Carboxymethylation of Cage Amines: Control of Alkylation by Metal Ion Coordination

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Reactions between chloroacetate and both "free" and coordinated forms of the cage amine diaminosarcophagine (1,8-diamino-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane) result in the introduction of between one and four pendent carboxymethyl substituents on the nitrogen atoms of the cage. While at least the first two steps in the reaction of the free ligand have been found to involve only the secondary nitrogen centers, in both the Cu(II) and Co(III) complexes alkylation occurs only at the primary (1,8) centers, the greater ease of achieving a higher degree of alkylation of the Cu(II) complex being attributed to the lower charge of this species causing a lesser reduction of the nucleophilicity of the uncoordinated primary nitrogen atoms. All the new ligands have been characterized by X-ray structure determinations of their Cu(II) or Co(III) complexes. In some cases, this has shown that the methods used to isolate the crystalline complexes result in lactamization of the ligand.

Introduction

The generally inert nature of complexes formed by cage hexamine ligands of the bicyclo[6.6.6]icosane type, given the trivial name of "sarcophagines",[1] should facilitate various applications of the complexes dependent upon the specific properties of the bound metal ion.[2,3] Some of these potential applications, such as to provide new radiopharmaceuticals,[4] require the tethering of the sarcophagine complex to a macromolecule such as a protein, and in this regard the "externally" functionalized sarcophagine, 1,8-diaminosarcophagine, must be seen as a useful starting material. In fact, it has already been used as the source for a number of cage amine derivatives.[2,3,5−8] We have sought to examine its reactions with chloroacetate to introduce carboxymethyl entities as functional groups, a procedure which has been widely and successfully applied to macromonocyclic polyamines[9,10] and which not only provides pendent arms for attachment reactions but also provides anionic carboxylate groups to neutralize the positive charge of a bound cation and so minimize osmotic effects.[4] There is a complication in the diaminosarcophagine system which does not arise in those of simpler macrocyclic compounds in that both primary and secondary amine centers are present, so that the possibilities for structural isomerism are somewhat more extensive, though the well-characterized coordination chemistry of diaminosarcophagine indicates that metal ion coordination should offer an obvious method of protecting all six secondary amine sites. A disadvantage to be anticipated here is that even uncoordinated, "external" amine sites such as the 1,8-amino groups of a diaminosarcophagine metal ion complex may be considerably weaker nucleophiles than those in the free base.[2,8] It is worthy of note also that peralkylation of sarcophagine with simple methyl groups alone is difficult to achieve,[11,12] indicating that steric effects may be more prominent in bicyclic systems than in monocyclic. We report herein our initial explorations of carboxymethylation reactions of both free and coordinated 1,8-diaminosarcophagine, reactions which have resulted in the selective introduction of between one and four substituents, as substantiated by structure determinations of cobalt(III) and copper(II) complexes of these new ligands.

Results and Discussion

Only what might be considered the most familiar and therefore the most obvious method of carboxymethylation of an amine, its reaction with chloroacetate ion,[9,13] has been examined in the present work, and no doubt there are alternative methods which might work equally well. Significantly, however, the results described herein show that both the degree and position of alkylation of diaminosarcophagine can be controlled by varying its form of coordination. It is convenient to begin with consideration of the results of alkylation reactions of the

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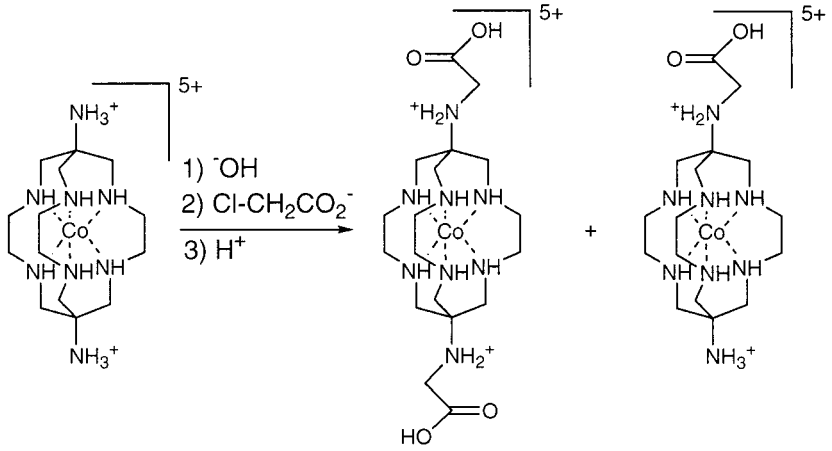
Scheme 1. Carboxymethylation of the Cobalt Complex of Diaminosarcophagine



cobalt(III) complex of diaminosarcophagine, since these, in fact, are simplest to interpret. Although trace amounts of other (unidentified) products have been detected, it appears that in a practical sense this is a pathway only to mono- and disubstituted derivatives, with reactions occurring exclusively at the primary amino groups (Scheme 1). Further, only the symmetrically disubstituted compound and none of its 1,1-bis(carboxymethylamino) isomer could be detected. Formation of the disubstituted complex requires the use of a very large excess of chloroacetate, and further reactions of the complex do not seem to be competitive with the hydrolysis of chloroacetate to glycolate in the aqueous solvent medium. The crystallization of a number of derivatives of the disubstituted complex was examined in efforts to obtain materials suitable for X-ray studies, and ultimately this resulted in the characterization of species formally containing the 5+, 3+, and 1+ cations. The structure of the 5+ cation as its chloride pentahydrate (**Co1a**) was fully defined by refinement. Figure 1 includes a view of the molecular unit, in which it is apparent that, at least in the crystalline form, the cation is one of the small group of cage amine complexes of this type to adopt the *ob*$_3$ conformation.[1,5,8,14−18] Although the structure, when viewed down *c*, can be regarded as layers of cations about the $z = 0$ plane interleaved by layers of chloride ions and water (about $z = {}^1/_4$), there is an intricate hydrogen-bonding network involving all species, particularly significant in relation to other structures being the fact that each of the five chloride ions is hydrogen-bound to but one coordinated NH of a given cation (Cl(1)···H(3a) 2.36(3); Cl(2)···H(3c′) 2.23(3); Cl(3)···H(3b) 2.36(3); Cl(4)···H(3a′) 2.36(3); Cl(5)···H(3b′) 2.40(3) Å), with the sixth NH forming a bond to lattice water oxygen (H(3c)···O(03) 2.14(3) Å). In addition, other outstandingly short chloride···hydrogen contacts are found: Cl(1)···H(1′) ($x - 1$, y, z) (a carboxylic acid hydrogen) 2.09(4); Cl(2)···H(04b) ($\bar{x} - {}^1/_2$, $y - {}^1/_2$, ${}^1/_2 - z$), H(05b) ($1 - x$, $\bar{y}$, $1 - z$) (water hydrogens) 2.29(4), 2.22(6); Cl(3)···H(02a,03a) ($1{}^1/_2 - x$, $y - {}^1/_2$, $1{}^1/_2 - z$) 2.29(5), 2.38(4); Cl(4)···H(1) ($1 + x$, y, z), H(3a′), H(01b) ($2 - x$, $\bar{y}$, $1 - z$) 2.02(4), 2.36(3), 2.33(4); Cl(5)···H(04a) 2.25(5) Å. The terminal amine hydrogens contact water molecules: H(0A)···O(05) 1.94(3); H(0B)···O(02) 1.81(3); H(0A′)···O(01) 2.05(3); H(0B′)···O(04) 1.86(4) Å. Of the remaining water molecule hydrogens interacting with other water molecules, H(02b)···O(01) ($x - {}^1/_2$, ${}^1/_2 - y$, ${}^1/_2 + z$) 1.98(5) Å is the only notably strong contact. The conformations of the carboxymethylamino substituents on the cage are such as to give the cation overall a slightly bowed shape, with the two CO_2 planes being oppositely inclined at small angles to the *ac* plane.

The effect of a different mode of ion association on the conformation of the cage cation is illustrated by the adoption of the *lel*$_3$ conformation in the disulfate−chloride salt (**Co1b**) of the disubstituted cage, again a structure fully defined by refinement (Figure 1). Once again there is an intricate hydrogen-bonding network within the lattice, but the chloride ion is involved in interaction with water and one of the NH_2^+ groups (Cl···H(01b) (x, y, $1 - z$) 2.13(6); Cl···H(0A) ($1 - x$, $2 - y$, $2 - z$) 2.44(4) Å), and it is the sulfate groups which are involved in bonding to the coordinated NH units of the complex. Here, one oxygen atom of each sulfate is symmetrically poised (O(13)···H(3a′,3c) 2.03(6), 1.97(4); O(23)···H(3b′,3a) 2.23(5), 2.15(5) Å) between a pair of NH groups on two of the three open edges of the CoN_6 octahedron. The remaining open edge is spanned by a symmetrically bound water molecule (O(03)···H(3c′,3b) 2.04(3), 2.08(5) Å). This "chelation" of hydrogen-bond acceptors has been recognized previously as a characteristic not just of many cage complexes[11] but also of many simpler complexes[19] which adopt a *lel*$_3$ conformation, and it may be a critical factor favoring this conformation, although there is theoretical and experimental evidence that *lel*$_3$ is intrinsically most favored.[15] As is shown in the present and other related structures,[8] the role of chloride as a hydrogen-bond acceptor is quite flexible and it remains difficult to predict the conformation that may be found in a particular crystalline complex. It is in addition only one component of a complicated array, the lattice of **Co1b** also involving NH_2^+···OSO_3^{2-} contacts (H(0B)···O(21) (x, $y - 1$, z) 1.80(5); H(0′A)···O(14) ($2 - x$, $2 - y$, $2 - z$) 1.86(5) Å; H(0′B)···O(12) (x, y, $z - 1$) 1.70(4) Å) and water−water plus water−sulfate contacts (H(01A)···O(24) 2.01(8); H(02A)···O(01) 1.93(6); H(02B)···O(12) (x, y, $z - 1$) 2.29(9); H(03A)···O(05) (x, y, $z - 1$) 1.81(6); H(03B)···O(01) (x, $y - 1$, z) 1.99(7); H(04A)···O(14) 2.03(5); H(04B)···O(05) 1.92(9); H(05A)···O(22) (x, $y - 1$, z) 1.58(6); H(05B)···O(11) 2.03(7) Å).

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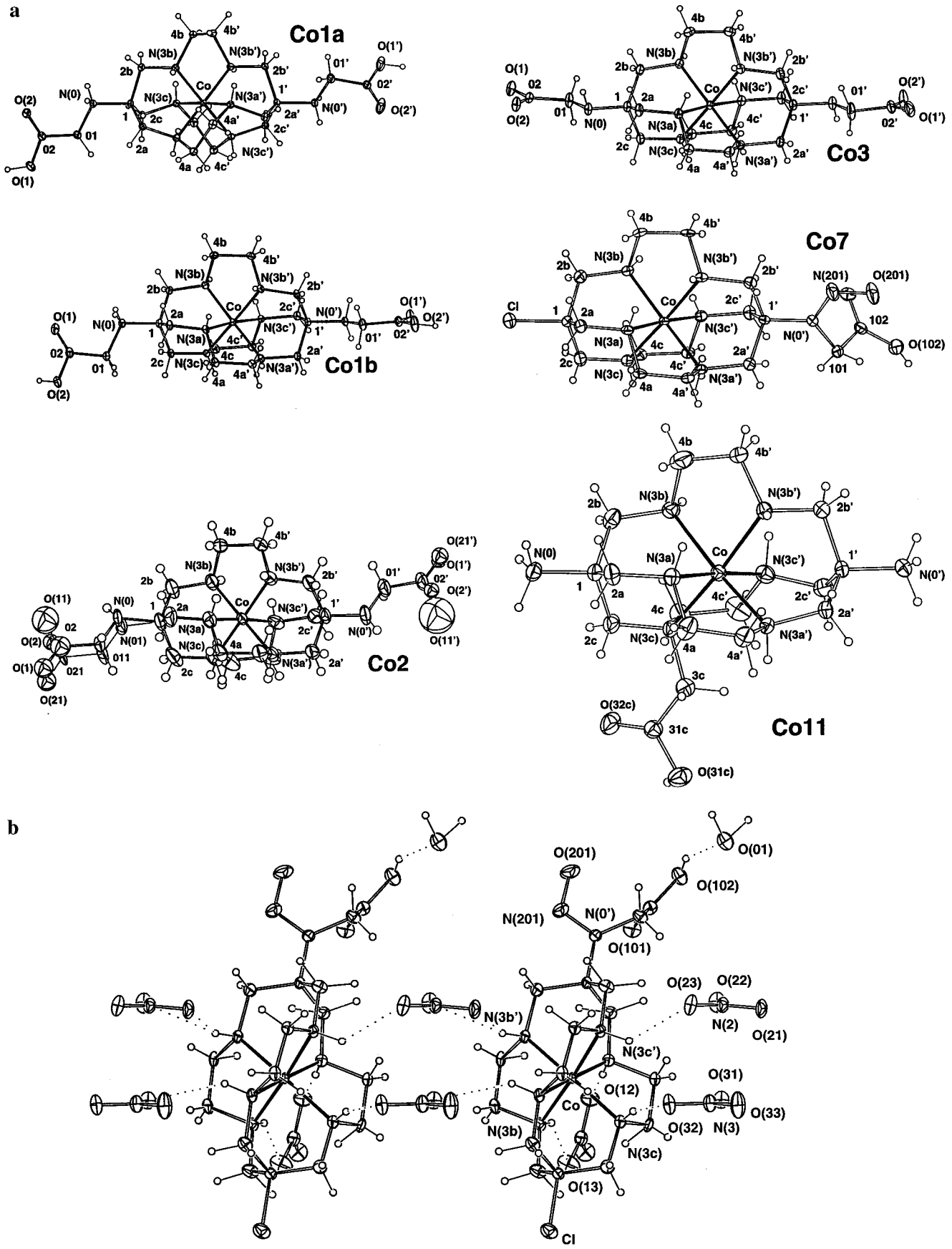

Figure 1. (a) Projections of the cations of the cobalt complexes with common orientations, chiralities, and numberings; probability amplitudes of the non-hydrogen atom envelopes are 20% (room temperature) or 50% (low temperature). (b) Projection of the cation string of **Co7** linked by pairs of hydrogen-bonded nitrate ions (the third being "chelated"), also inclusive of the hydrogen-bonded water molecule.

Support for the notion that "H-bond chelation" favors the *lel*$_3$ conformation is provided in the comparison of the cation structure described above of the chloride of the 5+ (fully protonated) complex with that of the chloride of the 3+ species

(**Co2**). Although a less precise determination (not involving H atom refinement) than either of the above despite its determination at low temperature, it is clear that the cation (Figure 1) does have the *lel*$_3$ conformation and that each open octahedral edge is spanned by a chloride ion symmetrically bound, albeit with some disorder (⟨Cl···N⟩ 3.15 Å; Cl(1)···N(3b′,3a) 3.12(2), 3.15(2) (3.17(2), 3.16(2) for Cl(1′)); Cl(2)···N(3c′,3b) 3.214(8), 3.01(1) (3.05(1), 3.43(2) for Cl(2′)); Cl(3)···C(3a′,3c) 3.184(5), 3.155(4) Å). In further contrast to the pentachloride, the cation has a steplike profile, with the opposed CO_2 planes lying more nearly parallel. The cations form chains along *b*, with contacts between carboxylate units of consecutive cations (O(1)···O(1′), O(21′)($x - 1$, $y - 1$, z) 2.73(1), 2.46(2) Å), as well as between carboxylate and water units (O(1)···O(03) ($1 - x$, $1 - y$, $1 - z$) 2.81(4), O(2)···O(04) ($1 - x$, $1 - y$, $2 - z$) 2.40(2), O(11′)···O(04) ($1 - x$, $1 - y$, $2 - z$) 2.13(3) Å). This indication of carboxylate hydrogen-bonding is consistent with the cage substituents being in their aminocarboxylic acid rather than ammoniocarboxylate form, an observation explicable in terms of the proximity of the Co(III) cation having a greater acidity enhancement effect on the substituent nitrogen center than on the carboxylate unit. It has of course already been noted as a cause of difficulty in synthesis that the basicity of the 1,8 amino groups of coordinated diaminosarcophagine is very low compared to that of a simple amine.

A satisfactorily precise structure was also determined on the (carboxyl) deprotonated, 1+ cation of the disubstituted cage as its perchlorate salt (**Co3**), though hydrogen atoms were refinable on only three of the water molecules, and three of the oxygen atoms on the perchlorate anion were modeled as rotationally disordered about the bond to the fourth. Another form of H-bond chelation is apparent in this structure in that zigzag columns quasi-parallel to the *bc* plane (and with the C1−Co−C8 axes of the complexes oriented in the *c* direction in this plane) result from symmetrical spanning of open octahedral edges by carboxylate moieties ({H(3a)···O(1′) ($1^1/_2 - x$, $y - {}^1/_2$, $1^1/_2 - z$) 1.86(3), H(3b′)···O(2′) ($1^1/_2 - x$, $y - {}^1/_2$, $1^1/_2 - z$) 1.90(4)}, {H(3b)···O(2) ($1^1/_2 - x$, ${}^1/_2 + y$, ${}^1/_2 - z$) 2.00(3), H(3c′)···O(1) ($1^1/_2 - x$, ${}^1/_2 + y$, ${}^1/_2 - z$) 1.97(2) Å}). On the one edge not spanned by carboxylate, a lattice water molecule is hydrogen-bonded to both NH (O(01)···H(3c,3a′) 2.05(4), 2.04(3) Å). Again the complex cations adopt the *lel*$_3$ conformation. As expected, there is no evidence of a strong, specific interaction of the cation with the perchlorate anion, the nearest perchlorate oxygen atom lying within 3.465(4) Å of a substituent group N perhaps being indicative of very weak hydrogen-bonding.

During early efforts to characterize all species observed in the product mixture from carboxymethylation of $[Co(NH_2)_2sar]^{3+}$, a material precipitated from chloride medium by addition of $HClO_4$ was clearly simply a mixed chloride/perchlorate of the reactant. We have in fact frequently obtained such materials and have found their composition (Cl^-:ClO_4^- ratio) to vary widely. In the case of **Co12**, crystals of sufficient quality to allow full definition by refinement (except for hydrogen atoms associated with two of the lattice water molecules) and to establish the stoichiometry $[Co(NH_3)_2sar]_3Cl_8(ClO_4)_7$ were obtained. This structure provides further useful insights into the factors identified above as seemingly influencing the conformation of these cage complexes. As has been found for the simple chloride of this cation,[20] the conformation of the cage is *lel*$_3$ in all three inequivalent cations of the unit cell with, for cations 1 and 2, a full complement of three chelated chlorides ({H(13b′,a)···Cl(13), 2.55(3), 2.30(4); H(13c′,b)···Cl(14) 2.40(3), 2.36(4); H(13a′,c)···Cl(11) 2.44(5), 2.24(4); H(23b′,a)···Cl(8) 2.43(3), 2.37(3); H(23c′,b)···Cl(5) 2.58(5), 2.35(3); H(23a′,c)···Cl(10) 2.35(4), 2.54(5) Å}), while about cation 3, Cl(9,12) are chelated similarly (H(33b′,a)···Cl(9) ($\bar{x}$, $1 - y$, $1 - z$) 2.29(3), 2.36(3), H(33c′,b)···Cl(12) (x, y, $1 + z$) 2.33(4), 2.31(4) Å), but in the last chelate site we find a water molecule oxygen (H(33a′,c)···O(05) (x, y, $1 - z$) 2.06(4), 1.99(4) Å). A diverse array of other H-bonding interactions interconnects the water, terminal ammonium, perchlorate, and chloride entities.

Indirect characterization of the monosubstituted Co(III) complex has been obtained through a structure determination of the product (**Co7**), fully defined by refinement, of its inadvertent nitrosation during preliminary crystallization attempts. The true monoalkylated complex has been used in a variety of syntheses which confirm its nature, and these will be reported in subsequent publications. The nature of the nitrosation product is consistent with earlier observations[1,11] that primary amino group substituents on sarcophagine complexes are largely replaced by chloride when the nitrosation is performed in chloride-containing media, presumably because NOCl is the actual nitrosating agent. The structure of the cation (Figure 1) shows that the secondary amino group substituent produced by the carboxymethylation reaction is converted, as would be expected,[21] to its simple *N*-nitroso derivative. As an unusually highly charged potential source of NO or NO^+, the complex may be of interest in its own right,[22] though we are yet to explore its properties in any detail and it may be noted that there are no significant intermolecular contacts involving the NO moiety. The differing substituents produce no significant distortions of the cage structure relative to that of the numerous other *lel*$_3$ species now known. The cation−anion interactions are, however, quite complicated in this material. One nitrate appears to span two NH units of an "open" octahedral edge in a manner similar to the carboxylate bridging described above (H(3c′)···O(12) 2.14(6), H(3b)···O(13) 2.02(7) Å), one of these oxygen atoms also being involved in a hydrogen bond to the lattice water molecule, which in turn binds to the cage carboxyl substituent, also interacting with other nitrate oxygen atoms (H(102)···O(01) 1.9(1) Å; H(01A)···O(12) ($1 - x$, $1 - y$, $2 - z$) 1.79(8); H(01B)···O(32) ($1 - x$, $1 - y$, $1 - z$) 2.0(1) Å). Another "open" edge of the complex involves NH interactions with oxygen atoms from independent nitrate anions (H(3a′)···O(23) 2.33(6), H(3c)···O(32) 2.18(1) Å), while the third edge involves links to two other oxygen atoms from these two anions translated by a unit in *a*: H(3a)···O(31) ($1 + x$, y, z) 2.38(5), H(3b′)···O(21) ($1 + x$, y, z) 1.91(6) Å, so that they link successive anions up *a* into a "stacked" column (Figure 1(b)).

It is important to note that the presently characterized compounds obtained by alkylation of the 1,8 amino groups of $[Co((NH_2)_2sar)]^{3+}$ are, like others earlier known,[3,5−8,18] very similar in many of their physical and chemical properties to the parent complex. They retain its remarkable stability under both acidic and basic conditions and have almost identical visible spectra, characterized by the $^1A_{1g} \rightarrow {}^1T_{1g}$ $\lambda_{max} = 472$ nm in solution. All also show a Co(III)/Co(II) reduction potential, determined by cyclic voltammetry, close to −0.54 V in aqueous media. Since the potential applications for such cage complexes may depend on the retention of their properties in complicated derivatives, it is essential to find methods of functionalization which enable this to be so.

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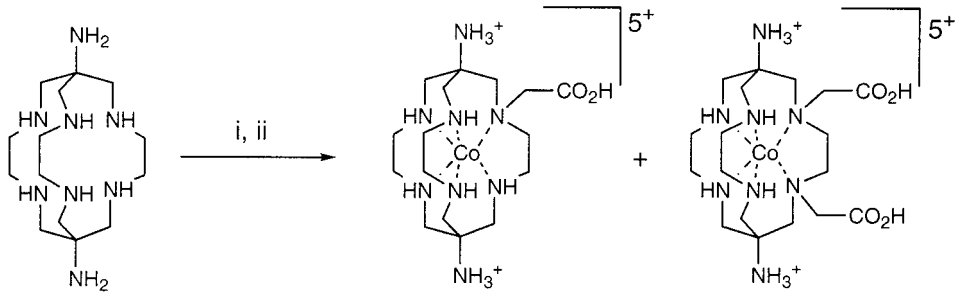
Scheme 2. Carboxymethylation of "Free" Diaminosarcophagine[a]



[a] (i) OH^-, $ClCH_2CO_2^-$; (ii) Co^{2+}, H_2O_2, H^+.

Reaction of "free" diaminosarcophagine with chloroacetate in greater than 1−2 molar amounts gave complicated product mixtures which we have not yet succeeded in fully separating. Multiple alkylation at secondary sites was indicated by the fact that products from reactions involving more than 2 molar amounts of chloroacetate did not react with Co(II) in the presence of oxygen to give Co(III) complexes, just as is the case with hexa-*N*-methyl sarcophagine.[11,12] Nonetheless, the formation of Co(III) complexes could be used as a means of separating and purifying the products from reaction at low molar ratios (Scheme 2). Significantly, the monoalkylated product, isolated and structurally characterized as its Co(III) complex (**Co11**; Figure 1), contains a carboxymethyl substituent on an originally secondary nitrogen atom. This results in significant distortion of the metal coordination sphere,[23] with the Co−N bond length (2.080(6) Å) to the tertiary center being approximately 0.09 Å greater than those to the remaining secondary centers, which differ by <0.03 Å, though the angular geometry at N(3c) is little changed except for diminution of Co−N(3c)−C(4c) to 102.8(4)°. The extent of this Co−N bond lengthening is presumably partly a consequence of the flexibility of the cage amine and the fact that the carboxymethyl arm is "free", since it is considerably greater than observed in complexes of ligands such as "tren" (tris(2-aminoethyl)amine), where the tertiary donor is tethered by three arms.[24] The bound cage structure is also affected, with the unprimed cap adjacent to the tertiary N adopting a conformation much closer to achiral than is the other. This observation moved us to consider the geometry of archetypical **Co12**, where three independent cations, ostensibly of *32* symmetry, two chelating three chloride ions each, are available for comparison in respect, in particular, of torsion angles. Despite the less symmetrical anion array about the third, the symmetry within all three remains high, so much so that rather than quoting individual values for individual strings for each, the mean (with su) suffices. These values are tabulated in Table 2. As might be expected, the values for cations 1 and 2 are closely comparable, and different from those of cation 3; remarkably, it is the latter whose symmetry most closely approximates *32*, that of cations 1 and 2 being degraded to *3* by virtue of inequivalence about the two caps, in a manner not too dissimilar from that found for **Co11** and casting doubt on the correlation between that distortion and the unsymmetrical substituent disposition. The cation in the latter has the familiar overall lel_3 conformation, though only one "open" edge is spanned by hydrogen-bonding interactions, here involving the chloride anion bound to one NH (HN(3b)···Cl(1) 2.995(9) Å) and a water molecule bound to the other (HN(3c′)···O(04)H_2 2.96(1) Å), with the chloride and water bound to one another (H_2O(04)···Cl(1) 2.78(1) Å). Extensive disorder and uncertainty in many of the proton locations render a detailed description of the lattice associations difficult, but this water molecule interacts further with other lattice water (O(04)···O(05) 3.18(1) Å), while another lattice water also binds to the NH_3^+ group of the cap remote from the carboxymethyl substituent (N(0′)···O(03) 2.75(1) Å) and another to the carboxylic acid group (O(31c)···O(02) 2.640(9) Å), this evidence together with geometry (C(31c)−O(31c,32c) 1.327(9), 1.187(10) Å suggesting it to be the protonated component. Hydrogen-bonding interactions involving the dithionate ligands generally appear to be very weak, except for that involving the NH_3^+ group of the cap adjacent to the carboxymethyl substituent (N(0)···O(01)S_2O_5 ($1-x$, $1-y$, $1-z$) 2.812(8) Å).

The complex of the dialkylated ligand, though not structurally characterized, appears on the basis of the pattern of NH resonances in its ^{1}H NMR spectrum to be a species in which two originally secondary nitrogen atoms have been alkylated. Constitutional isomers of dicarboxymethyldiaminosarcophagine are possible, but we have only been able to detect a single species as the Co(III) complex, and the 2-fold symmetry of this species (as reflected in its ^{13}C nuclear magnetic resonance spectrum) leads us to the conclusion that the 3,6 isomer only has been formed. The presence of tertiary N-donors in both complexes derived from the alkylation of the free ligand is reflected in their red colors (λ_{max} = 506 nm), which contrast with the yellow (λ_{max} = 472 nm) of a "normal" $Co^{III}N_6$ chromophore as exemplified in the 1,8-dicarboxymethylated ligand complex obtained by reaction of $[Co(NH_2)_2sar]^{3+}$ (as described above). The weaker ligand field of tertiary N-donors is presumably the reason why more highly alkylated products from diaminosarcophagine do not readily provide Co(III) complexes (though crimson-colored Co(III) complexes of "expanded" cages in which ⟨Co−N⟩ ∼ 2.02 Å are known[25]). This weaker ligand field is also reflected in an increase in the Co(III)/Co(II) reduction potential of the mono(3)-alkylated complex to −0.40 V from the −0.54 V of the normal species, so that functionalization of the N-donor groups of the cage ligand is obviously not a means of retaining the properties of the original cage complex.

Consistent with a lower central metal ion charge causing a lesser reduction in the nucleophilicity of "external" lone pairs on a bound ligand, reaction of $[Cu(NH_2)_2sar]^{2+}$ with chloroacetate enabled the isolation of species containing up to the tetraalkylated derivative of the cage (Scheme 3). Maintenance of six(secondary-N)-coordination by Cu(II) under the conditions of the alkylation reaction is indicated by the fact that the

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Table 1. Copper(II) Coordination Environments[a]

(a) The Parent $[Cu(diamsarH_2(CH_2COOH)_2)]^{4+}$ Array of **Cu6**[b]

atom	*r*	N(3b)	N(3c)	N(3a′)	N(3b′)	N(3c′)
N(3a)	2.264(8)	83.4(3)	83.7(3)	78.0(3)	150.9(3)	109.7(3)
N(3b)	2.174(8)		90.0(3)	(150.9(3))	121.6(3)	81.7(3)
N(3c)	2.075(7)			(109.7(3))	(81.7(3))	163.1(3)

(b) The Five-Coordinate, Substituted Dilactam Arrays

compd:	**Cu4**	**Cu5**	**Cu1a**	**Cu1b**
apical *X*:	*Cl*/2	*Cl*	ONO_2	$OClO_3$
1,8-subst:	(R)(H)	$(R)(H_2)$	(R)(R,H)	$(R,H)_2$
		Distances (Å)		
Cu−X	2.5000(7)	2.472(2)	2.257(4)	2.250(4), 2.222(4)
Cu−N(3a)	1.987(5)	1.967(4)	1.971(4)	1.988(4), 1.997(4)
Cu−N(3a′)	2.009(4)	2.005(5)	1.999(4)	2.004(4), 2.000(4)
Cu−N(3b)	2.012(4)	2.019(5)	2.002(4)	2.001(4), 2.000(4)
Cu−N(3b′)	1.972(5)	1.982(4)	1.960(5)	1.997(4), 1.986(4)
		Angles (deg)		
X−Cu−N(3a)	96.8(1)	101.4(1)	90.6(2)	92.4(1), 91.0(1)
X−Cu−N(3a′)	92.2(1)	98.7(1)	97.3(1)	92.1(1), 97.9(2)
X−Cu−N(3b)	95.4(1)	91.3(1)	89.9(2)	95.5(1), 90.1(1)
X−Cu−N(3b′)	97.9(1)	95.1(1)	104.4(2)	101.5(1), 104.9(1)
N(3a)−Cu−N(3a′)	87.6(2)	87.4(2)	87.7(2)	87.3(1), 87.9(1)
N(3a)−Cu−N(3b)	91.0(2)	91.0(2)	90.8(2)	91.9(1), 92.2(1)
N(3a)−Cu−N(3b′)	165.3(2)	163.5(2)	164.9(2)	166.3(2), 164.0(2)
N(3a′)−Cu−N(3b)	172.4(2)	170.0(2)	172.6(2)	172.4(2), 172.0(2)
N(3a′)−Cu−N(3b′)	91.2(2)	91.4(2)	92.1(2)	92.0(1), 91.0(1)
N(3b)−Cu−N(3b′)	88.2(2)	87.4(2)	87.4(2)	87.0(1), 86.6(1)
		Selected Torsion Angles (deg)[c]		
		(i) The "Metallacycles" (etc.): Five-Membered		
3a′−Cu−*3a*−4a	14.3(3)	14.9(3)	15.3(3)	13.7(3), 14.7(3)
3a−Cu−*3a′*−4a′	11.8(3)	11.0(3)	10.6(3)	12.9(3), 10.1(3)
3b′−Cu−*3b*−4b	11.3(3)	11.2(3)	11.8(3)	14.8(3), 12.7(3)
3b−Cu−*3b′*−4b′	14.6(3)	15.2(3)	14.3(3)	12.6(3), 14.4(3)
Cu−*3a*−4a−4a′	−37.9(5)	−38.4(5)	−39.0(5)	−38.0(4), −37.0(4)
Cu−*3a′*−4a′−4a	−35.2(4)	−33.6(5)	−34.1(4)	−36.6(4), −32.8(4)
Cu−*3b*−4b−4b′	−34.5(4)	−34.9(5)	−34.6(4)	−38.8(4), −36.8(4)
Cu−*3b′*−4b′−4b	−37.8(4)	−39.4(5)	−37.9(4)	−37.6(4), −39.0(4)
3a−4a−4a′−*3a′*	49.6(6)	48.1(6)	49.2(5)	50.0(5), 47.2(5)
3b−4b−4b′−*3b′*	49.0(5)	50.5(6)	48.3(5)	51.1(5), 50.6(5)
3a−4c−4c′−*3c′*	−86.2(7)	−88.0(6)	−86.2(6)	−83.5(5), −84.6(5)
2a−*3a*−4a−4a′	90.6(1)	89.2(5)	87.8(5)	91.4(4), 88.3(5)
2a′−*3a′*−4a′−4a	−170.4(4)	−168.7(5)	−168.2(4)	−171.7(4), −166.6(4)
2b−*3b*−4b−4b′	−168.2(4)	−170.2(4)	−169.7(4)	−171.8(4), −171.4(4)
2b′−*3b′*−4b′−4b	89.9(6)	88.0(5)	89.3(5)	87.2(4), 85.2(4)
2c−*3c*−4c−4c′	96.5(6)	91.0(6)	96.3(5)	94.9(5), 92.8(5)
2c′−*3c′*−4c′−4c	93.0(6)	98.1(6)	95.1(6)	95.2(5), 100.2(5)
		Six-Membered		
3b−Cu−*3a*−2a	59.5(3)	58.6(4)	62.0(3)	59.1(3), 61.5(3)
3a−Cu−*3b*−2b	−20.7(4)	−17.8(4)	−18.8(4)	−18.7(3), −16.6(3)
3b′−Cu−*3a′*−2a′	−18.5(4)	−17.6(4)	−20.0(3)	−18.6(3), −20.2(3)
3a′−Cu−*3b′*−2b′	60.1(3)	58.3(4)	60.1(3)	61.1(3), 63.6(3)
Cu−*3a*−2a−1	−40.0(5)	−44.3(5)	−47.6(5)	−41.0(4), −48.7(4)
Cu−*3a′*−2a′−1′	−37.2(5)	−38.7(6)	−35.9(5)	−36.8(5), −36.5(5)
Cu−*3b*−2b−1	−34.6(6)	−37.3(6)	−36.3(6)	−35.6(5), −37.9(5)
Cu−*3b′*−2b′−1′	−44.1(6)	−41.9(5)	−43.5(5)	−44.8(4), −47.6(4)
3a−2a−1−2b	−27.5(7)	−21.2(6)	−19.4(6)	−25.0(5), −16.6(5)
3a′−2a′−1′−2b′	67.5(6)	69.6(6)	66.8(5)	68.5(5), 67.7(5)
3b−2b−1−2a	69.8(7)	66.1(6)	65.8(6)	68.6(5), 65.5(5)
3b′−2b′−1′−2a′	−22.5(7)	−24.4(6)	−22.4(6)	−22.4(5), −20.2(5)
4a−*3a*−2a−1	−163.4(4)	−167.7(4)	−170.1(4)	−165.1(4), −170.1(3)
4a′−*3a′*−2a′−1′	93.6(5)	92.7(6)	94.1(5)	94.1(4), 93.4(5)
4b−*3b*−2b−1	94.4(5)	93.3(6)	94.5(5)	93.3(5), 92.8(5)
4b′−*3b′*−2b′−1′	−167.2(5)	−164.6(4)	−167.4(4)	−166.2(4), −168.5(4)
4c−*3c*−2c−1	−170.1(4)	−164.4(5)	−164.9(4)	−169.9(4), −163.5(4)
4c′−*3c′*−2c′−1′	−168.3(4)	−169.9(5)	−169.7(4)	−171.9(3), −168.0(4)
2c−1−2a−*3a*	99.6(6)	102.9(5)	106.0(5)	101.4(4), 109.5(4)
2c′−1′−2a′−3a′	−58.0(5)	−55.8(6)	−57.8(5)	−59.4(4), −60.7(4)
2c−1−2b−*3b*	−59.3(6)	−60.4(5)	−61.5(5)	−58.8(5), −62.1(5)
2c′−1′−2b′−3b′	99.5(5)	97.9(5)	99.7(5)	102.5(4), 105.4(4)

Table 1. (Continued)

compd:	**Cu4**	**Cu5**	**Cu1a**	**Cu1b**
apical *X*:	*Cl*/2	*Cl*	*O*NO_2	*O*ClO_3
1,8-subst:	(R)(H)	(R)(H_2)	(R)(R,H)	(R,$H)_2$
		Selected Torsion Angles (deg)[c]		
		(ii) The Lactam Rings		
2c−1−*0*−01	62.4(6)	64.8(6)	62.5(5)	61.3(4), 60.4(4)
2c′−1′−*0*′−01′	66.0(5)	64.8(6)	67.0(4)	61.9(4), 63.6(4)
0−1−2c−*3c*	−53.6(5)	−54.9(6)	−55.4(5)	−59.2(4), −57.1(4)
0′−1′−2c′−*3c*′	−53.3(5)	−53.4(6)	−51.9(5)	−52.1(4), −55.7(4)
1−*0*−01−02	−43.3(6)	−49.1(7)	−45.6(5)	−38.9(5), −39.2(5)
1′−*0*′−01′−02′	−48.7(6)	−52.6(6)	−51.7(5)	−50.2(5), −47.2(5)
1−2c−*3c*−02	25.4(7)	26.4(8)	29.7(6)	32.3(6), 31.0(6)
1′−2c′−*3c*′−02′	23.1(6)	28.9(7)	21.1(6)	29.1(5), 29.8(6)
0−01−02−*3c*	11.1(7)	16.6(8)	16.9(6)	8.7(6), 9.5(6)
0′−01′−02′−*3c*′	14.4(7)	23.7(8)	16.3(6)	23.7(6), 18.0(6)
2c−*3c*−02−01	−2.0(7)	−5.9(9)	−8.2(6)	−4.9(7), −5.2(7)
2c′−*3c*′−02′−01′	−1.9(7)	−12.1(8)	−1.5(6)	−12.7(6), −8.8(6)
2b−1−*0*−01	179.1(5)	−179.1(5)	178.2(4)	177.6(4), 175.5(4)
2b′−1′−*0*′−01	−56.2(6)	−57.4(6)	−53.3(5)	−58.9(4), −57.5(4)
2b−1−2c−*3c*	−168.5(4)	−167.2(5)	−170.2(4)	−173.0(4), −170.1(4)
2b′−1′−2c′−*3c*′	67.5(5)	67.5(6)	67.4(5)	64.5(5), 60.9(5)
2b−1−*0*−04			−57.5(5)	−56.1(5), −59.9(5)
2b′−1′−*0*′−04′	69.1(5)	68.5(6)	70.0(5)	67.6(4), 66.3(5)

[a] In **Cu1a**,**b**, Cu−O−X are 120.1(4)°, 121.1(2)/122.2(2)°; in **Cu4**, Cu−Cl−Cu′ is (obligate) 180°. In **Cu1a**,**b** intramolecular O···H < 2.7 Å are as follows: **Cu1a** O(11)···H(3a,b) 2.67(5) Å (×2), O(12)···H(3a′,b′) 2.49(4) Å, 2.56(6) Å; **Cu1b** O(4)···H(3a′,b′) 2.68(4) Å, 2.42(6) Å (mol 1), 2.69(5) Å, 2.42(6) Å (mol 2). In **Cu4**,**5** Cl···H < 2.8 Å are as follows: **Cu4** Cl···H(3a′) 2.75(5) Å, **Cu5** Cl(1)···H(3b) 2.8(−) Å. [b] *r* Å is the copper−ligand atom distance (Å), other entries being the angles (deg) subtended by the relevant atoms at the head of the row and column. Primed atoms are related by the *2*-axis. [c] Ligand atoms denoted by number only, *N* italicized.

Table 2. Cage Torsion Angles (deg), **Co11**, **Co12**

(a) **Co11**

x	*a*, *a*′	*b*, *b*′	*c*, *c*′
N(0)−C(1)−C(2x)−N(3x)	178.0(5), −165.8(6)	175.2(6), −162.5(5)	170.3(5), −162.9(6)
C(1)−C(2x)−N(3x)−C(4x)	−119.8(6), −146.7(6)	−113.5(7), −154.5(6)	−99.9(7), −157.8(6)
C(1)−C(2x)−N(3x)−Co	4.2(8), −22.9(7)	7.7(8), −28.7(7)	14.5(7), −29.6(7)
C(2x)−N(3x)−C(4x)−C(4x′)	170.1(7), 154.3(7)	169.9(7), 150.9(7)	168.3(6), 152.5(6)
Co−N(3x)−C(4x)−C(4x′)	39.4(8), 26.4(8)	42.0(8), 22.0(8)	47.7(7), 20.9(8)
N(3x)−C(4x)−C(4x′)−N(3x′)	−43.7(9)	−42.0(9)	−47.2(9)

(b) **Co12**[a]

cation/section	1/*x*′, *x*	2/*x*, *x*′	3/*x*, *x*′
N(0)−C(1)−C(2x)−N(3x)	−170.0(4), −177.5(10)	170.0(10), −177.1(4)	172.6(8), 176.0(16)
C(1)−C(2x)−N(3x)−C(4x)	−108.1(11), −132.3(14)	−108.4(17), −132.1(12)	−113.2(2), −120.2(7)
C(1)−C(2x)−N(3x)−Co	16.9(10), −4.3(13)	17.1(13), −4.9(7)	12.3(5), 6.8(10)
C(2x)−N(3x)−C(4x)−C(4x′)	176.2(9), 167.8(8)	176.8(14), 167.7(10)	174.7(10), 172.7(4)
Co−N(3x)−C(4x)−C(4x′)	45.1(7), 34.9(9)	45.1(9), 35.1(10)	43.1(5), 40.2(1)
N(3x)−C(4x)−C(4x′)−N(3x′)	−52.7(4)	−52.9(3)	−55.2(2)

[a] Mean values for the three strings *a*, *b*, *c* within each cation.

structures of all the isolated products (see below) show alkylation to have occurred at the primary, 1,8 amino substituents only. However, under the neutral to acidic conditions of the chromatography required to separate these products, it would appear that, as with simpler Cu(II) cage amine complexes,[3,12] as many as two of the coordinated secondary nitrogen atoms become detached. They then react in a presumably rapid intramolecular manner with the carboxymethyl substituents to generate lactam units. This, coupled to possible diastereoisomerism of the complexes of a given ligand, we presume to explain the fact that although six components were revealed in chromatography of the products of the carboxymethylation reaction, only tetra-, tri-, and dialkylated ligands were present. In the cases where reduction by Zn was used to provide a solution from the Cu complex which could be used for nuclear magnetic resonance measurements, the spectra showed that the cyclized forms of the ligands were probably retained (with the proviso that the spectrum of **Zn2** was that of a mixture of species). We have not yet studied the kinetics of the reaction in full detail, but opening of the lactam rings to allow the metal to reattain six-coordination by the cage occurs slowly under neutral conditions and more rapidly in base in the case of the dialkylated compound at least and is apparent in the change in color of the complex from the violet (λ_{max} = 510 nm) typical of square-planar $Cu^{II}N_4$ to the blue (λ_{max} = 660 nm) of $Cu^{II}N_6$.[26]

In $[Cu((NH_3)_2sar)](NO_3)_4$, we have previously reported, for Cu−N = *r*, values of $\langle r \rangle$ = 2.17, r_{eq} 2.088(3)−2.148(3), and r_{ax} 2.251(3), 2.298(4) Å.[26] Comparison with the present $[Cu(HO_2CCH_2NH_2)_2sar](NO_3)_4$, **Cu6** (see Experimental Section; Table 1, Figure 2), suggests that, as with the Co(III) analogues, alkylation of the 1,8 amino substituents does not produce any significant change in the metal ion coordination environment.

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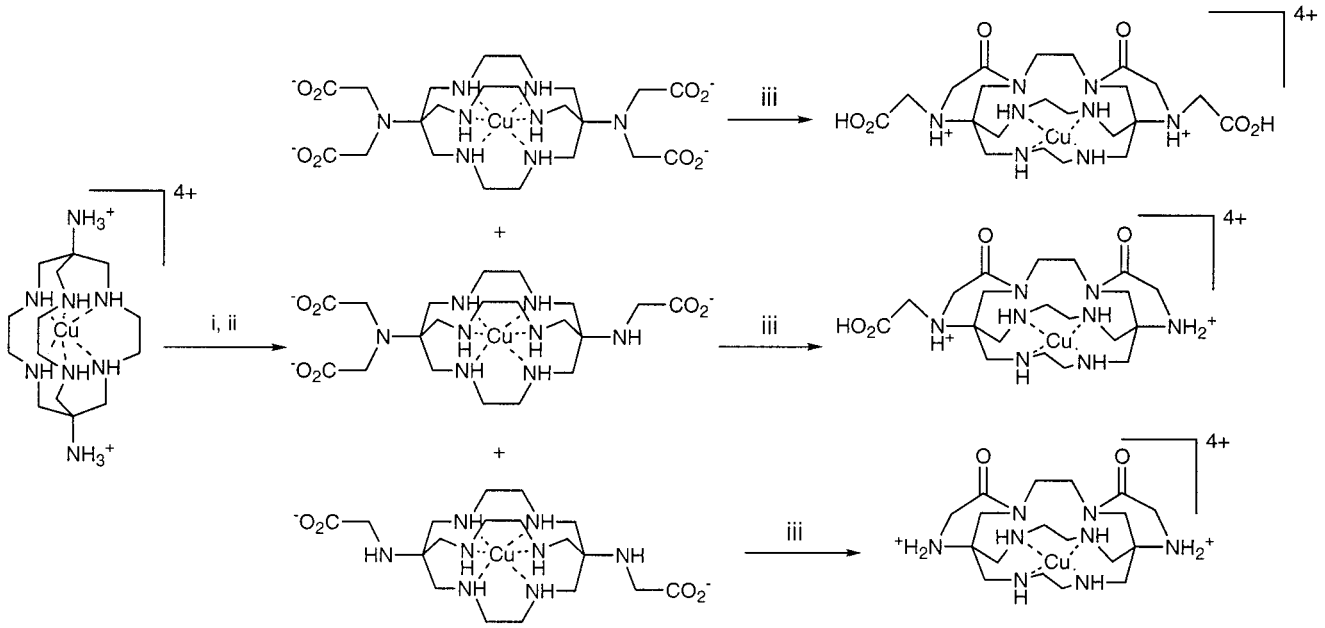
Scheme 3. Carboxymethylation of the Copper Complex of Diaminosarcophagine[a]



[a] (i) OH^-, (ii) $ClCH_2CO_2^-$, (iii) H^+.

The Cu(II) coordination environment is somewhat more regular in the present compound, though in both cases there are large distortions from octahedral stereochemistry. The cage conformation can still be described as *lel*$_3$, and hydrogen-bonding may again play a role in determining this. However, all such hydrogen atoms are involved in similar contacts to anionic oxygen atoms (H(3a)···O(11) ($^1/_2 - x$, $^1/_2 - y$, z) 2.5(1); H(3b)···O(21,22) 2.5(1) (×2); H(3c)···O(23) ($^1/_2 - x$, $1 - y$, $z - ^1/_2$) 2.5(1) Å), as is the terminal amino H(0A)···O(12) ($^1/_2 - x$, $1 - y$, $^1/_2 + z$) 2.0(1) Å. The carboxylate hydrogen H(52) hydrogen-bonds to the water molecule (H(52)···O(1) ($^1/_4 - x$, $^3/_4 + y$, $z - ^1/_4$) 1.64(5) Å), with the water molecule hydrogen atoms linking to a further carboxylate H(01B)···O(52) ($^1/_4 - x$, $y - ^3/_4$, $z + ^1/_4$) 2.3 Å (est.) (O···O 2.59(1) Å) and to an anion H(01A)···O(22) 2.3 Å (est.) (O···O 2.94(1) Å), the cations lying disposed on crystallographic *2*-axes parallel to *c* but with their long axes oriented along the long axis of the cell (*a*).

Unlike the Co(III) complexes, those of Cu(II) are susceptible to acid-assisted stripping of one arm of the macrobicycle to give relatively stable species in which the cage ligand is bound in a quadridentate form.[3,26] Added stability possibly results from the intramolecular reaction of the pendent carboxyl group(s) with the released amine groups to form six-membered ring amide (lactam) entities, revealed in several crystal structure determinations (**Cu1a**, **Cu1b** (two independent molecules), **Cu4**, **Cu5**). Thus, in all the Cu(II) complexes crystallographically characterized aside from the dicarboxymethylated cage complex described above, the Cu(II) can be described as five-coordinate in a tetragonal pyramidal CuN_4X environment, an anion (X) occupying the apical site, Cu−O comparable in **Cu1a**, **Cu1b** (2.257(4), 2.250(4)/2.222(4) Å) and Cu−Cl likewise (bridging a minor influence) in **Cu4**, **Cu5** (2.5000(7), 2.472(2) Å), with N−Cu−N, X−Cu−N dependent on the asymmetry induced by lactam formation and any proximity of X to H(3b′) (Table 1). The bound nitrogen atoms have configurations such that their attached hydrogen atoms are all directed toward the apical atom, giving the bound macrocyclic units a conformation similar to that found in many complexes of tetra-*N*-methylcyclam and in some other cage amine derivatives.[26−28] Given the "superstructure" created by the lactamized arm of the macrobicycle, the resultant complexes also resemble "cyclidene" systems,[29] suggesting that, with metals favoring six-coordination, these ligands may enforce a marked selectivity with respect to any ligand occupying the cavity including the sixth coordination site. Despite the plethora of amine-N and carboxyl-O sites, protonated or otherwise, close interspecies hydrogen-bonding interactions involving the cations are few, a fact in keeping with the ill-defined nature of the aggregates of accompanying counterion and solvent moieties. In **Cu1a**, there are no O···O, N distances from the cation to other moieties <3.0 Å suggestive of such interactions. The more highly protonated cations of **Cu1b** display interactions between protonated N(0) and perchlorate or water molecule oxygen atoms (N,H(10)···O(81) ($1 - x$, $1 - y$, $1 - z$) 2.823(6), 2.07(6); N,H(10′)···O(53) ($1 + x$, $^1/_2 - y$, $^1/_2 + z$) 2.704(6), 2.02(4); N,H(20′)···O(03) ($1 - x$, $1 - y$, $1 - z$) 2.709(6), 1.90(5) Å) and coordinated N(3) (i.e., *not* N(3c)) hydrogen atoms and diverse oxygenated species (N,H(13b)···O(72) ($1 - x$, $1 - y$, $1 - z$) 2.923(9), 2.18(5); N,H(13a)···O(202′) 2.824(5), 2.05(5) Å); carboxylate hydrogen atoms interact with perchlorate or water entities rather than among themselves (O,H(152)···O(02) ($1 - x$, $1 - y$, $1 - z$) 2.604(6), 1.78(7); O,H(152′)···O(31) ($1 + x$, $^3/_2 - y$, $^1/_2 + z$) 2.605(6), 2.00(5); O,H(252)···O(81) 2.599(6), 1.64(7); O,H(252′)···O(71) ($1 - x$, $\bar{y}$, $1 - z$) 2.593(6), 2.06(7) Å). In **Cu4**, the carboxylate hydrogen atom interacts with a water molecule (O,H(52′)···O(04) 2.639(7), 1.5(1) Å); in **Cu5**, lactam oxygen O(2) lies near a disordered water fragment O(04) (2.66(1) Å), while the carboxylate hydrogen atom again interacts with a water molecule (O,H(52′)···O(02) 2.613(6), 1.6(2) Å).

Some confusion was generated in initial studies of the products of the carboxymethylation of $[Cu((NH_2)_2sar)]^{2+}$ by the number of different species chromatographically separated. The eventual discovery that, through cycles of acid and base

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(28) Harrowfield, J. M.; Sargeson, A. M.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 181.
(29) Busch, D. H.; Cairns, C. *Prog. Macrocyclic Chem.* **1987**, *3*, 1.

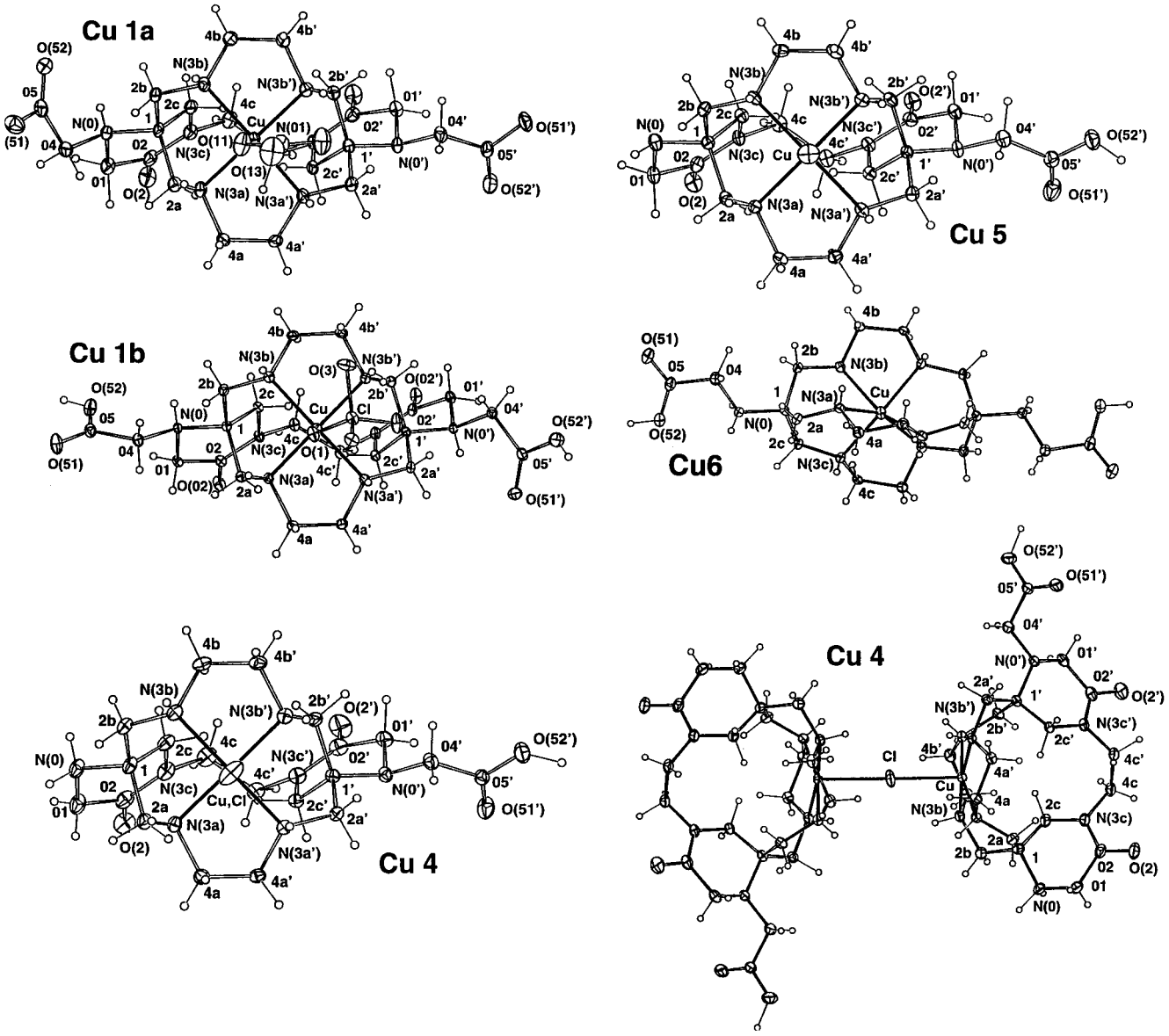

Figure 2. Projections of the five-coordinate copper environments down their unidentate ligand donor atom−copper vectors; for **Cu1b** the environment of only one of the two similar independent copper atoms is shown; also projection of the cation of **6**, normal to the crystallographic *2*-axis, and projection of the centrosymmetric binuclear cation of **Cu4**, showing the (general) disposition of the uncoordinated string.

treatment, various members could be interconverted led to the conclusion noted above that only dialkylated (**Cu6**), trialkylated (**Cu3**,**4**,**5**), and tetraalkylated (**Cu1**,**2**) derivatives were present. Kinetic studies to be reported elsewhere have shown that coordinated lactam forms of the complexes undergo ready base-catalyzed lactam-ring-opening reactions, and we consider on the basis of color changes observed during crystallization procedures that the initial material used to provide the crystals for the structure solution of the dicarboxymethyl compound (**Cu6**) described above was in fact the dilactam. In the more highly substituted complexes, this ring opening appears to occur less readily, and in these cases the crystals obtained were those of the lactam complexes. The extended efforts made to obtain crystals suitable for X-ray diffraction for as many of the different fractions as possible led fortuitously to the detection of various more subtle features of the coordination of these lactam species. Thus, the trialkylated ligand was characterized in two different complexes (one, the chloride−nitrate, obtained from fraction **Cu4** and a chloride from fraction **Cu5**; see Experimental Section). The complex ion units for **Cu4**, **Cu 5** showing only slight differences in conformation are shown in Figure 2. Although the existence of diastereomeric forms might have been anticipated, the cations in the two chlorides proved to be identical. The bound nitrogen atom configurations are *S*,*R*,*S*,*R* in both, but the solid state complex ion species are chiral due to the dissymmetric five-membered chelate ring conformations and the particular configurations of the two unbound amino centers. The structures show in all cases that two of the introduced carboxymethyl substituents have undergone intramolecular amide formation during isolation and crystallization of the complexes. Remarkably, in the chloride−nitrate (Figure 2) a binuclear species is found bridged by a single chloride ion, the two entities linked in this way being centrosymmetrically related enantiomers with the particular relative configurations at the nitrogen centers as seen in the mononuclear species.

The tetrasubstituted cage was structurally characterized in the form of two complexes, both derived from fraction **Cu1** of the chromatographic treatment. Both contained the ligand in its dilactam form, but in the nitrate salt (**Cu1a**) only one of the "external" amino groups was found to be protonated, whereas

in the perchlorate (**Cu1b**), protons were attached to two. The structures (Figure 2) show that, as with the trialkylated ligand, the Cu(II) adopts an essentially square pyramidal coordination geometry with four nitrogen donors in a near planar array with *R*,*S*,*R*,*S* configurations and one anion bound above the copper remote from the uncoordinated ligand strand. The ligand conformations are closely similar despite the difference in protonation, with, for a given conformation of the two five-membered chelate rings, the same configurations at the two non-(metal ion-)coordinated chiral nitrogen atoms. Thus, ignoring the coordinated anions and the missing proton of the nitrate compound, the complex ion species in both cases have close to *2* symmetry.

In aqueous solution, where presumably all the anions found to be coordinated in the solid state may be displaced, all the Cu(II) complexes of the carboxymethylated ligands, as chromatographically isolated, appear violet, with $\lambda_{max} = 510 \pm 10$ nm, similar to the absorption by a "typical" square-planar Cu(II) complex such as $[Cu(cyclam)]^{2+}$. Hydrolytic ring-opening reactions of lactam units, as most readily observed for the formation of $[Cu((HO_2CCH_2NH_2)_2sar)]^{4+}$, result in a shift of the absorption maxima to near 660 nm, as observed for octahedral CuN_6 in $[Cu((NH_3)_2sar)]^{4+}$. Cyclic voltammetry of the violet species in aqueous solutions shows Cu(II) → Cu(I) quasi-reversible reductions near $E = -0.46$ V, contrasting with the irreversible reduction near −0.80 V observed for $[Cu(sar)]^{2+}$. The lactam formation reactions which effectively convert the cage amine into a quadridentate ligand are presumably also the reason why the complexes readily retain a cationic form even when formally there are sufficient ionizable groups (as in the di-, tri-, and tetrasubstituted ligands) for neutral or anionic forms to be present. These forms are readily observed, however, when the lactam rings are opened by base hydrolysis, and although we have not yet completed measurements to allow full speciations to be described, at least some of the ligands do enable complexes of formal zero charge to be obtained, a desirable property when the minimization of osmotic shock in applications such as radiometallopharmaceuticals is considered.

Thus, the procedures described herein have led to the preparation of a range of potentially useful derivatives of the cage amine diaminosarcophagine through methods which enable control of both reactivity and selectivity. The syntheses of ligands through coordinated precursors are most useful when the new ligand can be easily removed from the metal ion involved. The relatively extreme conditions required to remove cage ligands from Co(II) are well-known, and no efficient method for the isolation of $(1\text{-}NH_2)(8\text{-}HO_2CCH_2NH)$sar or 1,8-$(HO_2CCH_2NH)_2$sar from their Co complexes has been found, though the latter ligand has been isolated. The Cu(II) complexes are more useful in this regard in that reductive procedures, such as stirring with Zn dust, can be used to very simply and effectively displace copper from the ligand, giving product complexes which can be broken down in acid. Nonetheless, the complexes characterized in the present work are themselves of interest, and we will report subsequently our further investigations of their properties. These include the formation of metallopolymers through the use of the cage substituents as coordinating units and the extension of the substituent structures through the formation of carboxyl group derivatives such as amides.

Experimental Section

General. Nuclear magnetic resonance spectra were acquired using a Varian Gemini 200 (^{1}H at 200 MHz and ^{13}C at 50.3 MHz) spectrometer or a Bruker ARX 500 (^{1}H at 500.13 MHz and ^{13}C at 125.8 MHz) spectrometer in D_2O. Chemical shifts are expressed in ppm relative to an internal standard of acetone, which was taken as being 2.04 ppm for ^{1}H NMR spectra and 29.4 ppm for ^{13}C NMR relative to TMS.

Microanalyses for carbon, nitrogen, and hydrogen were carried out by the Chemistry Centre of Western Australia using a LECO CHNS932 Determinator or by The Australian National University Microanalytical Service. Chlorine analyses were also 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.

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

All evaporations were performed at reduced pressure (~20 mmHg) using a Büchi rotary evaporator and a water aspirator.

The Schlenk technique using high-purity argon or high-purity nitrogen was employed wherever it was necessary to exclude oxygen from preparative mixtures.

UV−visible absorption spectra (200−800 nm) were recorded on a Hewlett-Packard 8452A diode array spectrophotometer. The spectra of the cobalt complexes were recorded using approximately 7×10^{-3} mol L^{-1} solutions in 0.1 mol L^{-1} HCl. In the case of the copper complexes the spectra were recorded using approximately 3×10^{-3} mol L^{-1} solutions in 1 mol L^{-1} HCl.

Deionized water was used in all preparations. All organic solvents were distilled prior to use. Acetonitrile was dried by distillation over CaH_2 and stored over 4 Å molecular sieves. Chloroacetic acid was supplied by Ajax Chemicals and was used as received.

Cyclic voltammograms were recorded with a MacLab potentiostat controlled by a Macintosh SE computer equipped with AD Instruments Echem Software, employing a platinum working electrode, a platinum counter electrode, and a silver/silver chloride reference electrode. All solutions were 1−5 mmol L^{-1} of analyte in 0.1 mol L^{-1} $NaClO_4$ solution. Water was purified using a Milli-Q Ultra-Pure Water System. Each solution was purged with argon and measured at ambient temperatures.

Synthesis. $[Co(en)_3]Cl_3$,[30] $[Co((NO_2)_2sar)]Cl_3$,[11] $[Co((NH_3)_2sar)]Cl_5$,[1] $[Cu((NH_3)_2sar)](NO_3)_4 \cdot H_2O$,[26] and $(NH_2)_2$sar[11] were all prepared according to literature methods.

To simplify the final discussion, all new complexes described below are designated by a number associated with the symbol for the metal involved, viz., **Co1**−**Co12**, **Cu1**−**Cu6**, and **Zn1**−**Zn4**.

Carboxymethylation of $[Co((NH_2)_2sar)]^{3+}$: 1-Ammonio-8-carboxymethylammoniosarcophaginecobalt(III) and 1,8-Di(carboxymethylammonio)sarcophaginecobalt(III). $[Co((NH_3)_2sar)]Cl_5 \cdot H_2O$ (5.0 g, 8.8 mmol) was dissolved in water (20 mL) and the pH of the solution adjusted to ~10 by the addition of sodium hydroxide. Sodium chloroacetate (60 g, 0.45 mol) was dissolved in water (300 mL). The two solutions were then combined and the resulting reaction mixture heated at 80 °C under a nitrogen atmosphere with constant stirring for 72 h. During this time the pH was maintained at approximately 10 by the dropwise addition of aqueous sodium hydroxide.

The reaction mixture was acidified by the addition of glacial acetic acid (pH <6), diluted, and then applied to a column (75 cm × 8 cm diameter) of SP Sephadex C25 (sodium form) cation exchange resin. The column was washed with water (1 L), and the orange compounds were eluted with sodium citrate solution (0.025−0.050 mol L^{-1}). The two major components of the chromatographic separation (band 1 and band 2; there were four other minor bands) were then separately absorbed on to a column of H^+ form Dowex 50Wx2 (10 cm × 4 cm), which was washed with water (200 mL) to remove the citrate and 1 mol L^{-1} HCl (200 mL) to remove the Na^+, and then the orange compounds were eluted with 3 mol L^{-1} HCl. The orange eluates were evaporated to dryness under reduced pressure.

(30) Broomhead, J. A.; Dwyer, F. P.; Hogarth, J. W. *Inorg. Synth.* **1960**, *6*, 183.

The orange residue from band 1 was dissolved in the minimum volume of water and precipitated by the addition of ethanol to afford an orange powder. This was recrystallized by dissolving the solid in the minimum volume of hot water, adding ethanol to the point of turbidity, and then slowly cooling to give needlelike, orange crystals of 1,8-di(carboxymethylammonio)sarcophaginecobalt(III) pentachloride, ([Co(sar($NH_2CH_2COOH)_2$)]Cl_5, **Co1a** (3.63 g, 5.4 mmol, 60%), which were collected by filtration. Anal. Found: C, 32.5; H, 6.4; N, 16.8. Calcd for $CoC_{18}H_{40}N_8Cl_5O_4$: C, 32.33; H, 6.03; N, 16.76. ^{1}H NMR (200 MHz): δ 2.90, 12H, m, methylene cage protons; 3.40 12H, m, methylene cage protons; 3.89, 4H, s, 2 × CH_2COOH. ^{13}C NMR (50.3 MHz): 42.6, 49.6, 53.5, 60.2 (methylene carbons) and 168.2 (carboxyl carbon). MS: m/z 244 = $[CoC_{18}H_{37}N_8O_4]^{2+}$. Visible spectrum: λ_{max} = 472 nm, ϵ = 139 M^{-1} cm^{-1}.

Crystals suitable for X-ray crystallography were grown by dissolving the compound in concentrated hydrochloric acid and slowly evaporating the solvent. Other crystalline derivatives were obtained as follows:

[Co(($NH_2CH_2COOH)_2$sar)]$(SO_4)_2Cl\cdot 5H_2O$, **Co1b.** Crystals were obtained on slow evaporation (at room temperature) of a solution of the chloride salt in 1 mol L^{-1} H_2SO_4.

[Co(($NHCH_2COOH)_2$sar)]$Cl_3\cdot 4.5H_2O$, **Co2.** Crystals were obtained on vapor diffusion of ethanol into a simple aqueous solution of the pentachloride.

[Co(($NHCH_2COO)_2$sar)]$ClO_4\cdot 7.5H_2O$, **Co3.** A sample of the chloride was converted to the acetate by shaking its aqueous solution with excess acetate form Dowex 1x8 anion exchange resin. The resulting solution was taken to dryness and the residue dissolved in the minimum volume of methanol. Addition of excess concentrated perchloric acid (**CAUTION!**) and cooling gave an orange precipitate, presumed to be the pentaperchlorate salt. This was used in a subsequent preparation in which its aqueous solution was adjusted to a pH ~7 by addition of a metal carbonate, and orange crystals were observed to readily precipitate. These were recrystallized from water by slow evaporation to give large tabular crystals, proving on the basis of the crystal structure determination to have the composition given above.

The orange residue from band 2 was dissolved in the minimum volume of water and precipitated by the addition of ethanol to afford an orange powder. The orange powder was recrystallized by dissolving the solid in a minimum volume of hot water, adding ethanol to the point of turbidity, and then slowly cooling to give efflorescent orange microcrystals of 1-ammonio-8-carboxymethylammoniosarcophaginecobalt(III) pentachloride trihydrate, [Co((NH_3)(NH_2CH_2COOH)sar)]$Cl_5\cdot 3H_2O$, **Co4a** (1.8 g, 2.7 mmol, 30%). Anal. Found: C, 29.1; H, 6.2; N, 16.5. Calcd for $CoC_{16}H_{38}N_8Cl_5O_2\cdot 3H_2O$: C, 28.91; H, 6.67; N, 16.86. ^{1}H NMR (200 MHz): δ 2.87, 12H, m, methylene cage protons; 3.42, 12H, methylene cage protons; 3.97, 2H, CH_2COOH. ^{13}C NMR (50.3 MHz): 42.8, 49.4, 50.6, 54.1, 56.0, 60.7 (methylene); 167.7 (carboxyl). MS: m/z 215 = $[CoC_{16}H_{35}N_8O_2]^{2+}$. Visible spectrum: λ_{max} = 472 nm; ϵ = 139 M^{-1} cm^{-1}.

The chloride salt (1.0 g) was readily converted to the corresponding perchlorate (**Co4b**) by addition of concentrated perchloric acid to its concentrated aqueous solution and subsequent cooling at 4 °C to provide orange crystals (0.93 g). Anal. Found: C, 20.7; H, 4.8; N, 12.0. Calcd for $CoC_{16}H_{38}N_8Cl_5O_{22}$: C, 20.65; H, 4.12; N, 12.04. MS: m/z 215 = $[Co\ C_{16}H_{35}N_8O_2]^{2+}$.

The chloride salts of both complexes can readily be converted to the air-stable mixed nitrate−chloride salts by essentially the same method for both. The chloride salt was dissolved in a minimum volume of water and an equal volume of 2 mol L^{-1} HNO_3 added, resulting in the formation of an orange precipitate. The orange precipitate was collected by filtration and washed with a small volume of cold water. Recrystallization from the minimum volume of hot (80 °C) water by slow cooling provided orange microcrystals.

From band 1: 1,8-di(carboxymethylammonio)sarcophaginecobalt(III) tetranitrate chloride trihydrate, [Co(($NH_2CH_2COOH)_2$sar)]$(NO_3)_4Cl\cdot 3H_2O$, **Co5** (62%; presence of chloride confirmed by Ag^+ test). Anal. Found: C, 26.1; H, 5.4; N, 20.9. Calcd for $CoC_{18}H_{46}N_{12}ClO_{19}$: C, 26.08; H, 5.59; N, 20.27. MS: m/z 613 = $[CoC_{18}H_{38}N_8O_4(NO_3)_2]^+$; 550 = $[CoC_{18}H_{37}N_8O_4(NO_3)]^+$; 487 = $[CoC_{18}H_{37}N_8O_4]^+$.

From band 2: 1-ammonio-8-(carboxymethylammonio)sarcophaginecobalt(III) tetranitrate chloride [Co((NH_3)(NH_2CH_2COOH)sar)]$(NO_3)_4Cl$, **Co6** (84%; presence of chloride confirmed by Ag^+ test). Anal. Found: C, 26.8; H, 5.2; N, 23.5. Calcd for $CoC_{16}H_{38}N_{12}O_{14}Cl$: C, 26.81; H, 5.34; N, 23.44. MS: m/z 555 = $[CoC_{16}H_{36}N_8O_2(NO_3)_2]^+$; 492 = $[CoC_{16}H_{35}N_8O_2(NO_3)]^+$; 429 = $[CoC_{16}H_{34}N_8O_2]^+$.

(1-Chloro-8-(*N*-nitroso-carboxymethylamino)sarcophagine)cobalt(III) Nitrate, Co7. During an early investigation of the precipitation of the nitrate salt of [Co((NH_3)(NH_2CH_2COOH)sar)]$^{5+}$ as above, the filtrate from the initial precipitate was heated under reduced pressure at 50 °C for approximately 1 h. On cooling and after further slow evaporation, large, orange, needlelike crystals deposited. These were identified following their structure determination by X-ray diffraction as the product of nitrosation of the original complex, NOCl presumably having been generated from reaction between HCl and HNO_3 during the heating and concentration steps.

(1-Ammonio-8-(methoxycarbonylmethylammonio)sarcophagine)cobalt(III) Sulfate, Co8 (from Esterification of [Co((1-NH_3)(8-NH_2CH_2COOH)sar)]$(ClO_4)_5$). 1-Ammonio-8-(carboxymethylammonio)sarcophagine cobalt perchlorate, [Co((1-NH_3)(8-NH_2CH_2COOH)sar)]$(ClO_4)_5$ (0.200 g, 0.21 mmol), was dissolved in anhydrous methanol (10 mL). Concentrated H_2SO_4 (0.5 mL) was added to the orange solution, resulting in the formation of a powdery precipitate. The mixture was heated at reflux for 24 h (**CAUTION**, a safety shield was used) and then allowed to cool, and the precipitate formed was collected by filtration and washed with diethyl ether (2 × 5 mL). The orange powder was recrystallized by dissolution in water and addition of acetone to give orange, microcrystalline 1-ammonio-8-(methoxycarbonylmethylammonio)sarcophagine cobalt(III) sulfate trihydrate, which was collected by filtration and washed with acetone (2 × 5 mL) and diethyl ether (2 × 5 mL). Yield: 0.15 g (0.20 mmol, 95%). Anal. Found: C, 29.6; H, 7.22; N, 15.9. Calcd for $CoC_{17}H_{39}N_8O_2(SO_4)_2\cdot 3H_2O$, $CoC_{17}H_{45}N_8O_{13}S_2$: C, 29.48 H, 6.55; N, 16.18. ^{1}H NMR (200 MHz): δ 2.4−3.4, m, methylene cage protons; 3.45, s, 2H, CH_2-CO; 3.60, s, 3H, $O-CH_3$. MS: m/z 223 = $[CoC_{17}H_{38}N_8O_2]^{2+}$.

Isolation of 1,8-Di(carboxymethylammonio)sarcophagine from Its Cobalt Complex (Acid Method). 1,8-Di(carboxymethylammonio)-sarcophagine cobalt(III) pentachloride (0.5 g, 0.75 mmol) was dissolved in 2 mL of deoxygenated water. Under an argon atmosphere, zinc dust (0.25 g, 3.8 mmol) was added to the orange solution and the reaction mixture was stirred for 1 h. The now green reaction mixture was filtered and added to deoxygenated concentrated HCl (20 mL). The reaction mixture was heated to reflux, under an argon atmosphere, for 1 week. The solution was now a darker green. Since there had been little color change due to the anticipated release of Co(II) as blue $[CoCl_4]^{2-}$, the yield of isolated free ligand was assumed to be low, and therefore more rigorous conditions were applied. The reaction mixture was transferred to a reinforced Schlenk flask. The HCl was removed by evaporation under reduced pressure and was replaced by "fresh" deoxygenated concentrated HCl (15 mL). The flask was evacuated and heated to 150 °C for 48 h. The flask was allowed to cool to room temperature, and the now green-blue solution was poured into ethanol (30 mL). A pale green precipitate formed, which was collected by filtration. The precipitate was dissolved in a minimum volume of 3 mol L^{-1} HCl, the orange solution was filtered, and colorless needles of the ligand were precipitated by the addition of ethanol to the point of turbidity and standing at 25 °C. These colorless needles were collected by filtration and washed with ethanol (2 × 5 mL) and diethyl ether (2 × 5 mL) to give pentaprotonated 1,8-di(carboxymethylammonio)-sarcophagine as its lactamized derivative (0.080 g, 0.13 mmol, 17%). Anal. Found: C, 34.5; H, 7.6; N, 17.7. Calcd for $C_{18}H_{45}N_8Cl_5O_5$: C, 34.27; H, 7.19; N, 17.76. ^{13}C NMR (50.3 MHz): $\boldsymbol{\delta}$ 42.5, 44.5, 47.2, 48.2, 50.2, 53.3, 55.2 and 165.5.

Carboxymethylation of [Cu((1,8-NH_2)$_2$sar)]$^{2+}$: Derivatives of Tetrakis-, Tris-, and Bis-Carboxymethyl Diaminosarcophagine. [Cu((NH_3)$_2$sar)]$(NO_3)_4\cdot H_2O$ (3.0 g, 4.6 mmol) was dissolved in the minimum volume of water and neutralized by the addition of NaOH (0.186 g, 4.65 mmol). A solution of sodium chloroacetate was prepared by dissolving chloroacetic acid (21.9 g, 0.23 mol) in water and adding sodium hydroxide (9.29 g, 0.23 mol). The two solutions were combined, and the blue reaction mixture was heated at 80 °C under an atmosphere of nitrogen for 48 h. During this period the pH was maintained at approximately 9−10 by addition of aqueous sodium hydroxide. The

final reaction mixture was acidified by the addition of glacial acetic acid (pH <5).

The reaction mixture was then diluted to a total volume of 8 L and absorbed onto a column (75 × 8 cm) of Na^+ form SP Sephadex C25. The column was washed with water (1 L) and eluted with sodium citrate solution. Five purple components were observed, and the separate eluates were then absorbed on to a column of H^+ Dowex 50Wx2 resin, which was washed with water (200 mL) to remove citrate and 1 mol L^{-1} HCl (200 mL) to remove sodium, and the absorbed copper complex was then eluted with 3 mol L^{-1} HCl. The first band to be eluted off Sephadex split into two purple bands on the Dowex column; the remaining bands did not separate further. The purple eluates were evaporated to dryness under vacuum and the complexes precipitated as solids by dissolving the residues in a minimum volume of water and adding acetone. The solids were collected by filtration and washed with acetone (2 × 5 mL). The six isolated compounds are referred to as **Cu1**−**Cu6** for simplicity. To obtain NMR spectra of some of the new ligands, the paramagnetic Cu(II) complexes were treated with zinc dust as follows to generate the diamagnetic Zn(II) complexes:

The copper complexes were dissolved in a minimum volume of D_2O, and an excess of zinc was added to the purple solutions. After stirring for 30 min, the mixtures were filtered to give colorless solutions suitable for NMR measurements.

Cu1. Yield: 0.20 g. Anal. Found: C, 39.5; H, 5.99; N, 16.5; Cl, 10.2. Calcd for $CuC_{22}H_{38}N_8Cl_2O_6 \cdot H_2O$: C, 39.85; H, 6.08; N, 16.90; Cl, 10.69. MS: *m*/*z* 672; 632; 608; 594; 584; 580; 572; 566. Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 508 nm; ϵ = 165 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 purple, platelike crystals (**Cu1a**). Similar results were obtained using perchloric in place of nitric acid, giving **Cu1b**.

Zn Analogue (Zn1). ^{13}C NMR (125.8 MHz): δ 43.4, 44.7, 45.6, 47.7, 50.2, 51.6, 52.1, 58.48, CH_2; 55.6, 168.8, 177.1, quaternary.

Cu2. Yield: 0.070 g. Anal. Found: C, 35.5; H, 6.2; N, 15.6; Cl, 13.1. Calcd for $CuC_{22}H_{38}N_8O_5Cl_3 \cdot 4H_2O$: C, 35.88; H, 6.29; N, 15.21; Cl, 14.44. MS: *m*/*z* 632; 574; 550; 514; 453. Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 496 nm; ϵ = 167 M^{-1} cm^{-1}.

Crystals were grown as described for **Cu1**, but none were found suitable for X-ray diffraction studies.

Zn Analogue (Zn2). ^{13}C NMR (50.3 MHz): δ 169.0, 169.2, 169.6, 177.3, carbonyl; signals in the methylene and quaternary regions were poorly resolved.

Cu3. Yield: 0.23 g. Anal. Found: C, 34.1; H, 6.4; N, 15.5; Cl, 15.3. Calcd for $CuC_{20}H_{38}N_8O_4Cl_4 \cdot 4H_2O$: C, 34.54; H, 6.52; N, 16.11; Cl, 15.29. MS: *m*/*z* 614; 588; 574; 550; 514. Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 508 nm; ϵ = 165 M^{-1} cm^{-1}.

Crystals were grown as described for **Cu1**, but none were found suitable for X-ray diffraction studies.

Cu4. Yield: 0.94 g. Anal. Found: C, 33.8; H, 6.1; N, 14.6; Cl, 16.7. Calcd for $CuC_{20}H_{38}N_8O_4Cl_4 \cdot 3H_2O$: C, 33.65; H, 6.21; N, 15.69; Cl, 19.86. MS: *m*/*z* 588; 574; 550; 514; 435. Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 508 nm; ϵ = 169 M^{-1} cm^{-1}.

Crystals suitable for X-ray studies were grown as described for **Cu1**, a structure solution showing that the isolated material, purple plates, was a nitrate−chloride.

Zinc Analogue (Zn3). ^{13}C NMR (50.3 MHz): δ 43.5, 43.7, 44.8, 45.8, 46.0, 47.9, 48.2, 50.5, 50.7, 51.5, 51.8, 52.1, 56.0, 57.9, 58.8, 169.2, 169.5, and 177.2.

Cu5. Yield: 0.48 g. Anal. Found: C, 33.6; H, 6.4; N, 15.8; Cl, 14.4. Calcd for $CuC_{20}H_{37}N_8O_4Cl_3 \cdot 5H_2O$: C, 33.67; H, 6.64; N, 15.70; Cl, 14.91. MS: *m*/*z* 614; 574; 550; 514; 453. Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 508 nm; ϵ = 170 M^{-1} cm^{-1}.

Crystals suitable for X-ray analysis were grown as large purple rhomboids by carefully layering ethanol onto an aqueous solution of the complex and allowing the solvents to slowly mix by diffusion at 25 °C.

Cu6. Yield: 1.49 g. Anal. Found: C, 31.2; H, 6.0; N, 16.0; Cl, 21.0. Calcd for $CuC_{18}H_{36}N_8O_2Cl_4 \cdot 5H_2O$: C, 31.24; H, 6.70; N, 16.19; Cl, 20.49. MS: *m*/*z* 516; 492; 456; 395.

Visible spectrum: λ_{max} in 1 mol L^{-1} HCl = 516 nm; ϵ = 160 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. The crystals deposited on slow evaporation were then recrystallized from water. Over the period of time required for the deposition, the solution obviously changed color from violet to blue.

Zinc Analogue (Zn4). ^{13}C NMR (50.3 MHz): δ 46.8, 46.9, 49.1, 51.4, 53.8, 54.8, 55.4, 61.3, and 173.0.

Carboxymethylation of Diaminosarcophagine: 1,8-Diamino-3-carboxymethyl-sarcophagine and 1,8-Diamino-3,6-di(carboxymethyl)sarcophagine. 1,8-$(NH_2)_2$sar (0.50 g, 1.6 mmol) was dissolved in the minimum volume of water. A solution of sodium chloroacetate was prepared by dissolving chloroacetic acid (0.15 g, 1.6 mmol) in water (15 mL) and neutralizing with sodium hydroxide. The two solutions were combined, and the reaction mixture was heated to 80 °C for 24 h. During this time the pH was maintained at approximately 10 by addition of aqueous sodium hydroxide. $CoCl_2 \cdot 6H_2O$ (0.378 g, 1.59 mmol) was added to the cooled solution, resulting in the formation of an orange-red solution. H_2O_2 (30% solution, 1 mL) was added to the orange-red solution,which was left open to the normal atmosphere for 3 h to ensure that all the complexed cobalt was in the +3 state; by this time the solution was red. The solution was diluted with water to a total volume of 400 mL and applied to a column of Na^+ form SP Sephadex C25. Elution with 0.5 mol L^{-1} NaCl resulted in the formation of two red bands (**Co9** and **Co10**). Both bands were then absorbed separately onto a column of H^+ Dowex 50Wx2 and washed with water (200 mL) and 1 mol L^{-1} HCl (200 mL) before the complexes were eluted with 3 mol L^{-1} HCl. The eluates were evaporated to dryness under reduced pressure to give red glasses.

Co9 was dissolved in hot acetonitrile, and the solution was allowed to cool slowly to afford 1,8-diammonio-3,6-dicarboxymethylsarcophagine cobalt(III) chloride trihydrate ($[Co((1,8\text{-}NH_3)_2(3,6\text{-}CH_2COOH)_2sar)]Cl_5 \cdot 3H_2O$) as a red solid (0.080 g, 0.11 mmol, 7%).

Anal. Found: C, 29.7; H, 6.36; N, 15.8. Calcd for $CoC_{18}H_{46}N_8Cl_5O_7$: C, 29.9; H, 6.4; N, 15.5. ^{13}C NMR (50.3 MHz): δ 54.8, 55.5, 56.5, 56.8, 61.0, 64.1, 67.9, 73.9, and 183.6. MS: *m*/*z* 487 = $[CoC_{18}H_{36}N_8O_4]^+$; 244 = $[CoC_{18}H_{37}N_8O_4]^{2+}$.

Co10 was isolated in the same manner as **Co9** to give 1,8-diammonio-3-carboxymethylsarcophagine cobalt(III) chloride dihydrate ($[Co(1,8\text{-}NH_3)_2(3\text{-}CH_2COOH)sar]Cl_5 \cdot 2H_2O$) as a red solid (0.77 g, 1.2 mmol, 75%). Anal. Found C, 29.6; H, 6.1; N, 17.4. Calcd for $CoC_{16}H_{42}N_8O_4Cl_5$: C, 29.71; H, 6.55; N, 17.33. ^{13}C NMR (50.3 MHz): δ 49.4, 49.6, 50.0, 51.0, 51.9, 52.1, 52.5, 53.0, 54.0, 54.8, 58.1, 60.6, 61.5, and 165.3. MS: *m*/*z* 215 = $[CoC_{16}H_{35}N_8O_2]^{2+}$. Visible spectrum: λ_{max} = 506 nm; ϵ = 173 M^{-1} cm^{-1}.

Crystals of a mixed chloride−dithionate salt (**Co11**) suitable for X-ray crystallography were grown by dissolving the complex in the minimum volume of water and adding an excess of $Li_2[S_2O_6]$. Slow evaporation of the solvent led to the formation of large red crystals.

1,8-Diammoniosarcophaginecobalt(III) Chloride Perchlorate Hydrate, $[Co((NH_3)_2sar)]_3Cl_8(ClO_4)_7 \cdot 13H_2O$, Co12. During initial efforts to characterize products of carboxymethylation of $[Co((NH_2)_2sar)]^{3+}$, a chromatographic fraction was precipitated by addition of perchloric acid to its aqueous solution and only then found to be a new salt of the reactant. Numerous efforts subsequently made to isolate this material directly gave solids with a variety of different Cl^-:ClO_4^- ratios, and numerous attempts to crystallize the solids provided many instances of crystals unacceptable for structure determination even though microanalytical data could be fitted to a relatively simple composition (e.g., found, C 19.9, H 4.7, N 13.1; calcd for $[Co((NH_3)_2sar)]Cl(ClO_4)_4 \cdot 2H_2O$ = $C_{14}H_{40}Cl_5CoN_8O_{18}$, C 19.91, H 4.77, N 13.27). On one occasion of acceptable crystal formation, however, a satisfactorily precise structure solution was obtained, defining this particular material as having the stoichiometry given above.

Structure Determinations. Diffraction data were acquired in a number of modes, at the various specified temperatures, all instruments being equipped with monochromatic Mo Kα radiation, $\lambda = 0.7107_3$ Å. Using a single-counter instrument in the $2\theta/\theta$ scan mode, *N* unique reflections were measured within the specified $2\theta_{max}$ limit, N_o with $I > 3\sigma(I)$ being considered "observed", Gaussian absorption corrections

being applied. Data were also measured using a Bruker AXS CCD instrument ($2\theta_{max} = 58°$), $N_{t(otal)}$ reflections within a full sphere being merged to N unique, R_{int} as specified after "empirical"/multiscan absorption correction within the proprietary/preprocessing software SMART/SAINT; the "observed" criterion applicable was $F > 4\sigma(F)$. Anisotropic thermal parameter forms were refined in a full-matrix context for non-hydrogen atoms, $(x, y, z, U_{iso})_H$ being constrained at estimated values. Conventional residuals R, R_w (statistical weights) on $|F|$ are quoted at convergence. Neutral atom complex scattering factors were employed within the Xtal 3.4 program system.[31] Pertinent results are given in the figures and tables and below; individual variations in procedure/difficulties/idiosyncrasies are cited as "variata". Other crystallographic data (excluding structure factor amplitudes) are lodged as CIF files in the Supporting Information.

Crystal/Refinement Data. Co1a, [Co(sar(NH$_2$CH$_2$COOH)$_2$)]Cl$_5$·5H$_2$O: $C_{18}H_{50}Cl_5CoN_8O_9$, $M = 758.8$. Single-counter instrument, T ca. 295 K. Monoclinic, space group $P2_1/n$ (C_{2h}^5, No. 14 (variant)), $a = 13.728(7)$ Å, $b = 13.655(1)$ Å, $c = 18.077(6)$ Å, $\beta = 111.11(4)°$, $V = 3161$ Å^3. D_c ($Z = 4$) = 1.59$_4$ g cm^{-3}; $F(000) = 1592$. $\mu_{Mo} = 10.2$ cm^{-1}; specimen: 0.85 × 0.52 × 0.38 mm; $T_{min,max} = 0.67, 0.72$. $2\theta_{max} = 50°$; $N = 5531$, $N_o = 4868$; $R = 0.040$, $R_w = 0.045$; $n_v = 571$, $|\Delta\rho_{max}| = 0.69$ e Å^{-3}.

Variata. Refinement was straightforward; $(x, y, z, U_{iso})_H$ were refined throughout. The ligand conformation is, alone among the present cobalt adducts, *ob*$_3$.

Co1b, [Co(sar(NH$_2$CH$_2$COOH)$_2$)](SO$_4$)$_2$Cl·5H$_2$O: $C_{18}H_{50}ClCoN_8O_{17}S_2$, $M = 809.2$. Single-counter instrument, T ca. 295 K. Monoclinic, space group $P\bar{1}$ (C_i^1, No. 2), $a = 17.937(2)$ Å, $b = 10.278(3)$ Å, $c = 10.058(4)$ Å, $\alpha = 115.99(3)°$, $\beta = 103.40(2)°$, $\gamma = 92.05(1)°$, $V = 1601$ Å^3. D_c ($Z = 2$) = 1.67$_8$ g cm^{-3}; $F(000) = 852$. $\mu_{Mo} = 8.4$ cm^{-1}; specimen: 0.35 × 0.42 × 0.32 mm; $T_{min,max} = 0.79, 0.83$. $2\theta_{max} = 55°$; $N = 7312$, $N_o = 5051$; $R = 0.049$, $R_w = 0.050$; $n_v = 625$, $|\Delta\rho_{max}| = 0.97$ e Å^{-3}.

Variata. Refinement was straightforward. $(x, y, z, U_{iso})_H$ were refined throughout.

Co2, [Co(sar(NHCH$_2$COOH)$_2$)]Cl$_3$·~4.5H$_2$O: $C_{18}H_{47}Cl_3CoN_8O_{8.5}$, M ca. 676.9. Area-detector instrument, T ca. 153 K. Triclinic, space group $P\bar{1}$, $a = 8.742(1)$ Å, $b = 12.730(2)$ Å, $c = 14.034(2)$ Å, $\alpha = 76.294(2)°$, $\beta = 79.011(2)°$, $\gamma = 70.788(2)°$, $V = 1422$ Å^3. D_c ($Z = 2$) = 1.58$_1$ g cm^{-3}; $F(000)$ ca. 714. $\mu_{Mo} = 9.4$ cm^{-1}; specimen: 0.28 × 0.18 × 0.12 mm; "T "$_{min,max} = 0.84, 0.94$. $N_t = 16726$, $N = 7023$ ($R_{int} = 0.025$); $N_o = 5744$; $R = 0.082$, $R_w = 0.086$; $n_v = 422$, $|\Delta\rho_{max}| = 1.9$ e Å^{-3}.

Variata. Such hydrogen atoms as could be discerned in difference maps or by estimation were modeled with $(x, y, z, U_{iso})_H$ constrained. The determination is not regarded as definitive of proton/anion/solvent stoichiometry, disorder being rife among two of the three chlorine moieties, the carboxylates, and water molecules. No evidence has been found for any superlattice in the structure, the sample being inferior.

Co3, [Co(sar(NHCH$_2$COO)$_2$)](ClO$_4$)·7.5H$_2$O: $C_{18}H_{51}ClCoN_8O_{15.5}$, M ca. 722.0. Area-detector instrument, T ca. 300 K. Monoclinic, space group $P2_1/n$, $a = 15.258(1)$ Å, $b = 13.223(1)$ Å, $c = 17.333(2)$ Å, $\beta = 114.785(1)°$, $V = 3175$ Å^3. D_c ($Z = 4$) = 1.51$_0$ g cm^{-3}; $F(000)$ ca. 1532. $\mu_{Mo} = 7.0$ cm^{-1}; specimen: 0.55 × 0.35 × 0.30 mm; "T "$_{min,max} = 0.71, 0.89$. $N_t = 36578$, $N = 7981$ ($R_{int} = 0.018$), $N_o = 6497$; $R = 0.048$, $R_w = 0.066$; $n_v = 571$, $|\Delta\rho_{max}| = 0.95$ e Å^{-3}.

Variata. $(x, y, z, U_{iso})_H$ refined meaningfully for both cation and water molecules O(1−3). The perchlorate was modeled with oxygen atoms disordered over two sets of sites, occupancies 0.894(8) and complement, and (water) O(8) with site occupancy 0.5, with high "thermal motion" among the anion and solvent oxygen atoms.

Co7, [Co(sar(Cl)(N(NO)CH$_2$COOH))](NO$_3$)$_3$·H$_2$O: $C_{16}H_{35}ClCoN_{11}O_{13}$, $M = 683.9$. Single-counter instrument, T ca. 295 K. Monoclinic, space group $P2_1/n$, $a = 8.565(7)$ Å, $b = 28.49(1)$ Å, $c = 10.798(5)$ Å, $\beta = 91.84(6)°$, $V = 2633$ Å^3. D_c ($Z = 4$) = 1.72$_5$ g cm^{-3}; $F(000) = 1424$. $\mu_{Mo} = 8.4$ cm^{-1}; specimen: 0.80 × 0.41 × 0.28 mm; $T_{min,max} = 0.61, 0.82$. $2\theta_{max} = 50°$; $N_t = 14677$, $N = 4419$ ($R_{int} = 0.063$); $N_o = 3886$; $R = 0.049$, $R_w = 0.054$; $n_v = 519$, $|\Delta\rho_{max}| = 0.79$ e Å^{-3}.

Variata. Over a hemisphere of data was measured. $(x, y, z, U_{iso})_H$ (all H) were refined.

Co11, [Co(sar(NH$_3$)$_2$(CH$_2$COOH))](S$_2$O$_6$)$_2$Cl·~4.5H$_2$O. $C_{16}H_{47}ClCoN_8O_{18.5}S_4$, M ca. 870.3. Single-counter instrument, T ca. 295 K. Monoclinic, space group $P2_1/c$ (C_{2h}^5, No. 14) $a = 11.060(7)$ Å, $b = 13.996(6)$ Å, $c = 21.517(13)$ Å, $\beta = 102.14(5)°$, $V = 3256$ Å^3. D_c ($Z = 4$) = 1.77$_5$ g cm^{-3}; $F(000)$ ca. 1820. $\mu_{Mo} = 9.6$ cm^{-1}; specimen: 0.40 × 0.35 × 0.45 mm; $T_{min,max} = 0.69, 0.78$. $2\theta_{max} = 50°$; $N = 5713$, $N_o = 3848$; $R = 0.072$, $R_w = 0.079$; $n_v = 485$, $|\Delta\rho_{max}| = 1.13$ e Å^{-3}.

Variata. Residues modeled as the chloride were distributed over a pair of sites, occupancies 0.643(7) and complement (caveat: cf. possible water molecule interchange); dithionate 2 was modeled as disordered over a pair of sets of sites occupancy 0.5 each. Solvent water O(5) is modeled as concerted with one of the disordered dithionate components with occupancy set at 0.5. $(x, y, z, U_{iso})_H$ were constrained for the cation, not being located for the lattice water molecules.

Co12, [Co(sar(NH$_3$)$_2$)]$_3$(ClO$_4$)$_7$Cl$_8$·13H$_2$O. $C_{42}H_{134}Cl_{15}Co_3N_{24}O_{41}$, $M = 2340.3$. Area detector instrument, T ca. 153 K. Triclinic, space group $P\bar{1}$, $a = 13.413(3)$ Å, $b = 17.210(4)$ Å, $c = 21.561(5)$ Å, $\alpha = 66.628(3)°$, $\beta = 83.144(4)°$, $\gamma = 89.451(4)°$, $V = 4532$ Å^3. D_c ($Z = 2$) = 1.71$_5$ g cm^{-3}; $F(000) = 2436$. $\mu_{Mo} = 10.8$ cm^{-1}; specimen: 0.30 × 0.12 × 0.10 mm; "T "$_{min,max} = 0.65, 0.88$. $N_t = 40151$, $N = 21441$ ($R_{int} = 0.034$), $N_o = 15122$; $R = 0.045$, $R_w = 0.048$; $n_v = 1667$, $|\Delta\rho_{max}| = 1.08$ e Å^{-3}.

Variata. Perchlorate 7 was modeled rotationally disordered about Cl−O(1), O(72−4) being refined to occupancies 0.676(7) (and complements for the disordered components). $(x, y, z, U_{iso})_H$ were refined throughout except for those associated with water molecule 12, for which they were constrained at ("improved") difference map estimates.

The following **copper(II)** adducts are all complexes of 1,8-diamino-3,6-di(carboxymethyl)sarcophagine, denoted L, variously additionally substituted at the 1,8-nitrogens by up to two moieties; we denote these substituted ligands as L (R,R′)(R″,R‴), with substituents H or CH$_2$-COOH.

Cu1a, [(O$_2$NO)Cu{L(R)(R,H)}](NO$_3$)$_2$·~4.5H$_2$O: $C_{22}H_{48}CuN_{11}O_{19.5}$, $M = 842.2$. Single-counter instrument, T ca. 295 K. Monoclinic, space group $P2_1/n$, $a = 15.529(3)$ Å, $b = 11.075(5)$ Å, $c = 20.422(3)$ Å, $\beta = 98.12(1)°$, $V = 3477$ Å^3. D_c ($Z = 4$) = 1.60$_9$ g cm^{-3}; $F(000) = 1768$. $\mu_{Mo} = 7.3$ cm^{-1}; specimen: 0.25 × 1.5 × 0.70 mm; $T_{min,max} = 0.68, 0.83$. $2\theta_{max} = 50°$; $N_t = 10095$, $N = 6105$ ($R_{int} = 0.051$), $N_o = 4408$; $R = 0.058$, $R_w = 0.071$; $n_v = 645$, $|\Delta\rho_{max}| = 1.00$ e Å^{-3}.

Variata. Hydrogen atoms were not located in association with solvent or carboxylate moieties; all others were refined in (x, y, z, U_{iso}). Site occupancies of water molecule oxygen fractions O(4−6) were set at 0.5 after trial refinement.

Cu1b, [(O$_3$ClO)Cu{L(R,H$_2$)}](ClO$_4$)$_2$}](ClO$_4$)$_3$·~3.5H$_2$O: $C_{22}H_{47}Cl_4CuN_8O_{25.5}$, M ca. 1037.0. Area-detector instrument, T ca. 300 K. Monoclinic, space group $P2_1/c$, $a = 20.135(1)$ Å, $b = 19.269(1)$ Å, $c = 19.774(1)$ Å, $\beta = 97.742(1)°$, $V = 7602$ Å^3. D_c ($Z = 8$) = 1.81$_2$ g cm^{-3}; $F(000) = 4288$. $\mu_{Mo} = 9.6$ cm^{-1}; specimen: 0.25 × 0.20 × 0.20 mm; "T "$_{min,max} = 0.81, 0.91$. $N_t = 88501$, $N = 18826$ ($R_{int} = 0.025$), $N_o = 11879$; $R = 0.055$, $R_w = 0.057$; $n_v = 1467$, $|\Delta\rho_{max}| = 2.3$ e Å^{-3}.

Variata. All hydrogen atoms except those associated with the lattice solvent molecules were refined. Disorder was resolved among the oxygen atoms of perchlorates 7, 8, these being rotationally disordered over two sets of sites, occupancies 0.612(5), 0.665(5) and complements.

Cu4, [Cl{Cu(L(R)(H$_2$))}$_2$](NO$_3$)$_4$Cl·~11H$_2$O: $C_{40}H_{96}Cl_2Cu_2N_{20}O_{31}$, M ca. 1551.3. Single-counter instrument, T ca. 300 K. Triclinic, space group $P\bar{1}$, $a = 13.087(3)$ Å, $b = 12.561(2)$ Å, $c = 10.449(3)$ Å, $\alpha = 73.69(2)°$, $\beta = 80.19(3)°$, $\gamma = 78.71(2)°$, $V = 1612$ Å^3. D_c ($Z = 1$) = 1.59$_8$ g cm^{-3}; $F(000)$ ca. 826. $\mu_{Mo} = 8.5$ cm^{-1}; specimen: 0.20 × 0.55 × 0.22 mm; $T_{min,max} = 0.65, 0.94$. $2\theta_{max} = 50°$; $N = 5661$, $N_o = 4519$; $R = 0.058$, $R_w = 0.064$; $n_v = 617$, $|\Delta\rho_{max}| = 1.2$ e Å^{-3}.

Variata. Cationic $(x, y, z, U_{iso})_H$ were refined. Disorder problems occurred, first, between the anionic chloride and solvent water, and second, in respect of nitrate 2 which was modeled as disordered over two sets of sites, occupancies 0.69(2) and complement.

Cu5, [ClCu{L(R)(H)}]Cl·~3.9H$_2$O: $C_{20}H_{43.8}Cl_2CuN_8O_{7.9}$, M ca. 652.3. Area-detector instrument, T ca. 300 K. Monoclinic, space group $P2_1/n$, $a = 10.197(4)$ Å, $b = 14.556(5)$ Å, $c = 19.280(7)$ Å, $\beta =$

(31) Hall, S. R., King, G. S. D., Stewart, J. M., Eds. *The Xtal 3.4 User's Manual*; University of Western Australia, Lamb: Perth, 1995.

100.810(7)°, $V = 2812$ Å^3. D_c ($Z = 4$) $= 1.55_2$ g cm^{-3}; $F(000) = 1384$. $\mu_{Mo} = 10.3$ cm^{-1}; specimen: $0.20 \times 0.12 \times 0.05$ mm; "T "$_{min,max} = 0.63, 0.89$. $N_t = 31499$, $N = 7146$ ($R_{int} = 0.045$), $N_o = 2599$; $R = 0.051$, $R_w = 0.042$; $n_v = 362$, $|\Delta\rho_{max}| = 0.80$ e Å^{-3}.

Variata. Site occupancy of O(4) was set at 0.5 in regard to its proximity to its symmetry-generated image; the occupancy of O(5) refined to 0.39(2). Such hydrogen atoms as could be reasonably estimated were included constrained thus.

The structure of the simple protonated 1,8-bis(carboxy-methylammonio)sarcophagine complex of copper(II) (cf. **Co1a**) is also recorded as its tetranitrate salt:

Cu6, [Cu(sar(NH$_2$CH$_2$COOH)$_2$)](NO$_3$)$_4$·2H$_2$O: $C_{18}H_{44}CuN_{12}O_{18}$, $M = 780.2$. Area-detector instrument, T ca. 300 K. Orthorhombic, space group $Fdd2$ (C_{2v}^{19}, No. 43) $a = 43.505(4)$ Å, $b = 10.441(1)$ Å, $c = 13.711(1)$ Å, $V = 6228$ Å^3. D_c ($Z = 8$) $= 1.66_4$ g cm^{-3}; $F(000) = 3272$. $\mu_{Mo} = 8.0$ cm^{-1}; specimen: $0.25 \times 0.20 \times 0.07$ mm; "T "$_{min,max} = 0.64, 0.89$. $N_t = 18156$, $N = 2089$ ($R_{int} = 0.040$), $N_o = 1418$; $R = 0.049$, $R_w = 0.050$ (both hands); $n_v = 302$, $|\Delta\rho_{max}| = 0.69$ e Å^{-3}.

Variata. Refinement was straightforward; (x, y, z, U_{iso})$_H$ were refined throughout, except those associated with the water molecule oxygen which were constrained.

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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