precipitate of $[Co(H\mathbf{L^2})](ClO_4)_3\cdot 2H_2O$, which was collected by filtration and washed with ethanol and diethyl ether. (Found: C, 27.8; H, 5.2; N, 13.6. Calcd for $CoC_{18}H_{36}N_8O_2(ClO_4)_3\cdot 2H_2O$: C, 27.37; H, 5.10; N, 14.19.) MS: *m*/*z* 552 = $[CoC_{18}H_{34}N_8O_2(ClO_4)]^+$. Visible spectrum (in DMSO): λ_{max} = 422 nm, ϵ = 122 $M^{-1}cm^{-1}$.

$[Zn(H_2L^3)]Cl_4\cdot 4H_2O$. Starting with $[\{Cu(H\mathbf{L^3})\}_2Cl](NO_3)_4Cl\cdot 11H_2O$,[3] the same reductive procedure as described above for the complex of $\mathbf{L^2}$ resulted in the isolation of colorless crystals of the simple chloride $[Zn(H_2\mathbf{L^3})]Cl_4\cdot 4H_2O$. (Found: C, 32.4; H, 5.7; N, 14.9. Calcd for $ZnC_{20}H_{38}N_8Cl_4O_4\cdot 4H_2O$: C, 32.73; H, 6.32; N, 15.27.) ^1H NMR (300 MHz): δ 2.75−3.80, complex m, 28 H, methylene protons; 4.28, AB quartet, 2H, CH_2CO_2H. ^{13}C NMR (125 MHz): δ 44.6, 45.1, 46.0, 46.1, 49.0, 49.1, 49.2, 51.0, 51.6, 52.6, 52.9, 53.0, 57.1 (CH_2), 58.5, 59.0 C (quaternary C), 169.8, and 175.7 (amide). MS: *m*/*z* 551 = $[ZnC_{20}H_{36}N_8O_4Cl]^+$.

$[H_2L^3][ZnCl_4]\cdot 6H_2O$. Liquid diffusion of ethanol into an aqueous solution of $[Zn(H_2\mathbf{L^3})]Cl_4\cdot 4H_2O$ slowly produced crystals of a quality suitable for an X-ray study. The structure solution showed, however, that the isolated crystals were of the protonated ligand, as its hydrated tetrachlorozincate salt.

Structure Determinations. Five single-crystal structure determinations underpin the present work; in each case the compound is modeled as ionic, the cation containing the ligand variously coordinated, substituted, and (de-) protonated. One such species with associated counterions and solvent molecules, devoid of crystallographic symmetry, comprises the asymmetric unit of the structure in each case. The modeling of the counterionic and solvent components in a number of cases is fraught with difficulty arising from disorder and/or incomplete site occupancy and/or large displacement parameters. Nevertheless, in each case, the cationic component is well-defined as also its protonation and substitution pattern.

Full spheres of CCD area-detector diffractometer data were measured (Bruker AXS instrument; ω scans, $2\theta_{max}$ = 58°; monochromatic Mo Kα radiation, λ = 0.7107$_3$ Å), $N_{t(otal)}$ reflections being merged after "empirical"/multiscan absorption correction (proprietary software) to yield *N* independent (R_{int} quoted), N_o with $F > 4\sigma(F)$ considered "observed" and used in the full-matrix least-squares refinement. Anisotropic displacement parameter forms were refined for the non-hydrogen atoms, hydrogen atom treatment as specified individually. Conventional residuals *R*, R_w (weights: $(\sigma^2(F_o) + 0.0004F_o^2)^{-1}$) are quoted at convergence, neutral atom complex scattering factors being employed within the Xtal 3.4 program system.[6] Pertinent results are given below and in the tables and figures, the latter showing displacement envelopes at the 20% (300 K) or 50% (153 K) probability levels; individual difficulties, variations, and idiosyncrasies are described under "variata". Other crystallographic data are lodged as CIF files (see Supporting Information).

$[Cu(H_2L^1)](NO_3)_{3.5}Cl_{0.5}\cdot 2.5H_2O$: $C_{16}H_{43}Cl_{0.5}CuN_{11.5}O_{15}$; M = 717.9. Monoclinic, space group $P2_1/c$ (C_{2h}^5, No. 14), a = 11.010(1) Å, b = 12.943(1) Å, c = 19.680(2) Å, β = 92.506(1)°, V = 2802 Å^3. $D_c(Z=4)$ = 1.70$_2$ g cm^{-3}. μ_{Mo} = 9.2 cm^{-1}; specimen: 0.20 × 0.12 × 0.07 mm; "$T_{min,max}$" = 0.81, 0.93. N_t = 33222, N = 7216 (R_{int} = 0.031), N_o = 5737; R = 0.054, R_w = 0.066. n_v = 594, $|\Delta\rho_{max}|$ = 1.47(4) e Å^{-3}. $T \sim$ 153 K.

Variata. (*x*, *y*, *z*, U_{iso}) were refined for those hydrogen atoms in association with the cation. Nitrates 1−3 were well-defined, the remaining nitrate and associated residues designated as anionic and solvent moieties being disorderly with high displacement parameters, eventually modeled as shown, the water complement being made up of five fragments, site occupancies set at 0.5 after trial refinement.

$[Ni(HL^1)]Cl_3\cdot 2.5H_2O$: $C_{16}H_{43}Cl_3N_8NiO_5$; M = 584.6. Orthorhombic, space group $Fdd2$ (C_{2v}^{19}, No. 43), a = 23.443(5) Å, b = 23.566(5) Å, c = 18.408(4) Å, V = 10170 Å^3. $D_c(Z=16)$ = 1.52$_7$ g cm^{-3}. μ_{Mo} = 11.2 cm^{-1}; specimen: 0.35 × 0.13 × 0.10 mm; "$T_{min,max}$" = 0.77, 0.93. N_t = 30690, N = 3397 (R_{int} = 0.068), N_o = 2391; R = 0.048, R_w = 0.046. n_v = 293, $|\Delta\rho_{max}|$ = 1.4(3) e Å^{-3}. $T \sim$ 153 K.

Variata. "Friedel pair" data were retained distinct in the merging of data, x_{abs} refining to 0.00(2). Water molecule oxygen assignments O(03,04) were assigned occupancies of 0.5 after trial refinement. (*x*, *y*, *z*, $U_{iso})_H$ were included restrained at estimates for the cation, not located for the solvent component.

$[Cu(HL^2)Cl]Cl_2\cdot 2H_2O\cdot EtOH$: $C_{20}H_{45}Cl_3CuN_8O_5$; M = 647.5. Monoclinic, space group $P2_1/n$ (C_{2h}^5, No. 14; variant), a = 9.804(1) Å, b = 14.558(2) Å, c = 20.358(3) Å, β = 103.913(2)°, V = 2820 Å^3. $D_c(Z=4)$ = 1.52$_5$ g cm^{-3}. μ_{Mo} = 11.1 cm^{-1}; specimen: 0.20 × 0.07 × 0.06 mm; "$T_{min,max}$" = 0.70, 0.84. N_t = 28169, N = 7196 (R_{int} = 0.036), N_o = 5417; R = 0.041, R_w = 0.046. n_v = 498, $|\Delta\rho_{max}|$ = 1.22(6) e Å^{-3}. $T \sim$ 153 K.

Variata. All hydrogen atoms were located, all being refined in (*x*, *y*, *z*, U_{iso}) except those associated with the two water molecules. The present compound is isomorphous with compound **Cu5** of ref 3, $[CuCl(\mathbf{L^3})]Cl \sim 3.9H_2O$, for which a = 10.197(4) Å, b = 14.556(5) Å, c = 19.280(7) Å, β = 100.810(7)°, V = 2812 Å^3, at 300 K, and was refined in that setting. Coordinates for the atoms of the cation (except those of the pendent carboxymethyl group), the two corresponding chlorine atoms and water molecule O(01) correspond closely throughout. The pendent carboxyl group of **Cu5** is (broadly) replaced by the ethanol of the present compound, while the present additional chloride and water molecule are disposed in the vicinity of the remaining solvent content of **Cu5**.

$[Ni(H_2L^2)OClO_3](ClO_4)_3\cdot 6H_2O$: $C_{18}H_{48}Cl_4N_8NiO_{24}$; M = 961.1. Monoclinic, space group Pn (C_s^2, No. 7; variant), a = 12.966(4) Å, b = 11.265(3) Å, c = 13.096(4) Å, β = 108.753(4)°, V = 1811 Å^3. $D_c(Z=2)$ = 1.76$_2$ g cm^{-3}. μ_{Mo} = 9.3 cm^{-1}; specimen: 0.45 × 0.35 × 0.30 mm; "$T_{min,max}$" = 0.52, 0.89. N_t = 20336, N = 4558 (R_{int} = 0.040), N_o = 3015; R = 0.064, R_w = 0.073. n_v = 491, $|\Delta\rho_{max}|$ = 0.90(6) e Å^{-3}. $T \sim$ 293 K.

Variata. "Friedel pair" data were retained distinct in the merging of data, x_{abs} refining to 0.07(4) in the final cycles. (*x*, *y*, *z*, $U_{iso})_H$ were included constrained at estimates for the cation, not being located for the water molecules, whose displacement parameters were generally high (also true of the perchlorate oxygen atoms, disorder not being resolvable). O(06) was refined with an isotropic displacement parameter form.

$[H_2L^3][ZnCl_4]\cdot 6H_2O$: $C_{20}H_{50}Cl_4N_8O_{10}Zn$; M = 769.9. Monoclinic, space group $P2_1/c$, a = 10.045(2) Å, b = 21.739(5) Å, c = 15.077(3) Å, β = 94.781(4)°, V = 3281 Å^3. $D_c(Z=4)$ = 1.55$_8$ g cm^{-3}. μ_{Mo} = 11.4 cm^{-1}; specimen: 0.30 × 0.14 × 0.05 mm; "$T_{min,max}$" = 0.55, 0.84. N_t = 38938, N = 8419 (R_{int} = 0.067), N_o = 5580; R = 0.044, R_w = 0.045. n_v = 589, $|\Delta\rho_{max}|$ = 1.2(2) e Å^{-3}. $T \sim$ 153 K.

Variata. Difference map residues modeled plausibly as waters of crystallization, (*x*, *y*, *z*, $U_{iso})_H$ being located and refined throughout except for O(6), comprising two fragments separated by 0.67(2) Å, modeled with equal (0.5) occupancy after trial refinement, associated hydrogen atoms not being located.

Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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