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Stereochemistry in Functionalized Macrocycle Complexes: Control of Hydroxyl Substituent Orientation

Jack M. Harrowfield,*,† Yang Kim,*,‡ George A. Koutsantonis,† Young Hoon Lee,‡ and Pierre Thuéry§

Chemistry, School of Biomedical and Chemical Sciences, University of Western Australia,
35 Stirling Highway, Crawley, WA 6009, Australia, Department of Advanced Materials, Kosin
University, 149-1, Dongsam-dong, Yeongdo-gu, Busan, 606-701, South Korea, and CEA/Saclay,
DSM/DRECAM/SCM, Bâtiment 125, 91191, Gif-sur-Yvette, France

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Use of a hydroxyl-functionalized open chain tetramine in a template reaction based on its Cu(II) complex leads, after reduction, to a new tetraaza macrocycle with both amino and hydroxyl substituents. The macrocycle is formed predominantly as its trans (anti) isomer, though the cis form is detectable and both have been structurally characterized in the form of their metal complexes. Although both the Cu(II) and the Co(III) complexes of the tetramine precursor ligand have the hydroxyl group in an axial position of a chair six-membered chelate ring, the trans macrocycle forms Co(III) complexes with this substituent in both equatorial and axial positions.

Introduction

Functionalization of a macrocyclic ligand in such a way as to introduce pendent arms which may diverge from any bound metallic center has obvious applications in immobilizing the ligand on polymers and for application in extraction or sensing devices, as well as in attachment to biomolecules such as antibodies, where radiometal labeling may be desired.[1−4] Commonly, functionalization reduces the symmetry of the original ligand and thus raises the prospect of its complexes forming in a greater number of isomeric forms.[5] This is not necessarily disadvantageous, since it may well lead to enhanced subtlety in the range of ligand applications, but it is necessary then to fully characterize the stereochemistry of the complex ion systems that can be obtained. In seeking to explore the use of a simple hydroxyl group attached to the "exterior" of a macrocyclic complex as a useful form of functionalization, we have used a familiar template reaction[2,3,6−8] to prepare the ligand **1** (Chart 1), reduced the ligand to its amine form **2**, and prepared Co(III) complexes of this ligand. We report herein a detailed analysis of the stereochemistry of this system based upon the determination of the crystal structures of the various

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* Authors to whom correspondence should be addressed. E-mail: cages@chem.uwa.edu.au (J.M.H.);. ykim@kosin.ac.kr (Y.K.).

† University of Western Australia.

‡ Kosin University.

§ CEA/Saclay.

(1) Lindoy, L. F. *Adv. Inorg. Chem.* **1998**, *45*, 75.

(2) Bernhardt, P. V.; Lawrance, G. A. *Coord. Chem. Rev.* **1990**, *104*, 297.

(3) For recent publications concerning pendent-arm derivatives of macrocycles closely related to those presently discussed, see: (a) Bernhardt, P. V.; Hayes, E. J. *Inorg. Chem.* **2003**, *42*, 1371; *Inorg. Chem.* **2002**, *41*, 2892. (b) Bernhardt, P. V.; Moore, E. G.; Riley, M. J. *Inorg. Chem.* **2002**, *41*, 3025. (c) Comba, P.; Lampeka, Y. D.; Nazarenko, A. Y.; Prikhod'ko, A. I.; H. Pritzkow, H. *Eur. J. Inorg. Chem.* **2002**, 1464.

(4) Such applications have been particularly thoroughly explored in recent times for the group of phenolic macrocycles known as calixarenes—see, for example: *Calixarenes 2001*; Asfari, Z., Böhmer, B., Harrowfield, J. M., Vicens, J., Eds.; Kluwer Academic Press: Dordrecht, 2001.

(5) (a) Exemplification of this point may be found in: Donnelly, P. S.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2001**, 3078. (b) A more general discussion is given by: Harrowfield, J.; Wild, S. B. In *Comprehensive Coordination Chemistry*; Wilkinson, G., McCleverty, J. A., Gillard, R. D., Eds.; Pergamon Press: Oxford, 1987; Vol. 1, Chapter 5, pp 179−212.

(6) Suh, M. P. *Adv. Inorg. Chem.* **1997**, *44*, 93.

(7) See, for example: (a) Comba, P.; Curtis, N. F.; Lawrance, G. A.; Sargeson, A. M.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1986**, *25*, 4260. (b) Bernhardt, P. V.; Lawrance, G. A.; Hambley, T. W. *J. Chem. Soc., Dalton Trans.* **1989**, 1059. (c) Bernhardt, P. V.; Lawrance, G. A.; Patalinghug, W. C.; Skelton, B. W.; White, A. H.; Curtis, N. F.; Siriwardena, A. *J. Chem. Soc., Dalton Trans.* **1990**, 2853. (d) Bernhardt, P. V.; Lawrance, G. A.; Comba, P.; Martin, L. L.; Hambley, T. W. *J. Chem. Soc., Dalton Trans.* **1990**, 2859. (e) Bernhardt, P. V.; Comba, P.; Curtis, N. F.; Hambley, T. W.; Lawrance, G. A.; Maeder, M.; Siriwardena, A. *Inorg. Chem.* **1990**, *29*, 3208. (f) Bernhardt, P. V.; Jones, R. A.; Sharpe, P. *J. Chem. Soc., Dalton Trans.* **1997**, 1169.

(8) Choi, M.-H.; Kim, B.-J.; Kim, I.-C.; Kim, S.-H.; Kim, Y.; Harrowfield, J. M.; Lee, M.-K.; Mocerino, M.; Rukmini, E.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2001**, 707 and references therein.

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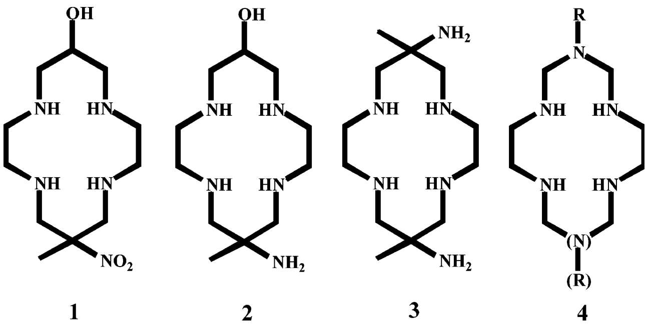
Chart 1



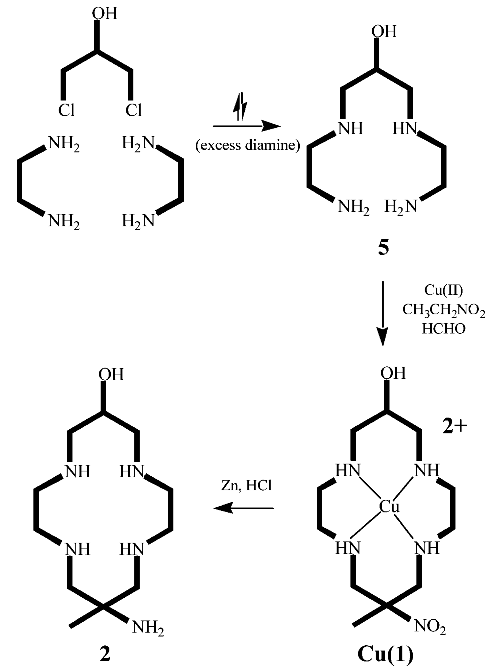
complexes involved. Ligand **2** is a close analogue of the well-studied[7] ligand “diammac”, **3**, but it was anticipated that the introduction of the two different “external” functional groups via two different reactions might give rise to a very different distribution over the diastereomeric “cis” (syn) and “trans” (anti) forms.

It is important to note that in all complexes of *trans*-diammac functionalized at the pendent amine (whether at one or both) the six-membered chelate ring to which the functional group is attached adopts a chair conformation with this substituent axial.[3b] Thus, the orientation of the pendent arm relative to the metallomacrocycle is controlled and is quite different from that obtained for macrocycles of type **4**, where the essentially planar nature of the bridging nitrogen atom directs the substituent orientation.[3a,c] The possibility of obtaining **2** in the cis configuration holds therefore the prospect of further subtlety in controlling pendent-arm orientation, though in the event, following the syntheses described herein, this diastereomer proved to be no more abundant than in the diammac system.

Results and Discussion

Ligand Synthesis. The ligand **2** was prepared (Scheme 1) from an open chain hydroxytetramine precursor, **5**, this in turn being prepared using procedures for polyamine synthesis we have previously investigated extensively,[3] though an alternative synthesis of **5** is known.[9] To further characterize the basic coordination characteristics of **5**, its Co(III) complex was prepared by a conventional procedure and crystallized, and a single-crystal, X-ray diffraction structure determination was conducted (see below), the structure of the Cu(II) complex already being available from the literature.[9] As its Cu(II) complex, **5** was reacted with nitroethane and formaldehyde to give the macrocyclic nitrotetramine, **1**, still as its Cu(II) complex, which was then reduced with Zn/HCl to give **2**, finally isolated as its hydrochloride. This material proved to be mainly the trans isomer, its separation from a small amount of cis isomer being readily accomplished through formation and chromatographic treatment of the Co(III) complexes of the mixture. Attempted fractional crystallization of the hydrochloride by addition of ethanol to its aqueous solution did not result in ready isolation of the pure trans form, despite its predominance in the mixture.

Scheme 1. Outline of the Macrocycle Synthesis



Coordination Chemistry of the Ligands. To establish a reference point to assess the behavior of the more restricted **2**, the Co(III) complex of **5** was synthesized conventionally and then crystallographically characterized. As a complex of a “232tet” type of ligand,[10] giving a green *trans*-dichlorocobalt(III) species of low solubility as its perchlorate,[11] its basic properties (e.g., visible spectrum in water: λ_{max} 623 nm, ϵ_{max} 16.4 M^{-1} cm^{-1}) are unexceptional and most aspects of the structure (Figure 1) are exactly as expected for such a familiar system. Under acidic conditions, there was no evidence for any coordination of the pendent hydroxyl group. The bound form of the ligand in its Cu(II) complex[9] is almost identical with that in the Co(III) species, both MN$_4$ arrays forming good planes, and more detailed comparisons of the two species are given in the discussion of structural results below and in Table 1.

The Cu(II) complex of ligand **1** was used as a reaction intermediate only, but its spectroscopic (e.g., visible spectrum in water: λ_{max} 524 nm, ϵ_{max} 41.0 M^{-1} cm^{-1}) and chromatographic properties seem typical[3] of the large number of such complexes of “cyclam-like” ligands now known, and it was anticipated that it would be a square-planar or tetragonally distorted octahedral species with the ligand in the *trans*-III conformation[12] and the nitro substituent in an axial orientation.[2] In fact, the crystal structure of [Cu(**1**)Cl]ClO$_4$ shows

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[9] Bernhardt, P. V.; Sharpe, P. C. *J. Chem. Soc., Dalton Trans.* **1998**, 1087.

[10] (a) Bosnich, B.; Gillard, R. D.; McKenzie, E. D.; Webb, G. A. *J. Chem. Soc. A* **1966**, 1331. (b) House, D. A. In *Comprehensive Coordination Chemistry*; Wilkinson, G., McCleverty, J. A., Gillard, R. D., Eds.; Pergamon Press: Oxford, 1987; Vol. 2, Chapter 13, p 23.

[11] See, for example: Harrowfield, J. M.; Kim, Y.; Mocerino, M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1995**, 2431 and references therein.

[12] (a) Bosnich, B.; Poon, C. K.; Tobe, M. L. *Inorg. Chem.* **1965**, *4*, 1102. (b) Donnelly, M. A.; Zimmer, M. *Inorg. Chem.* **1999**, *38*, 1650.

Table 1. Environment of the Metal Atom in Compounds 1-8: Selected Distances (Å) and Angles (deg)

$[Co(\mathbf{5})Cl_2]ClO_4$		$[Cu(\mathbf{5})(OClO_3)]ClO_4$[a]	
Co−N1	1.968(3)	Cu1(2)−N1(5)	2.011(3); 2.014(3)
Co−N2	1.971(3)	Cu1(2)−N2(6)	2.004(3); 2.019(3)
Co−N3	1.967(4)	Cu1(2)−N3(7)	2.028(3); 2.017(3)
Co−N4	1.968(3)	Cu1(2)−N4(8)	2.015(3); 2.018(3)
Co−Cl1	2.2633(12)	Cu1(2)−O4(5′)	2.596(3); 2.554(3)
Co−Cl2	2.2637(11)	Cu1(2)−O8(7)	2.604(3); 2.664(3)
N1−Co−N2	86.30(14)	N1(5)−Cu1(2)−N2(6)	85.38(14); 85.38(13)
N2−Co−N3	93.72(14)	N2(6)−Cu1(2)−N3(7)	93.30(13); 94.38(13)
N3−Co−N4	86.56(14)	N3(7)−Cu1(2)−N4(8)	84.63(14); 84.93(13)
N4−Co−N1	93.35(14)	N4(8)−Cu1(2)−N1(5)	96.71(15); 95.32(14)
Cl1−Co−Cl2	177.55(5)	O4(5′)−Cu1(2)−O8(7)	175.90(10); 165.78(10)
$[Cu(\mathbf{1})Cl]ClO_4$		$[Co(\mathbf{2}H)Cl_2]Cl_2{\cdot}2H_2O$ (**Co2A**)[a]	
Cu−N1	2.027(3)	Co1(2)−N1A(B)	1.977(4); 1.979(4)
Cu−N2	2.022(3)	Co1(2)−N2A(B)	1.973(4); 1.968(4)
Cu−N3	2.002(3)	Co1(2)−N3A(B)	1.975(4); 1.976(4)
Cu−N4	2.013(3)	Co1(2)−N4A(B)	1.981(4); 1.977(4)
Cu−Cl1	2.8445(10)	Co1(2)−Cl1(3)	2.2570(14); 2.2507(13)
N1−Cu−N2	93.98(13)	Co1(2)−Cl2(4)	2.2423(14); 2.2703(13)
N2−Cu−N3	85.75(13)	N1A(B)−Co1(2)−N2A(B)	92.88(16); 93.74(17)
N3−Cu−N4	94.06(14)	N2A(B)−Co1(2)−N3A(B)	86.06(16); 85.39(16)
N4−Cu−N1	86.21(13)	N3A(B)−Co1(2)−N4A(B)	94.35(16); 94.49(17)
		N4A(B)−Co1(2)−N1A(B)	86.70(16); 86.38(16)
		Cl1(3)−Co1(2)−Cl2(4)	179.41(6); 178.83(5)
$[Co(\mathbf{2})Cl]Cl_2{\cdot}2H_2O$ (**Co2B**)		$[Co(\mathbf{2})Cl]Cl_2{\cdot}H_2O$ (**Co2C**)	
Co−N1	1.947(2)	Co−N1	1.968(3)
Co−N2	1.955(2)	Co−N2	1.966(3)
Co−N3	1.955(2)	Co−N3	1.953(3)
Co−N4	1.963(2)	Co−N4	1.965(3)
Co−N5	1.954(2)	Co−N5	1.961(3)
Co−Cl1	2.2581(7)	Co−Cl1	2.2597(9)
N1−Co−N2	88.71(9)	N1−Co−N2	95.19(12)
N2−Co−N3	87.71(9)	N2−Co−N3	87.44(12)
N3−Co−N4	96.16(9)	N3−Co−N5	80.74(11)
N4−Co−N1	87.43(9)	N5−Co−N1	96.50(12)
N5−Co−Cl1	174.02(7)	N4−Co−Cl1	176.88(8)
$[Co(\mathbf{2}H)Cl_2]Cl_2{\cdot}H_2O$ (**Co2D**)		$[Co(\mathbf{2})Cl](ClO_4)_2$ (**Co2E**)	
Co−N1	1.973(2)	Co−N1	1.962(3)
Co−N2	1.971(2)	Co−N2	1.942(3)
Co−N3	1.973(2)	Co−N3	1.965(3)
Co−N4	1.974(2)	Co−N4	1.968(3)
Co−Cl1	2.2596(7)	Co−N5	1.958(3)
Co−Cl2	2.2499(7)	Co−Cl1	2.2492(10)
N1−Co−N2	92.79(9)	N2−Co−N3	87.14(12)
N2−Co−N3	87.04(8)	N3−Co−N4	95.17(12)
N3−Co−N4	93.84(8)	N4−Co−N5	95.81(13)
N4−Co−N1	86.32(8)	N5−Co−N2	81.74(13)
Cl1−Co−Cl2	178.50(3)	N1−Co−Cl1	173.91(9)

[a] Values for the two independent molecules. Symmetry code: $' = x, y - 1, z$.

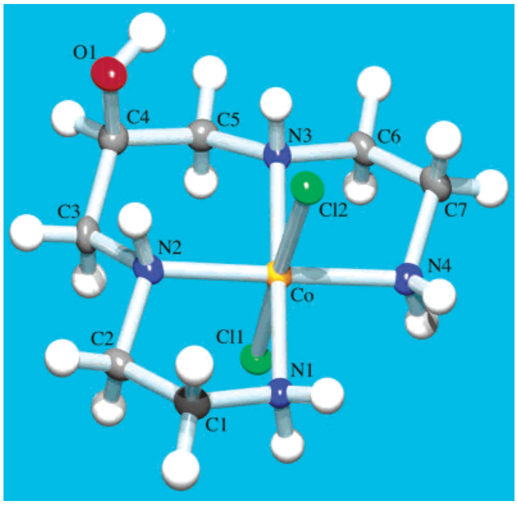

Figure 1. View of the complex $[Co(\mathbf{5})Cl_2]ClO_4$, with the perchlorate anion omitted for clarity. Displacement ellipsoids drawn at the 20% probability level.

that the coordination geometry of the copper is tetragonally distorted octahedral CuN_4Cl_2, with the ligand indeed in the *trans*-III conformation and both the nitro and hydroxyl substituents axial (viz., with respect to these substituents, the macrocycle present should be termed trans in a second sense). It is possible that, under alkaline conditions, the hydroxyl group might function as an alkoxide ligand, but this has not been investigated. In light of subsequent detection of a small amount of the cis (syn) isomer of the ligand (**2**) obtained by reduction of **1**, it seems probable that the crystallization of $[Cu(\mathbf{1})Cl]ClO_4$ for the structure determination may have resulted in fractionation out of the major macrocycle complex component.

The focus of the present work, of course, is upon the ligand **2** and the stereochemical outcomes of its coordination, and these are discussed below in relation to the results of the crystal structure determinations. The synthesis of the Co(III) complex of **2** followed the conventional method of oxidation of the Co(II) precursor complex, but because the product separation required extensive chromatographic treatment under conditions which certainly would have led to some hydrolysis of chloro ligands and perhaps to ring opening of any chelate unit involving hydroxyl group coordination, it cannot be stated that the species crystallographically characterized were all necessarily present in or simply related to those in the initial reaction mixture. More significantly, it cannot be stated that an equilibrium mixture of species was necessarily obtained, though this is essentially beside the point, since it is the orientation of the functional group in any specific complex ion that is of greatest importance. On the basis of our exhaustive chromatographic experiments, it is assumed that each of the finally isolated components was a pure species and thus that the crystal structure defines the nature of the ligand in the whole sample, though it must be noted for systems of the present type that it is possible to select crystals of different complex ion diastereomers from the one crystalline mass.[8]

Structure Determinations. The crystal structure determination for [Co(**5**)Cl$_2$]ClO$_4$ shows the anticipated *trans*-CoN$_4$Cl$_2$ array in the primary coordination sphere and the gauche-chair-gauche conformation of the bound tetramine (Figure 1). Bond lengths and bond angles are all unexceptional, with a mean Co−N bond length of 1.97 Å (Table 1). The four nitrogen donor atoms define a plane with a maximum deviation of 0.002(2) Å, the metal atom being at 0.032(2) Å from it. Such a nearly perfectly planar N$_4$-coordination environment is encountered in all the structures reported herein. The hydroxy substituent is in an axial orientation on the six-membered chelate ring, and it is involved in a hydrogen bond with the chlorine atom Cl1 of a neighboring molecule [O1−H1 0.85, H1···Cl1′ 2.39, O1···Cl1′ 3.211(3) Å, O1−H1···Cl1′ 162°; ′ = 1 + *x*, *y*, *z*]. The two secondary nitrogen donor atoms can be considered to be within hydrogen bonding distances of O1, with two possible rather weak bonds [N−H 0.95 and 0.94, H···O1 2.37 and 2.56, N···O1 2.832(5) and 2.928(4) Å, N−H···O1 109° and 104°, for N2 and N3, respectively]. This may be the factor which determines the configuration, and this conclusion is supported by molecular modeling at the MM2 level[13] of protonated 1,3-diazacyclohexan-5-ol which indicates that the axial orientation of the hydroxyl substituent is preferred by strong charge-dipole attractions.

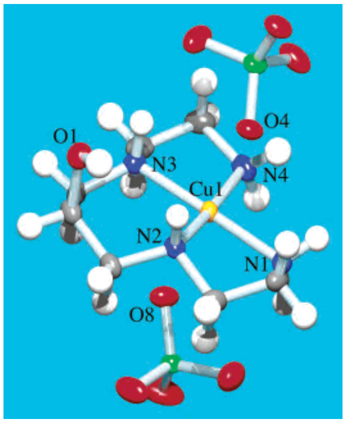

Figure 2. View of one of the two independent molecules in the complex [Cu(**5**)(OClO$_3$)]ClO$_4$, with bonds to perchlorate donors O4 and O8 omitted for clarity. Displacement ellipsoids drawn at the 20% probability level.

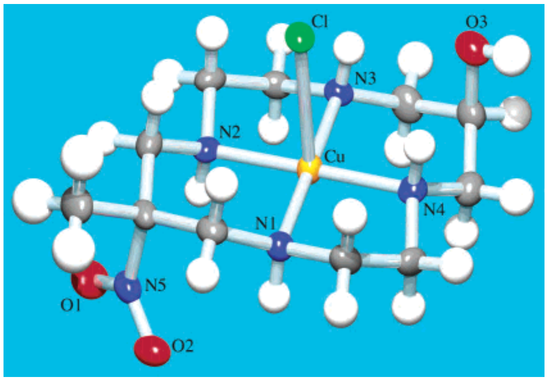

Figure 3. View of the complex [Cu(**1**)Cl]ClO$_4$. Nonbonded perchlorate ion omitted for clarity. Displacement ellipsoids drawn at the 20% probability level.

Further evidence that the axial orientation of the hydroxyl substituent is the thermodynamically preferred form is provided by the fact that the structure of the Cu(II) complex of **5**, as [Cu(**5**)(OClO$_3$)]ClO$_4$, shows an almost identical ligand conformation (both in the present redetermination, at 100 rather than 293 K, and in the original[9] structure). Cu(II)−donor atom bond lengths are generally slightly longer than their Co(III) equivalents, with a mean Cu−N bond length of 2.02 Å. Two weak bonds are also formed with two perchlorate oxygen atoms, and the Cu environment (Figure 2) may be considered as tetragonally distorted N$_4$O$_2$ rather than as (tetragonally distorted) N$_4$Cl$_2$ as in the Co(III) species, but the ligand conformation is again gauche-chair-gauche. Due to the bridging nature of the bound perchlorate ions (through two different oxygen atoms), polymeric chains parallel to the *b*-axis are formed. The axial hydroxyl substituent of the first molecule is involved in a bifurcated hydrogen bond with two perchlorate oxygen atoms O$_p$ [O1−H1 1.01, H···O$_p$ 1.97 and 1.92, O1···O$_p$ 2.863(5) and 2.886(9) Å, O1−H1···O$_p$ 147° and 160°], whereas the hydroxyl group of the second molecule is involved in hydrogen bonding with that of the first [O2−H2 0.90, H···O1 2.00, O2···O1 2.863(4) Å, O2−H2···O1 160°]. An axial hydroxyl group is also found in [Cu(**1**)Cl]ClO$_4$ (Figure 3), though here it is uncertain as to what extent this may be influenced by the axial disposition of the pendent nitro group. Though this in turn may be a consequence of coordination of the nitro group to an axial Cu coordination site during the synthesis,[2,7] it is apparent in the present structure that both the hydroxyl and nitro groups, because of their axial positioning, can be hydrogen bond acceptors with respect to adjacent NH centers [N1···O1 3.111(5) Å, N1−H1···O1 113°; N2···O2 2.976(4) Å, N2−H2···O2 118°; N3···O3 2.833(5) Å, N3−H3···O3 102°; N4···O3 2.796(5) Å, N4−H4···O1 109°]. Thus, there is probably a cooperative confluence of effects arising from the combination of the *trans*-III ligand conformation, the trans arrangement of the OH and NO$_2$ substituents, and the axial disposition of both. The axial hydroxyl group is once more involved in a hydrogen bond with the perchlorate oxygen atom O4 [O3−H3 0.91, H3···O4 2.10, O3···O4 3.005(5) Å, O3−H3···O4 169°]. The chloride ligand bridges copper/macrocycle units

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(13) As implemented in Chem3D, Version 4.0, 1997, CambridgeSoft Corporation.

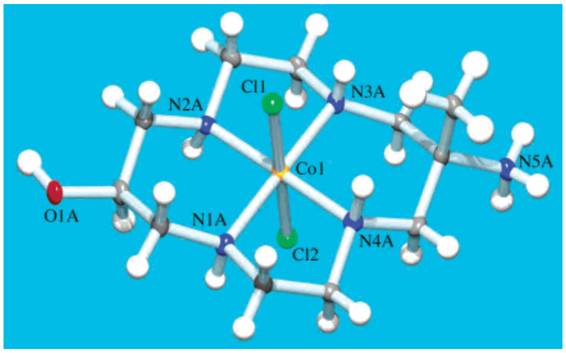

Figure 4. View of one of the two independent molecules in the complex [Co(**2**H)Cl$_2$]Cl$_2$·2H$_2$O (**Co2A**). Nonbonded chlorine ions and water molecules omitted for clarity. Displacement ellipsoids drawn at the 20% probability level.

into polymeric chains, giving the Cu(II) a tetragonally distorted N$_4$Cl$_2$ coordination environment.

The ligand "*trans*-diammac", **3**, is known to form Co(III) complexes in which it is quadridentate, quinquedentate, and sexidentate,[7,14] suggesting **2** might well form both quadri- and quinquedentate species, and possibly sexidentate, especially if the hydroxyl group could be bound in its alkoxide form. Given that all complexes were isolated under acidic conditions, however, it is perhaps unsurprising that the ligand has been observed only in either quadri- or quinquedentate forms. Thus, the species eluted first in the chromatographic separation of the products of the complexation reaction, [Co(**2**H)Cl$_2$]Cl$_2$·2H$_2$O (**Co2A**), provided a complex containing a *trans*-CoN$_4$Cl$_2$ chromophore and with the trans form of **2** bound in the cyclam *trans*-III form, with both the ammonium and hydroxyl pendent groups in equatorial dispositions (one of the two independent molecules of **Co2A** is represented in Figure 4). Since the protonated amine pendent group obviously cannot act as a hydrogen bond acceptor and presumably would in fact experience some repulsion by the coordinated amine nitrogen atoms, the initial formation of a Co(II) complex by a partly protonated form of the macrocycle may involve the pendent amine adopting an equatorial disposition, so that, assuming the Co(II) form to have the *trans*-III overall form, this would require the hydroxyl group to also adopt an equatorial position. This may explain the observed form of the final Co(III) complex. The hydroxyl groups of both molecules are involved in hydrogen bonds with water molecules, whereas the ammonium groups behave as hydrogen bond donors to hydroxyl groups of neighboring molecules, water molecules, and chlorine atoms.

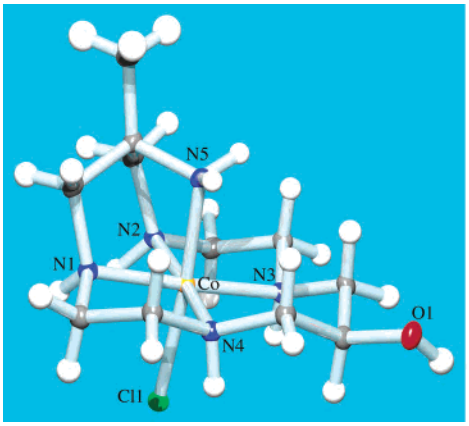

Figure 5. View of the complex [Co(**2**)Cl]Cl$_2$·2H$_2$O (**Co2B**). Nonbonded chlorine ions and water molecules omitted for clarity. Displacement ellipsoids drawn at the 30% probability level.

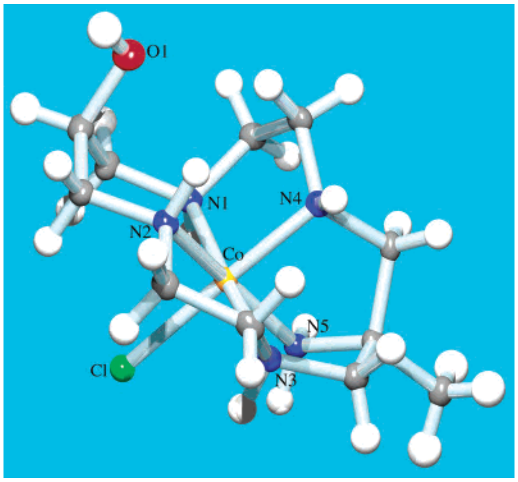

Figure 6. View of the complex [Co(**2**)Cl]Cl$_2$·H$_2$O (**Co2C**). Nonbonded chlorine ions and water molecule omitted for clarity. Displacement ellipsoids drawn at the 30% probability level.

The second species chromatographically isolated, [Co(**2**)Cl]Cl$_2$·2H$_2$O (**Co2B**), differs very considerably from the first in that it contains the cis form of **2** and the ligand in a quinquedentate form (Figure 5). However, the complex ion retains a pseudosymmetry plane, with the primary (pendent) amino group trans in the coordination sphere to Cl1, and the hydroxyl its equatorial orientation, the latter presumably resulting because intramolecular hydrogen bonding could only occur (given that the pendent amine nitrogen remains coordinated) if the hydroxyl group were to be axial in a boat form of the chelate ring to which it is attached. In the crystal, the hydroxyl group is hydrogen bonded to a water molecule [O1−H1 0.86, H1···Ow 1.90, O1···Ow 2.744(3) Å, O1−H1···Ow 165°]. **Co2B** is the only species isolated in which the cis form of ligand **2** is present and it constitutes only ~6% of the total product, indicating that **2** is very like "diammac"[7] in being predominantly of the trans form.

The third species isolated from the chromatographic treatment, [Co(**2**)Cl]Cl$_2$·H$_2$O (**Co2C**) (one of the two principal components of the product mixture), proved also to be a complex of **2** in a quinquedentate form but here of the trans form of **2**, with a Cl ligand trans in the Co coordination sphere to a secondary N-donor of the macrocyclic ring and the hydroxyl group axial on its chair chelate ring (Figure 6). The four nitrogen atoms N1, N2, N3, and N5 define a plane with a maximum deviation of 0.007(2) Å, with the metal atom displaced by 0.047(1) Å, on the same side as Cl1. In the crystal, the hydroxyl group is involved in a hydrogen bond with a chloride ion and it can only accept hydrogen bond donation from the adjacent "planar" N2 of its own macrocycle unit, with albeit a far from perfect

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(14) Bernhardt, P. V.; Lawrance, G. A.; Natitupulu, M.; Wei, G. *Inorg. Chim. Acta* **2000**, *300*−*302*, 604.

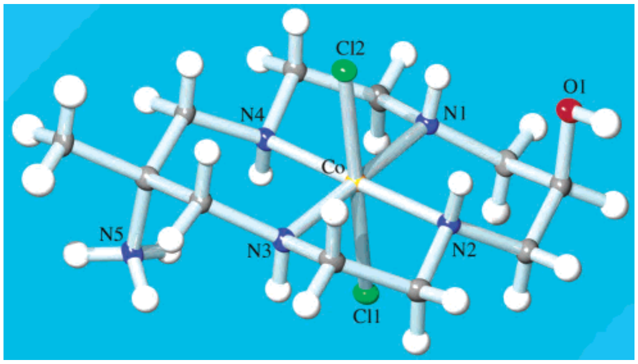

Figure 7. View of the complex [Co(**2**H)Cl_2]Cl_2·H_2O (**Co2D**). Nonbonded chlorine ions and water molecule omitted for clarity. Displacement ellipsoids drawn at the 30% probability level.

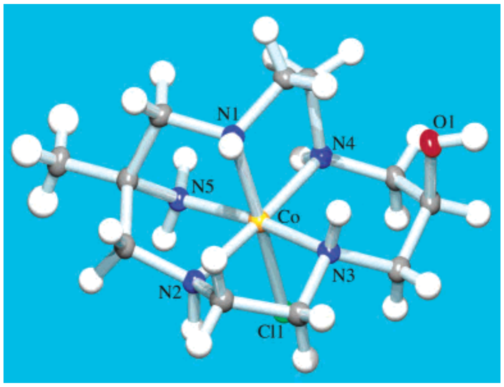

Figure 8. View of the complex [Co(**2**)Cl]$(ClO_4)_2$ (**Co2E**). Nonbonded perchlorate ions omitted for clarity. Displacement ellipsoids drawn at the 10% probability level.

geometry [N2−H2 0.97, H2···O1 2.58, N2···O1 2.922(4) Å, N2−H2···O1 101°].

The next species isolated, [Co(**2**H)Cl_2]Cl_2·H_2O (**Co2D**), a component of similar abundance to **Co2C**, contains the trans macrocycle in its quadridentate form bound through just the secondary N-donor atoms, and it is in fact the inverted, diaxial isomer of **Co2A** (Figure 7). Once again, intermolecular hydrogen bonding to both pendent groups is apparent in the solid state, since the hydroxyl and ammonium groups are hydrogen bonded to two and three chloride ions, respectively, whereas the former accepts also hydrogen bond donation from a water molecule. The observed configuration might arise if the Co(II) precursor binds the ligand in a quinquedentate manner through all five N-donors (or four plus the hydroxyl) but coordination to the pendent group is lost during the conversion to the Co(III) complex.

The final species to be isolated in a significant amount, [Co(**2**)Cl]$(ClO_4)_2$ (**Co2E**), proved, aside from its crystallization as a perchlorate rather than as a chloride, to be identical with **Co2C**, containing the trans ligand in a quinquedentate form with the pendent amino group cis in the Co coordination sphere to Cl and the hydroxyl group axially disposed (Figure 8). Presumably, the initial chromatographic separation may have involved chloro and aqua species derivative of the same CoN_5 unit. The hydroxyl group is hydrogen bonded to a chloride ion and is also possibly linked to the nearer "planar" nitrogen atom, N3.

Conclusions

Although it seems that synthesis of the ligand **2** presently developed does not lead an efficient synthesis of the cis isomer, the different modes of coordination to Co(III) observed for the trans isomer do involve different orientations of the hydroxyl substituent. Thus, the objective of controlling the orientation of sophisticated substituents about a metallomacrocycle species should be realizable in this system provided appropriate functionality can be attached to the pendent hydroxyl group. It would be expected, of course, that the reactivity of such a nucleophile would be reduced due to its proximity to the metal ion center,[15] but preliminary experiments have indicated that the pendent groups in coordinated **2** can at least be acylated. It is hoped that this might ultimately give rise to a greater variety of pendent-arm systems than the alternative procedure of conducting the template synthesis of the macrocycle with functionalized nitroethanes.[16]

Experimental Section

Synthesis. The synthesis and purification of the hydroxytetramine **5** followed procedures we have used for a variety of related compounds.[8] Separation and purification of the various metal complexes also employed cation-exchange chromatographic methods we have described in detail previously.[8] The ion-exchange resins used were analytical grade 200−400 mesh Dowex 50W-X2 and SP Sephadex C-25, initially provided as the H^+ and Na^+ forms, respectively.

(a) 1,3-Bis(2-aminoethylamino)propan-2-ol, 5, Isolated as Its Complex with Cu(ClO_4)$_2$. 1,3-Dichloro-2-propanol (1.0 g, 7.8 mmol) was added dropwise, with stirring, over 30 min to ethane-1,2-diamine (2.4 g, 39 mmol), and the mixture was then heated at 90 °C for 72 h under a nitrogen atmosphere. Excess diamine was evaporated off under reduced pressure, and NaOH (0.62 g in 100 mL of methanol) was added to the yellowish oil remaining. The methanol and some remaining diamine were again evaporated off under reduced pressure. The residue was dissolved in a solution of $CuCl_2$·$2H_2O$ (1.4 g) in methanol (100 mL) and the methanol then evaporated off. The deep blue product mixture was dissolved in water and subjected to cation-exchange chromatography on a column of SP Sephadex C-25 (7 cm × 120 cm), using 0.3 mol L^{-1} NaCl solution as eluant to give two blue bands. The separate eluates were evaporated to dryness and the residues were triturated with methanol to dissolve out the complexes from excess NaCl. After filtration, the extracts were taken to dryness to give F1, 1.1 g, and F2, 0.24 g. A portion of F1 was dissolved in water and the complex [Cu(**5**)($OClO_3$)]ClO_4, subsequently characterized by a structure determination, precipitated by the addition of $NaClO_4$. The bulk of F1 was treated with HCl to enable isolation of **5** as its hydrochloride (see below). F2 was not further characterized except by measurement of the ^{13}C NMR spectrum of the ligand after displacement from Cu(II) with HCl, this spectrum (six resonances) indicating that it was a hexamine species similar to those obtained as minor products in related systems.[8]

(b) [Co(5)Cl_2]ClO_4. [Cu(**5**)]$(ClO_4)_2$ (0.88 g, 2 mmol) was dissolved in water (10 mL) and 3 mol L^{-1} HCl (10 mL) added to

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(16) Amadei, G. A.; Dickman, M. H.; Wazzeh, R. A.; Dimmock, P.; Earley, J. P. *Inorg. Chim. Acta* **1999**, *288*, 40.

cause breakdown of the complex. The resulting pale blue solution was absorbed on a column of Dowex 50W-X2 (3 cm × 5 cm). The column was washed with water and then eluted with 0.5 mol L^{-1} HCl to remove Cu(II) and subsequently with 3 mol L^{-1} HCl to remove the protonated ligand. This final eluate was evaporated to dryness under reduced pressure, and the residue was dissolved in methanol (50 mL) and neutralized with NaOH (0.32 g). $CoCl_2 \cdot 6H_2O$ (0.50 g) was added and the solution was aerated for 1 h, then evaporated to dryness under reduced pressure. Chromatography (SP Sephadex C-25/0.3 mol L^{-1} NaCl) revealed a single green component, which was recovered as the perchlorate by reducing the eluate volume to 5 mL and then adding $NaClO_4$. Yield, 0.60 g. Anal. Calcd for $C_7H_{20}Cl_3CoN_4O_5$ C, 20.73; H, 4.97; N, 13.82. Found C, 21.0; H, 5.1; N, 13.5%.

(c) [Cu(13-Methyl-13-nitro-1,4,8,11-tetraazacyclotetradecan-6-ol)Cl]ClO$_4$, [Cu(1)Cl]ClO$_4$. A solution of [Cu(**5**)]Cl_2 (2.0 g) in methanol (100 mL) was mixed with formaldehyde (37%, 9 mL), nitroethane (0.8 g), and triethylamine (1.3 g) and then heated at 60 °C for 12 h. After cooling the mixture to room temperature, reaction was quenched by the addition of acetic acid (2 mL) and the red-violet solution evaporated to dryness. The residue was dissolved as completely as possible in water (2 L), some insoluble material filtered out, and the solution absorbed on a column of SP Sephadex C-25 (3 cm × 50 cm). The column was washed with water (200 mL) and then eluted with 0.3 M NaCl to give a single red-violet band. The eluate was absorbed onto a column of Dowex 50W-X2, Na^+ removed by elution with 0.5 mol L^{-1} HCl (500 mL), and the complex then eluted with 2.0 mol L^{-1} HCl. The eluate was evaporated to dryness under reduced pressure. Yield, 1.6 g. Anal. Calcd for [Cu(**1**)]$Cl_2 \cdot 3H_2O$ = $C_{11}H_{25}Cl_2CuN_5O_7$ C, 27.89; H, 5.32; N, 14.78. Found C, 27.6; H, 5.8; N, 14.8%. This chloride salt was converted to the chloride−perchlorate by dissolution in water (5 mL) and addition of $NaClO_4$ to give a crystalline precipitate (suitable for structure determination). Anal. Calcd for [Cu(**1**)Cl]-ClO_4 = $C_{11}H_{25}Cl_2CuN_5O_7$ C, 27.88; N, 14.78. Found C, 28.7; N, 15.0%.

(d) Co(III) Complexes of 13-Amino-13-methyl-1,4,8,11-tetraazacyclotetradecan-6-ol, 2. [Cu(**1**)]Cl_2 (4.7 g) was dissolved in 3 mol L^{-1} HCl (100 mL) and Zn powder (10 g) added with stirring. The color of solution rapidly changed from red to colorless. After continuing stirring for 3 h, unreacted Zn powder was filtered off; the filtrate was diluted to 2 L with water and absorbed onto a column of Dowex 50W-X2 resin. This was washed with water (200 mL) and Zn(II) eluted with 0.5 mol L^{-1} HCl (1 L) before the protonated ligand was eluted with 4 mol L^{-1} HCl. The eluate was evaporated to dryness under reduced pressure to give a white powder, **2**·*n*HCl. Yield, 2.6 g. Significantly, the 500 MHz ^{1}H NMR spectrum, D_2O solvent, though exceedingly complicated in the methylene region, showed two methyl resonances at δ 1.390 (major) and 1.396 (minor), consistent with the presence of both cis and trans diastereomers of the ligand. Crude **2**·*n*HCl (2.0 g) was suspended in methanol (200 mL) and NaOH (1.0 g) added with stirring. $CoCl_2 \cdot 6H_2O$ (1.3 g) in methanol (100 mL) was added and the mixture aerated for 2 h before 2 mol L^{-1} HCl (50 mL) was added. The solvent was removed under reduced pressure, and the residue was dissolved in water (500 mL). Chromatography on Dowex 50W-X2 using 2 mol L^{-1} HCl as eluant produced five components, F1 (green), F2 (red), F3 (red), F4 (green), and F5 (orange). (Some band broadening which occurred during development was attributed to the effects of chloro-ligand aquation, since residues obtained by evaporating fractions from a given band gave identical spectra.) Each eluate was taken to dryness under vacuum, and the residue obtained crystallized from the minimum volume of water by addition of ethanol. The quantities thereby obtained were the following: F1, 100 mg; F2, 80 mg; F3, 500 mg; F4, 490 mg; F5, 150 mg. Anal. (for the species used as chlorides, after recrystallization) Calcd for $C_{11}H_{28}Cl_4CoN_5O \cdot 2H_2O$ (F1) C, 27.35; H, 6.68; N, 14.49. Found C, 27.2; H, 6.4; N, 15.0%. Calcd for $C_{11}H_{27}Cl_3CoN_5O \cdot 2H_2O$ (F2) C, 29.58; N, 15.68 (for $C_{11}H_{27}Cl_3CoN_5O \cdot 2.5H_2O$ C, 28.99; N, 15.43). Found C, 29.0; N, 14.8%. Calcd for $C_{11}H_{27}Cl_3CoN_5O \cdot H_2O$ (F3) C, 30.82; N 16.34. Found C, 30.8; N, 15.9%. Calcd for $C_{11}H_{30}Cl_4CoN_5O_2$ (F4) C, 28.41; N, 15.06. Found C, 28.1; N. 14.4%. The complex in F5 was analyzed after conversion to the perchlorate: Calcd for $C_{11}H_{27}Cl_3CoN_5O_9 \cdot 0.5H_2O$ C, 24.12; N, 12.79. Found C, 24.1; N, 12.0%.

To obtain crystals suitable for diffraction measurements, the complexes [Co(**5**)Cl_2]$^+$, [Cu(**5**)]$^{2+}$, and [**Co2E**]$^{2+}$, initially as chlorides, were precipitated as the corresponding perchlorates from aqueous solutions by the addition of $NaClO_4$. In all other cases, satisfactory crystals of the chloride salts were obtained by the vapor diffusion of ethanol into aqueous solutions of the chromatographic fraction residues. The compositions defined in the structure solutions were [Co(**5**)Cl_2]ClO_4, [Cu(**5**)($OClO_3$)]ClO_4, [Cu(**1**)Cl]ClO_4, [Co(**2**H)Cl_2]$Cl_2 \cdot 2H_2O$ (**Co2A**), [Co(**2**)Cl]$Cl_2 \cdot 2H_2O$ (**Co2B**), [Co(**2**)Cl]$Cl_2 \cdot H_2O$ (**Co2C**), [Co(**2**H)Cl_2]$Cl_2 \cdot H_2O$ (**Co2D**), and [Co(**2**)Cl](ClO_4)$_2$ (**Co2E**).

Crystallography. Data for all compounds were collected on a Nonius Kappa-CCD area detector diffractometer[17] using graphite-monochromated Mo Kα radiation (λ 0.710 73 Å). The crystals were introduced in glass capillaries with a protecting "Paratone-N" oil (Hampton Research) coating. The unit cell parameters were determined from 10 frames and then refined on all data. A 180° φ-range was scanned with 2° steps during data collection, with a crystal-to-detector distance fixed at 28 mm. The data were processed with DENZO-SMN.[18] The structures were solved by direct methods with SHELXS-97[19] and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXL-97.[19] Absorption effects were corrected empirically with the program DELABS from PLATON.[20] In [Cu(**5**)($OClO_3$)]ClO_4, three oxygen atoms of one perchlorate ion were found disordered over two positions which were refined with occupancy factors constrained to sum to unity and some restraints on bond lengths and displacement parameters. All non-hydrogen atoms were refined with anisotropic displacement parameters, except the disordered ones when present. Hydrogen atoms bound to oxygen and nitrogen atoms were found on Fourier-difference maps, and all the other hydrogen atoms were introduced at calculated positions. All protons were treated as riding atoms with a displacement parameter equal to 1.2 (OH, NH_n, CH, CH_2) or 1.5 (CH_3) times that of the parent atom. Compounds [Co(**2**H)Cl_2]$Cl_2 \cdot 2H_2O$ and [Co(**2**)Cl]$Cl_2 \cdot H_2O$ crystallize in chiral space groups, with Flack parameters[21] refined to values of −0.019(16) and 0.383(17), respectively, indicating correct determination of the direction of the polar axis in the first case and the presence of racemic twinning in the second. The compound [Co(**5**)Cl_2]ClO_4 also crystallizes in a polar space group, with the Flack parameter value (0.024(19)) again indicating correct choice of the axis. Crystal data and structure refinement parameters are given in Table 2. The molecular plots were drawn using the POVRay

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Table 2. Crystal Structure and Refinement Details

	[Co(**5**)Cl$_2$]ClO$_4$	[Cu(**5**)(OClO$_3$)]ClO$_4$	[Cu(**1**)Cl]ClO$_4$	[Co(**2**H)Cl$_2$]Cl$_2$·2H$_2$O (**Co2A**)
chemical formula	$C_7H_{20}Cl_3CoN_4O_5$	$C_7H_{20}Cl_2CuN_4O_9$	$C_{11}H_{25}Cl_2CuN_5O_7$	$C_{11}H_{32}Cl_4CoN_5O_3$
M/g mol^{-1}	405.55	438.71	473.80	483.15
space group	Pn (No. 7)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1$ (No. 4)
a/Å	6.4187(4)	15.1051(6)	10.3444(8)	11.0797(5)
b/Å	11.2814(12)	13.7762(6)	16.5635(13)	10.5669(5)
c/Å	10.2144(9)	15.4565(4)	11.3634(7)	18.1390(7)
β/deg	101.998(6)	103.066(2)	105.720(4)	107.301(3)
V/Å^3	723.49(11)	3133.1(2)	1874.2(2)	2027.59(15)
Z	2	8	4	4
D_{calcd}/g cm^{-3}	1.862	1.860	1.679	1.583
μ (Mo Kα)/mm^{-1}	1.763	1.787	1.495	1.394
crystal size/mm	0.18 × 0.10 × 0.05	0.30 × 0.18 × 0.15	0.35 × 0.08 × 0.03	0.32 × 0.30 × 0.12
λ/Å	0.71073	0.71073	0.71073	0.71073
T/K	100(2)	100(2)	100(2)	100(2)
$R_1{}^a$	0.031	0.041	0.047	0.041
$wR_2{}^b$	0.071	0.092	0.096	0.095

	[Co(**2**)Cl]Cl$_2$·2H$_2$O (**Co2B**)	[Co(**2**)Cl]Cl$_2$·H$_2$O (**Co2C**)	[Co(**2**H)Cl$_2$]Cl$_2$·H$_2$O (**Co2D**)	[Co(**2**)Cl](ClO$_4$)$_2$ (**Co2E**)
chemical formula	$C_{11}H_{31}Cl_3CoN_5O_3$	$C_{11}H_{29}Cl_3CoN_5O_2$	$C_{11}H_{30}Cl_4CoN_5O_2$	$C_{11}H_{27}Cl_3CoN_5O_9$
M/g mol^{-1}	446.69	428.67	465.13	538.66
space group	$P2_1/c$ (No.14)	$P2_12_12_1$ (No. 19)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a/Å	12.7995(6)	8.9797(5)	7.8667(3)	9.1093(5)
b/Å	9.6639(4)	12.4108(4)	15.5972(4)	19.3619(8)
c/Å	15.9984(8)	15.5528(9)	15.3810(6)	11.8689(7)
β/deg	106.256(3)	90	97.962(2)	103.985(3)
V/Å^3	1899.78(15)	1733.29(15)	1869.03(11)	2031.31(18)
Z	4	4	4	4
D_{calcd}/g cm^{-3}	1.562	1.643	1.653	1.761
μ (Mo Kα)/mm^{-1}	1.344	1.466	1.505	1.295
λ/Å	0.71073	0.71073	0.71073	0.71073
T/K	100(2)	100(2)	110(2)	100(2)
$R_1{}^a$	0.033	0.032	0.031	0.039
$wR_2{}^b$	0.070	0.071	0.073	0.092

[a] $R_1 = \sum||F_o| - |F_c||/|F_o|$ ("observed" reflections). [b] $wR_2 = [\sum w(|F_o{}^2| - |F_c{}^2|)^2/\sum w|F_o{}^2|^2]^{1/2}$ ("observed" reflections).

option within XTAL 3.7,[22] with displacement ellipsoids at the 20% probability level. All calculations were performed on a Silicon Graphics workstation.

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Supporting Information Available: Crystallographic summary data in the form of CIF files. Additional figures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. CIF files have deposition numbers with the CCDC 208366−208373.

IC034912O

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