Inorganic Chemistry

Article

Functionalized Macrocycles from Functionalized Tetra-Amines: Pendent-Arm Macrocycles Derived from Dichloropivalic Acid

Paul V. Bernhardt,[†] Jack M. Harrowfield,*,[‡] Yang Kim,*,[§] George A. Koutsantonis,[‡] Young Hoon Lee,[§] and Pierre Thuéry[||]

Department of Chemistry, University of Queensland, Brisbane, Qld 4072, Australia, 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 (CNRS URA 331), Bâtiment 125, 91191, Gif-sur-Yvette, France

Reaction between ethane-1,2-diamine and 3,3′-dichloropivalic acid results in different, isomeric tetra-amine derivatives, one a tetraamino carboxylic acid and the other a carboxamidotriamino alcohol, depending upon reaction conditions. Intended conversion of the Cu(II) complex of the former to a cyclam-like macrocycle through reaction with nitroethane and formaldehyde results in isolation of derivatives of both the former and the latter. This can be rationalized by assuming the intermediacy of an azetidinone, a species similar to that seen in simpler reactions of dichloropivalates. A single reaction thereby provides pendent-arm macrocycles where one has an electrophilic and the other a nucleophilic substituent. Parallel chemistry is not seen in the reaction between propane-1,3-diamine and 3,3′-dichloropivalate.

Introduction

Reactions between diamines and polyalkylating agents are a convenient method for the production of a variety of polyamines, useful in turn for the synthesis of both macromonocyclic and macrobicyclic derivatives.[1,2] While our interests have been largely focused on the use of such compounds as metal complexants, polyamines also have obvious potential as bioactive materials,[3] especially given that many are readily obtained in chiral forms.[1,4] A compli-

cation in the synthesis of polyamines from polyalkylating species can be the occurrence of a temperature-dependent competition between inter- and intramolecular reaction pathways, though isolable reaction intermediates can provide reagents useful in adding further variety to the possible range of ultimate products.[2] In exploring the use of polyalkylating species suitable for the generation of pendent-arm macrocycles, we have found that dichloropivalic acid (2,2-bis-(chloromethyl)propanoic acid) reacts with ethane-1,2-diamine to give two different tetra-amines (**2** and **3**, Figure 1), both possibly formed via the intermediacy of the azetidinone **1**, depending upon the reaction time and temperature. These tetra-amines can subsequently be employed in metal template reactions to generate macrocycles with either nucleophilic (CH$_2$OH) or electrophilic (CO$_2$H) pendent functional groups, in certain instances at chiral centers, though it transpires that rearrangement occurring in accompaniment with macrocyclization actually renders preliminary separation of the tetra-amines irrelevant. Because of the constitutional and stereochemical complexities of these systems[5] and the isolation of numerous species ligated to paramagnetic Cu(II) centers, we have focused strongly on their characterization through

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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 Queensland.

‡ University of Western Australia.

§ Kosin University.

|| CEA/Saclay.

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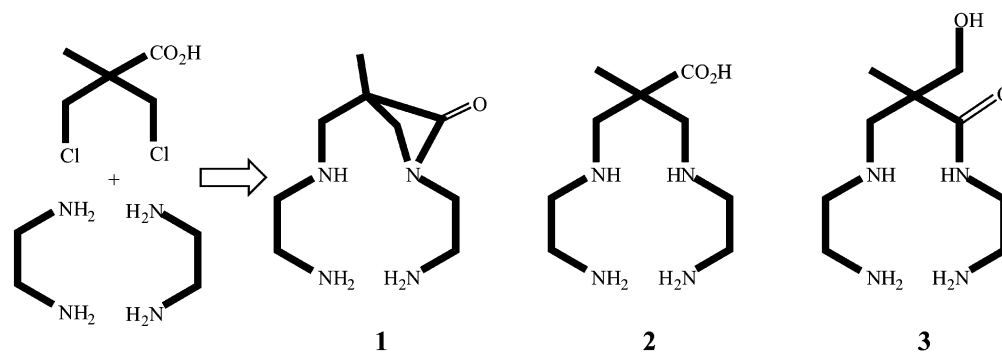
Figure 1. Possible N$_4$-donor ligands from the reaction between ethane-1,2-diamine and dichloropivalic acid.

Chart 1
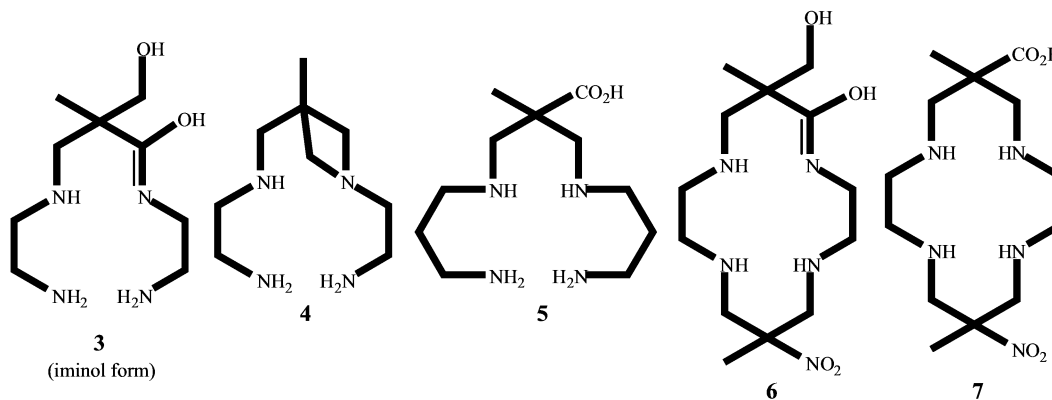
single-crystal, X-ray structure determinations. A structure determination has also been performed on the Cu(II) complex of **4**, the simple azetidine analogue of **1**, in order to obtain some indication of the distortions of the coordination sphere that may result from the formation of a four-membered ring as in the presumed azetidinone intermediate.

Experimental Section

Reagents. 3,3′-Dichloropivalic acid (2,2-bis(chloromethyl)pro-panoic acid), ethane-1,2-diamine, and propane-1,3-diamine were purchased from Aldrich Chemical Co. and used as received. The quadridentate azetidine, **4**, derived from reaction between 1,1,1-tris(benzenesulfonyloxy)ethane and ethane-1,2-diamine, was available from earlier work[2a] in the form of its Co(III) complex, [Co(**4**)Cl$_2$]ClO$_4$. Structures of the ligands (in addition to **2**) characterized in the present work are shown in Chart 1.

Syntheses. (a) Reaction of 3,3′-Dichloropivalic acid with Ethane-1,2-diamine. (i) "Low-Temperature" Method Giving 3,7-Diaza-5-hydroxycarbonyl-5-methylnonane-1,9-diamine, 2, Isolated (Deprotonated) as Its Cu(II) Complex. Ethane-1,2-diamine (9.0 g) was cooled to ~0 °C in an ice/salt bath while 3,3′-dichloropivalic acid (5.0 g) was added slowly. The resultant mixture was then heated at 90 °C under N$_2$ for 12 h. (An alternative procedure allowing more certain temperature control was to conduct this step of the reaction at reflux in acetonitrile solvent.) Most of the excess diamine was removed by distillation in vacuo before NaOH (3.5 g) in methanol (100 mL) was added and distillation continued until further evolution of ethane-1,2-diamine was not apparent. CuCl$_2$·2H$_2$O (5.0 g) in methanol (200 mL) was added to the viscous residual liquid to give a violet solution, which was then evaporated to dryness. The solid residue was dissolved in H$_2$O (1 L) and chromatographed with 0.3 M NaCl on SP Sephadex C-25 to give two blue bands. Their separate eluates were evaporated to

dryness and the complexes extracted into methanol (leaving NaCl as an insoluble residue). Evaporation of these extracts gave F1, 3.8 g, and F2, 3.1 g. By precipitating Cu(II) with sulfide and subsequently determining the ^{1}H NMR spectrum of the released ligand, F2 was shown to be a complex of ethane-1,2-diamine and was discarded. F1 was dissolved in ethanol, NaClO$_4$ added, and gaseous diffusion of diethyl ether used to provide crystals of the complex (precipitated along with some NaClO$_4$) suitable for X-ray measurements, the structure solution providing the formulation Na$_2$[Cu(**2**H$_{-1}$)](ClO$_4$)$_3$·1.5H$_2$O for the solid phase obtained. The bulk complex was recrystallized from water to obtain material free of additional sodium salts. Anal. Calcd for C$_9$H$_{24}$Cl$_3$CuN$_4$Na$_2$O$_{15.5}$ C, 16.57; H, 3.71; N, 8.59. Found C, 16.6; H, 3.5; N, 8.3%. Note that a considerable quantity of green material remained on the column after the elution of F1 and F2, and this remained adherent even with eluate concentrations up to 1 mol L^{-1} NaCl.

(ii) "High-Temperature" Method Giving 3,7-Diaza-5-hy-droxymethyl-5-methyl-6-oxononane-1,9-diamine, 3, Isolated (Deprotonated) as Its Cu(II) Complex. A mixture of 3,3′-dichlo-ropivalic acid (3 g) and ethane-1,2-diamine (5.3 g) was prepared as above and then heated at reflux (~120 °C) for 24 h, again under N$_2$. Chromatography (SP Sephadex/0.3 mol L^{-1} NaCl) of the product complexes formed from CuCl$_2$·2H$_2$O (3 g) again resulted in the separation of two blue-violet species with the trailing component being a simple ethane-1,2-diamine complex. A considerable amount of yellowish material (containing no Cu) was flushed with water from the column prior to the elution of the two complex components. Crystals of the complex present in the first component were also obtained as above, the structure solution here providing the formulation [{Cu(**3**H$_{-1}$)}$_2$Cl]ClO$_4$·H$_2$O = C$_{18}$H$_{44}$Cl$_2$Cu$_2$N$_8$O$_9$.

(b) Cobalt(III) Complexes of 2. Crude [Cu(**2**)]Cl$_2$ (3.2 g) was dissolved in 1 mol L^{-1} HCl (100 mL), the pale blue color of the resultant solution indicating that ligand release was rapid, and the

solution was absorbed onto a column of H$^+$ form Dowex 50W-X2. Cu(II) was eluted with 0.5 mol L^{-1} HCl before the ligand was eluted with 3 mol L^{-1} HCl. The ligand eluate was evaporated to dryness, and the residue (3.0 g) was neutralized and dissolved in methanol (100 mL) containing NaOH (1.7 g). CoCl$_2$·6H$_2$O (2.0 g) was dissolved in this solution, which was then aerated for 3 h. Ten milliliters of 2 mol L^{-1} HCl was added to ensure conversion of any remaining peroxo dimer species to monomers, and the solution evaporated to dryness. The residue was dissolved in water and chromatographed on Dowex 50W-X2 with 2 mol L^{-1} HCl as eluant. Two major bands, the first red in color and the second green, were observed (along with three trace components which were not further characterized). Their eluates were evaporated to dryness, and the residues crystallized from water by addition of ethanol to give F1, 0.16 g, and F2, 1.1 g, crystals of the latter being suitable for structure determination. Anal. Calcd for C$_9$H$_{21}$Cl$_2$CoN$_4$O$_2$ (F1) C, 31.14; N, 16.14. Found C, 31.3; N, 15.9. Anal. Calcd for C$_9$H$_{22}$Cl$_3$CoN$_4$O$_2$ (F2) C, 28.18; N, 14.61. Found C, 28.0; N, 14.0%. For a structure determination, F1 was converted to its perchlorate by adding NaClO$_4$ to an aqueous solution. Formulations for the crystalline solids were F1 → [Co(**2**H$_{-1}$)Cl]ClO$_4$ = C$_9$H$_{21}$Cl$_2$CoN$_4$O$_6$; F2 → [Co(**2**)Cl$_2$]Cl = C$_9$H$_{22}$Cl$_3$CoN$_4$O$_2$.

(c) [Cu(4)(OClO$_3$)]ClO$_4$. [Co(**4**)Cl$_2$]ClO$_4$ (6.0 g) was dissolved in water (500 mL), and a large excess of NaBH$_4$ (5 g) was added, followed by 3 M HCl (100 mL, dropwise). After effervescence had subsided, the mixture was diluted to 1 L and absorbed onto Dowex 50W-X2 (10 cm × 5 cm). The column was washed with water (500 mL), Co(II) and Na(I) eluted with 0.5 mol L^{-1} HCl (500 mL), and the protonated ligand then eluted with 3 mol L^{-1} HCl. This eluate was taken to dryness under reduced pressure to give the crude tetra-amine hydrochloride (4.0 g). A portion (0.8 g) was slurried in ethanol (20 mL), and an ethanolic solution of NaOH (0.4 g in 20 mL) was added. NaCl was filtered out and the solution taken down under reduced pressure to an oily liquid. This was dissolved in water (10 mL) and CuCl$_2$·2H$_2$O (0.4 g) was added. The blue solution was filtered to remove some Cu(OH)$_2$, and the product precipitated by addition of excess NaClO$_4$. (Yield, 0.9 g.) Anal. Calcd for C$_9$H$_{22}$Cl$_2$CuN$_4$O$_8$ C, 24.09; H, 4.94; N, 12.48. Found C, 24.1; H, 5.3; N, 12.6%.

(d) Preparation of 4,8-Diaza-6-hydroxycarbonyl-6-methylundecane-1,11-diamine, 5, Isolated (Deprotonated) as Its Cu(II) Complex. The "high-temperature" procedure described above, with the period at reflux extended from 24 to 48 h, was used to achieve reaction between propane-1,3-diamine (6.7 g) and 3,3′-dichloropivalic acid (3.0 g). Chromatography (SP Sephadex/0.3 mol L^{-1} NaCl) of the Cu(II) complexes of the product mixture revealed four blue components, the second being simply a complex of unreacted propanediamine and the third and fourth species requiring the use of 0.6 mol L^{-1} NaCl for their efficient removal from the column. The major (first) component (yield, 2.5 g) was recrystallized from ethanol by vapor diffusion of ether into the solution to provide crystals suitable for a structure determination, resulting in the formulation [Cu(**5**H$_{-1}$)Cl]·2H$_2$O = C$_{11}$H$_{29}$ClCuN$_4$O$_4$. Anal. Calcd for [Cu(**5**H$_{-1}$)Cl]·2.5H$_2$O = C$_{11}$H$_{30}$ClCuN$_4$O$_{4.5}$ C, 33.93; N, 14.39. Found C, 33.7; N, 14.0%. Despite numerous efforts, the third and fourth components could not be obtained in crystalline forms, so that ultimately the complexes were broken down by dissolution in HCl and the ligands recovered as hydrochlorides via Dowex 50W-X2/HCl chromatography, with 1.0 g of amorphous material being obtained from each. Electrospray mass spectra of these materials were extremely complicated, but both showed 1+ ions corresponding to the hexamine derived from reaction of 2 mol of acid with 3 mol of diamine, a species which should exist in diastereomeric

forms and one analogous to a species structurally characterized as a side product of a similar reaction.[1]

(e) Macrocyclic Complexes Derived from [Cu(2H$_{-1}$)]$^+$. [Cu(**2**H$_{-1}$)]Cl (1.0 g) was dissolved in methanol (100 mL), and paraformaldehyde (1.1 g), nitroethane (0.6 g), and triethylamine (1.5 g) were added successively. The mixture was heated at reflux for 12 h and evaporated to dryness under reduced pressure, and the residue was then dissolved as completely as possible in water (200 mL) before filtration through Celite to remove some exceedingly insoluble green material. Chromatography (SP Sephadex/0.3 mol L^{-1} NaCl) of the product mixture in the filtrate revealed two components. Each eluate was evaporated to dryness under reduced pressure, the residue extracted with methanol to leave NaCl, and the extract evaporated to dryness. (Yields, F1, 0.30 g; F2, 0.80 g.) Slow evaporation of aqueous solutions of the complexes containing NaClO$_4$ provided crystals of both compounds suitable for structure determinations, the formulations thereby deduced being F1 → [Cu(**6**)](ClO$_4$)$_2$ = C$_{13}$H$_{27}$Cl$_2$CuN$_5$O$_{12}$ and F2 → [Cu(**7**H$_{-1}$)(OH$_2$)]ClO$_4$·1.5H$_2$O = C$_{13}$H$_{31}$ClCuN$_5$O$_{10.5}$. Elemental analysis of the perchlorate from F2 was indicative of a higher degree of solvation for the bulk material: Calcd for [Cu(**7**H$_{-1}$)(OH$_2$)]ClO$_4$·4.5H$_2$O = C$_{13}$H$_{37}$ClCuN$_5$O$_{13.5}$ C, 26.99; N, 12.11. Found C, 26.9; N, 11.5%.

Crystallography. The data for all compounds except [{Cu(**3**H$_{-1}$)}$_2$Cl]ClO$_4$·H$_2$O were collected in Saclay on a Nonius Kappa-CCD area detector diffractometer[6] 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, 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.[7] The structures were solved by direct methods with SHELXS-97[8] and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXL-97.[8] Absorption effects were corrected empirically with the program DELABS from PLATON.[9] Special details related to disorder in two of the compounds are as follows:

(i) Na$_2$[Cu(**2**H$_{-1}$)](ClO$_4$)$_3$·1.5H$_2$O: Three oxygen atoms of a perchlorate anion were found disordered over two positions which were refined with occupancy parameters constrained to sum to unity. One of the water molecules was affected with a 0.5 occupancy parameter in order to keep a physically acceptable displacement factor.

(ii) [Cu(**4**)(OClO$_3$)]ClO$_4$: The nonbonding perchlorate anion was found disordered over two positions sharing the chlorine atom, which were refined with occupancy parameters 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 in [Cu(**4**)(OClO$_3$)]-ClO$_4$. The hydrogen atoms bound to nitrogen and oxygen atoms were found on Fourier-difference maps (except those of the partially occupied water molecule in the first structure and those of the water molecule occupying a special position in the last structure), and all the other ones were introduced at calculated positions. All hydrogen atoms were treated as riding atoms with a displacement parameter equal to 1.2 (NH, OH, CH$_2$) or 1.5 (CH$_3$) times that of the parent atom. The Flack parameter[10] was refined to a value of

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Table 1. Crystal and Refinement Data

	$Na_2[Cu(2H_{-1})](ClO_4)_3 \cdot 1.5H_2O$	$[Co(2H_{-1})Cl]ClO_4$	$[Co(2)Cl_2]Cl$	$[\{Cu(3H_{-1})\}_2Cl]ClO_4 \cdot H_2O$
chemical formula	$C_9H_{24}Cl_3CuN_4Na_2O_{15.5}$	$C_9H_{21}Cl_2CoN_4O_6$	$C_9H_{22}Cl_3CoN_4O_2$	$C_{18}H_{44}Cl_2Cu_2N_8O_9$
M/g mol^{-1}	652.19	411.13	383.59	714.6
space group	$P2_1/c$ (No. 14)[a]	$P2_1/n$ (No. 14)[a]	$Pna2_1$ (No. 33)	$Pbnm$ (No. 62)[b]
a/Å	9.1961(4)	10.8115(6)	12.5225(8)	9.522(1)
b/Å	11.5011(4)	8.6745(5)	9.1018(4)	14.165(4)
c/Å	21.1280(10)	16.8259(11)	13.6155(8)	21.528(4)
β/deg	95.729(3)	98.476(3)	90	90
V/Å^3	2223.45(16)	1560.77(16)	1551.86(15)	2904(1)
Z	4	4	4	4 (dimer units)
D_{calcd}/g cm^{-3}	1.948	1.750	1.642	1.635
μ (Mo Kα)/mm^{-1}	1.466	1.475	1.625	1.708
λ/Å	0.710 73	0.710 73	0.710 73	0.710 73
T/K	100(2)	100(2)	100(2)	296(2)
$R_1{}^c$	0.042	0.046	0.029	0.075
$wR_2{}^d$	0.098	0.110	0.063	0.210

	$[Cu(4)(OClO_3)]ClO_4$	$[Cu(5H_{-1})Cl] \cdot 2H_2O$	$[Cu(6)](ClO_4)_2$	$[Cu(7H_{-1})(H_2O)]ClO_4 \cdot 5H_2O$
chemical formula	$C_9H_{22}Cl_2CuN_4O_8$	$C_{11}H_{29}ClCuN_4O_4$	$C_{13}H_{27}Cl_2CuN_5O_{12}$	$C_{13}H_{31}ClCuN_5O_{10.5}$
M/g mol^{-1}	448.75	380.37	579.84	524.42
space group	$P2_12_12_1$ (No. 19)	$Pbca$ (No.61)	$P2_1/c$ (No. 14)	$C2/c$ (No. 15)
a/Å	7.1300(3)	16.4548(12)	8.2116(3)	34.4254(15)
b/Å	9.3351(5)	9.4028(7)	20.1409(11)	8.4635(6)
c/Å	25.8486(13)	21.5332(10)	13.2167(6)	14.1699(12)
β/deg	90	90	99.051(3)	100.494(4)
V/Å^3	1720.46(15)	3331.6(4)	2158.68(17)	4059.5(5)
Z	4	8	4	8
D_{calcd}/g cm^{-3}	1.732	1.517	1.784	1.716
μ (Mo Kα)/mm^{-1}	1.626	1.491	1.332	1.274
λ/Å	0.71073	0.71073	0.71073	0.71073
T/K	100(2)	100(2)	100(2)	100(2)
$R_1{}^c$	0.050	0.050	0.060	0.060
$wR_2{}^d$	0.117	0.099	0.145	0.145

[a] Variant of $P2_1/c$. [b] Variant of $Pnma$. [c] $R_1 = \sum||F_o| - |F_c||/|F_o|$ ("observed" reflections). [d] $wR_2 = [\sum w(|F_o{}^2| - |F_c{}^2|)^2/\sum w|F_o{}^2|^2]^{1/2}$ ("observed" reflections).

0.45(2) for $[Cu(4)(OClO_3)]ClO_4$, indicating racemic twinning. Crystal data and structure refinement parameters are given in Table 1 and selected bond lengths and angles in Table 2. All calculations were performed on a Silicon Graphics R5000 workstation.

Intensity data at 296 K for $[\{Cu(3H_{-1})\}_2Cl]_2ClO_4$ were collected in Brisbane on an Enraf-Nonius CAD4 four-circle diffractometer using graphite-monochromated Mo Kα radiation (λ 0.710 73 Å) in the $\omega-2\theta$ scan mode. Lattice dimensions were determined by a least-squares fit of the setting parameters of 25 independent reflections. Data reduction and empirical absorption corrections (ψ-scans) were performed with the WINGX package.[11] The structure was solved by the heavy-atom method with SHELXS and refined by full matrix least-squares analysis with SHELXL97.[8] All non-H atoms were refined with anisotropic thermal parameters, and H-atoms were constrained at estimated positions. The hydroxymethyl group was rotationally disordered about the C4−C8 bond, which resulted in two different positions for the hydroxyl group and the adjacent methylene protons. The two rotamers were refined with complementary occupancies (69:31 O2A:O2B).

For all structures, the atomic nomenclature is defined in the figures drawn with ORTEP3[12] (Supporting Information) or the POVRay option within Xtal 3.7.[13] Displacement ellipsoids are drawn at the 20% probability level.

Results and Discussion

The presumption that dichloropivalic acid would undergo deprotonation in ethane-1,2-diamine to give a weakly electrophilic carboxylate site led us to assume initially that the favored product of reaction between these two species would be the polyamino acid **2** resulting from reaction at the chloromethyl centers only. Indeed, this does appear to be the exclusive tetra-amine product when the reaction is conducted under relatively mild conditions, viz., a "low" temperature of 90 °C and a "short" reaction period of 12 h. There are, however, considerable amounts of other products in the reaction mixture. These materials appear to be poor complexants for Cu(II) or at least to be ligands which do not bind predominantly through N-donor atoms, so we have not pursued their characterization in detail. (For some, spectroscopic measurements indicate they are not the products of reaction between the diamine and acid in a 2:1 ratio.) The crystal structure of **2** when bound to Cu(II) (Figure 2) shows it to behave as a typical "232tet"-like ("232tet" = 3,7-diaza-1,9-nonanediamine) ligand[14] in binding in an overall achiral δ-gauche-chair-λ-gauche conformation, and given the similar dimensions (and H-bonding propensities?) of carboxylato and nitro entities, it is unsurprising to see that the carboxylato substituent in the $[Cu(2H_{-1})]$ entity adopts the axial disposition on the six-membered chelate ring seen in many related complexes with nitro groups in place of the carboxylate here.[1,15] Also, the tetragonal N_4O_2 coordination environment at Cu is similar to that in [Cu-(232tet)(OClO$_3$)$_2$],[16] though the coordination polymer which

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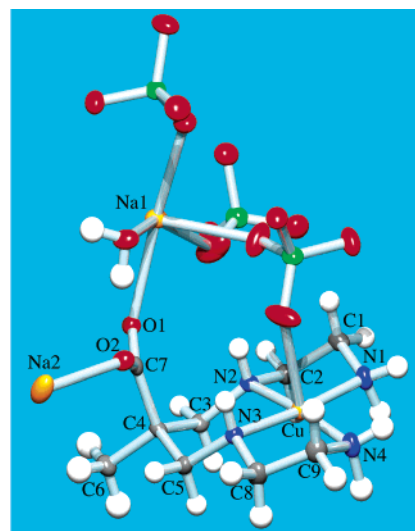(15) Bernhardt, P. V.; Lawrance, G. A. *Coord. Chem. Rev.* **1990**, *104*, 297.

Table 2. Selected Bond Lengths (Å) and Angles (deg)

Na₂[Cu(**2**H₋₁)](ClO₄)₃·1.5H₂O			
Cu−N1	2.017(3)	N1−Cu−N2	85.59(12)
Cu−N2	2.015(3)	N2−Cu−N3	93.10(12)
Cu−N3	2.027(3)	N3−Cu−N4	85.21(12)
Cu−N4	2.012(3)	N4−Cu−N1	96.52(12)

[Co(**2**H₋₁)Cl]ClO₄			
Co−N1	1.959(3)	N1−Co−N2	86.95(13)
Co−N2	1.964(3)	N2−Co−N3	90.35(13)
Co−N3	1.960(3)	N3−Co−N4	87.14(13)
Co−N4	1.963(3)	N4−Co−N1	95.61(14)
Co−O1	1.886(3)	O1−Co−Cl1	175.22(9)
Co−Cl1	2.2594(10)		

[Co(**2**)Cl₂]Cl			
Co−N1	1.957(3)	N1−Co−N2	86.03(11)
Co−N2	1.989(3)	N2−Co−N3	94.80(10)
Co−N3	1.980(3)	N3−Co−N4	86.31(11)
Co−N4	1.958(3)	N4−Co−N1	92.84(11)
Co−Cl1	2.2514(9)	Cl1−Co−Cl2	178.37(4)
Co−Cl2	2.2626(8)		

[Cu(**3**H₋₁)ClCu(**3**H₋₁)]ClO₄			
Cu−N1	1.989(7)	N1−Cu−N2	85.4(3)
Cu−N2	1.970(6)	N2−Cu−N3	94.6(3)
Cu−N3	1.999(7)	N3−Cu−N4	84.7(3)
Cu−N4	2.030(7)	N4−Cu−N1	94.1(3)

[Cu(**4**)(OClO₃)]ClO₄			
Cu−N1	2.007(5)	N1−Cu−N2	85.0(2)
Cu−N2	2.014(5)	N2−Cu−N3	88.9(2)
Cu−N3	2.015(5)	N3−Cu−N4	85.3(2)
Cu−N4	1.998(5)	N4−Cu−N1	100.7(2)
Cu−O1	2.465(4)		

[Cu(**5**H₋₁)Cl]·2H₂O			
Cu−N1	2.059(4)	N1−Cu−N2	90.30(14)
Cu−N2	2.079(3)	N2−Cu−N3	95.12(14)
Cu−N3	2.089(4)	N3−Cu−N4	86.30(14)
Cu−N4	2.046(3)	N4−Cu−N1	85.29(14)
Cu−Cl	2.5308(10)		

[Cu(**6**)](ClO₄)₂			
Cu−N1	1.961(5)	N1−Cu−N2	93.03(19)
Cu−N2	2.007(4)	N2−Cu−N3	86.64(17)
Cu−N3	2.002(4)	N3−Cu−N4	93.90(16)
Cu−N4	2.018(4)	N4−Cu−N1	86.58(18)

[Cu(**7**H₋₁)(H₂O)]ClO₄·1.5H₂O			
Cu−N1	2.012(4)	N1−Cu−N2	92.15(16)
Cu−N2	2.017(4)	N2−Cu−N3	85.75(16)
Cu−N3	2.034(4)	N3−Cu−N4	94.85(16)
Cu−N4	2.008(4)	N4−Cu−N1	86.61(16)
Cu−O5	2.343(3)		

Figure 2. Partial view of the lattice of Na₂[Cu(**2**H₋₁)](ClO₄)₃·1.5H₂O, showing one of the cyclic structures linking Cu and Na in the coordination polymer.
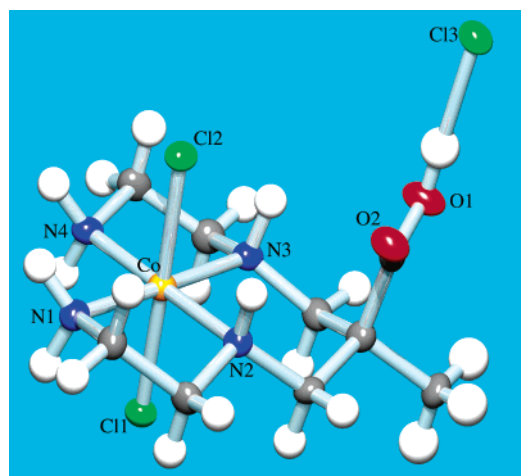
Figure 3. View of the complex [Co(**2**)Cl₂]Cl, showing a hydrogen bond between the carboxyl substituent and chloride anion. (C atom numbering is as in Figure 2.)

comprises the lattice here is considerably more complicated, with sodium cations, other perchlorate anions, and the carboxylato groups involved in structures which bridge O₃-ClO−Cu−OClO₃ entities. The sodium cations are of two types, 6- and 7-coordinate, the latter chelated by one perchlorate ligand, with oxygen atoms from two different carboxylate entities being involved in Na₂O₂ rhombs (a common feature of the structural chemistry of Na(I)[17]) forming links between the 6-coordinate metal ions. The complex cation unit is very similar to that found in the Cu(II) complex of the isomer of **2**, 3,7-diaza-5-methoxycarbonyl-nonane-1,9-diamine, a ligand derived from reaction between [Cu(en)₂]²⁺, HCHO, and dimethylmalonate.[18]

For ligands of the present tetra-amine type, M−N bond lengths are usually only just slightly shorter for M = Co(III) than for M = Cu(II),[1,5,19] so the ligand conformations are closely similar for both metals, given also that coplanar arrays

of the four N-donors appear to be favored. Comparison of the M(**2**) entities in Na₂[Cu(**2**H₋₁)](ClO₄)₃·1.5H₂O (Figure 2) and [Co(**2**)Cl₂]Cl (Figure 3) fortifies this generalization. Cobalt(III), however, binds fifth and sixth ligands considerably more strongly than does Cu(II), and the binding of the pendent carboxylato group of (**2**H₋₁) in [Co(**2**H₋₁)Cl]ClO₄ (Figure 4) results not only in a rather different overall ligand conformation but also in significant bond length and bond angle changes. Indeed, despite the fact that the central, six-membered chelate ring adopts a formally achiral boat conformation, the adjacent gauche five-membered rings have the same conformation (viz., $\delta\delta$ or $\lambda\lambda$), so that the molecule overall is chiral. (The complex resembles in both structure and conformation the closely related Co(III) complex of 3,7-diaza-5-carboxylatononane-1,9-diamine.[20]) Given that struc-

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(17) See, for example: Harrowfield, J. M.; Sharma, R. P.; Shand, T. M.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1998**, *51*, 707.

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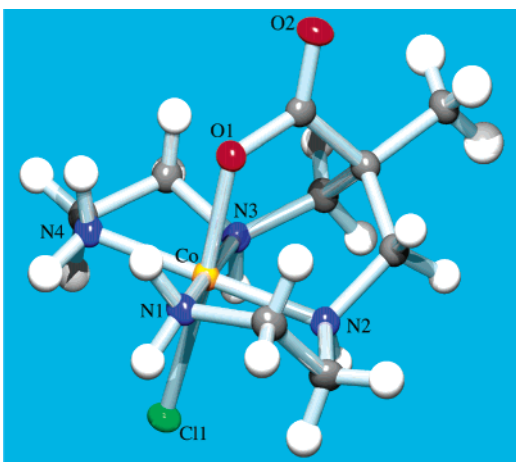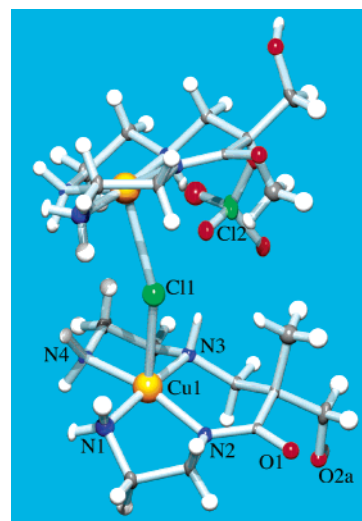
Figure 4. View of the complex [Co($2H_{-1}$)Cl]ClO$_4$. The counterion is omitted for clarity. (C atom numbering is as in Figure 2.)

tural and conformational differences between bound tetra-amine ligands appear to have a strong influence upon the ease of macrocycle formation from them[15,21] (see below also), this indicates that a lack of binding to the pendent carboxylate group in [Cu($2H_{-1}$)]$^+$ may be one important factor determining the ease of its conversion to the macrocycle **7**.

There is evidence[2] that reactions of R$_2$C(CH$_2$X)$_2$ (X = halide, sulfonate) compounds with amines may involve azetidine intermediates, and since it is also established that such reactions of dichloropivalate esters pass through azetidinones,[22] it seems plausible that more extreme reaction conditions might convert **2** to the azetidinone **1**. Given the present use of complex formation in aqueous media for isolation of the reaction products, an obvious question is whether **1** would be stable to such treatment. The simplest interpretation of the isolation of the Cu(II) complex of **3** from the product of the reaction at higher temperature is that it is not. Ring opening, which may involve water or hydroxide given that the complexation was conducted under at least mildly basic conditions and which may occur on or off the metal ion, seemingly occurs with complete selectivity for the CH$_2$–N bond over the CO–N. Solution of the crystal structure of the isolated Cu(II) complex of **3** (Figure 5) is consistent with the presence of centrosymmetric, chloro-bridged dimer units associated with but one perchlorate anion per dimer, indicating that the ligand is present in its iminolate form. Possibly it is the metal ion's preference for a formally unsaturated donor atom type (imine-N) that determines the bond cleavage site. Indeed, it must be argued that some rather powerful metal ion activation of the azetidinone must occur in order to explain why it apparently does not react with more ethane-1,2-diamine in the initial reaction mixture to give a hexamine derivative as the product.

Related to the presumed azetidinone intermediate is the isolable azetidine complex [Cu(**4**)(OClO$_3$)](ClO$_4$) (Figure 6), which, although it can be regarded as a complex of a 232tet

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(22) Bartholomew, D.; Stocks, M. J. *Tetrahedron Lett.* **1991**, *32*, 4795.

Figure 5. View of the centrosymmetric, chloro-bridged dimer present in [{Cu($3H_{-1}$)}$_2$Cl]ClO$_4$·H$_2$O, with the planarity of the iminolate group involving N2, O1 apparent.
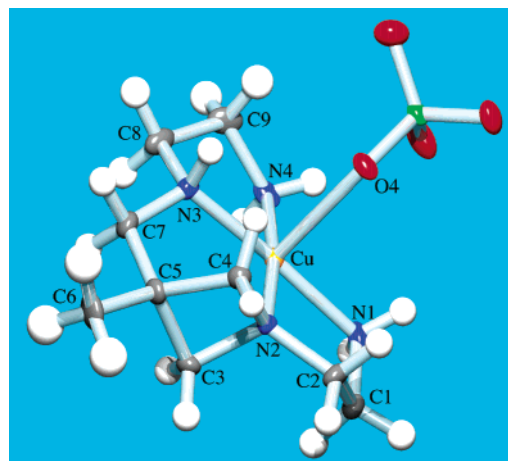
Figure 6. View of the repeat unit of the coordination polymer found in the complex [Cu(**4**)(OClO$_3$)]ClO$_4$. The nonbonding counterion is omitted for clarity.
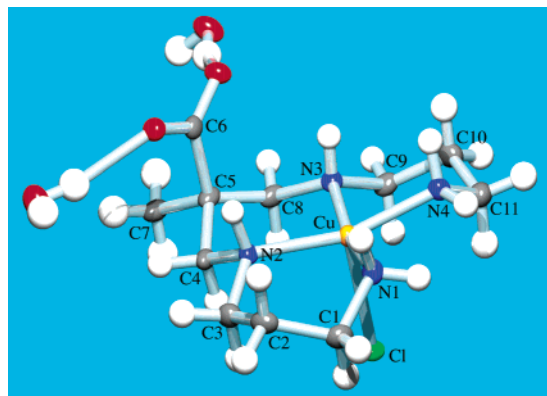
derivative, shows significant distortions of the coordination sphere relative to that species.[14,16] This we interpret as indicating that opening of the four-membered ring, whether of the azetidine or azetidinone species, should be energetically favored. The presence of the azetidine ring in the central donor atom bridge engenders chirality within the complex ion structure such that the gauche five-membered terminal chelate rings are of the same conformation ($\delta\delta$ or $\lambda\lambda$). Note that the procedure used to isolate the azetidine ligand prior to formation of its Cu(II) complex indicates that the ligand is stable in aqueous acid and ostensibly, therefore, much less reactive than its azetidinone analogue.

The reaction between propane-1,3-diamine and dichloropivalate under conditions which lead to the amide product from ethane-1,2-diamine gives, as one of three N-donor Cu(II) complexants, at least predominantly the tetra-amine carboxylato species **5** (along with, once again, other products which appear to be O-donor Cu(II) complexants). This may mean that the reaction is truly as simple as the displacement of the two chloro groups by two separate molecules of
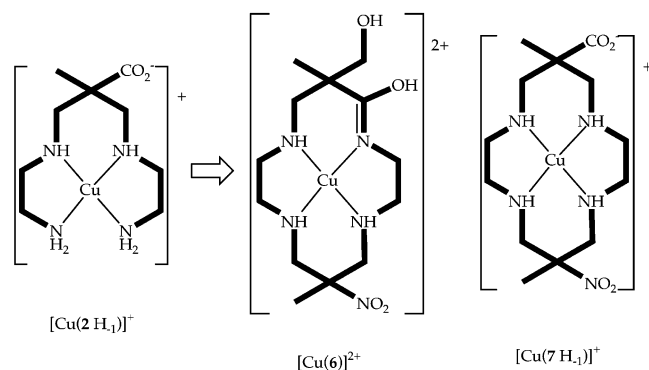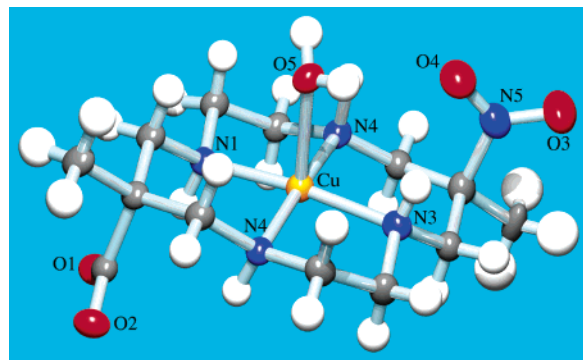
Figure 7. View of the complex [Cu($\mathbf{5}$H$_{-1}$)Cl]·2H$_2$O, showing hydrogen bonding of two water molecules to the pendent carboxylate unit.

Figure 8. Macrocycle formation from the Cu(II) complex of $\mathbf{2}$.

Figure 9. View of the complex [Cu($\mathbf{7}$H$_{-1}$)(H$_2$O)(OClO$_3$)]·1.5H$_2$O (bound perchlorate omitted for clarity).

Figure 10. View of the complex [Cu($\mathbf{6}$)(OClO$_3$)]ClO$_4$, showing a hydrogen bond between the hydroxymethyl substituent and the iminol unit, and the perchlorate ligands involved in formation of a coordination polymer within the solid.

diamine or that the azetidinone does form but undergoes ring opening by exclusive CO–N bond cleavage. While this issue is yet to be resolved, the crystal structure of the Cu(II) complex of the product (Figure 7) shows bound $\mathbf{5}$ to adopt a chair–chair–chair conformation, though the three chair entities are not identical; their fusion into the tetra-amine results both in distortions of their form relative to that of a simple 1,3-diamine chelate ring and in significant distortions of the metal ion coordination sphere when compared to that in a complex of a 333tet-like ligand.

The initial objective of the present work was the synthesis of a cyclam-like macrocycle with a carboxylate pendent group (Figure 8). Such a species, $\mathbf{7}$, is indeed obtained on reacting the Cu(II) complex of deprotonated $\mathbf{2}$ with nitroethane and formaldehyde. In the species characterized in the solid state (Figure 9), the macrocycle has the common *trans*-III conformation with the carboxylate and nitro substituents axial on their separate, chair six-membered rings, i.e., with both methyl substituents equatorial. The Cu(II) has a tetragonal N$_4$O$_2$ environment, also common for Cu(II) macrocycle complexes, though often both oxygen atoms are derived from perchlorate ligands, whereas here one oxygen is that of a water molecule and the other is from perchlorate. Given that the complex was chromatographically purified under conditions where separations of possible isomeric forms of the ligands do occur in closely related systems, we tentatively conclude on the basis of the structural results that there is selective formation of the anti or trans (NO$_2$/CO$_2{}^-$) form of the macrocycle. It is known for other related systems,

however, that this isomer is the dominant species and it is not really possible at present to exclude the formation here of a small amount of the syn or cis form. Presently more interesting, however, is the fact that this "obvious" product of the reaction of the complex of $\mathbf{2}$ is accompanied by the complex of the isomeric ligand $\mathbf{6}$, isolated in its iminol, rather than its amide form (Figure 10). Here, with regard to the pendent substituents (CH$_2$OH and NO$_2$) on the macrocycle, the cis species is apparently predominant. This can be explained if an azetidinone is formed after the formation of the trans macrocycle, since ring formation followed by nucleophilic CH$_2$–N cleavage (by water?) would effectively interchange the pendent groups at the central C of the six-membered chelate ring involved (Figure 11). Details of the mechanism of formation of ligands $\mathbf{6}$ and $\mathbf{7}$ remain to be established, but the Cu(II) complex of $\mathbf{7}$, when redissolved in nitroethane/HCHO/triethylamine/methanol medium after separation, undergoes conversion, over a period of days at ambient temperature, to the complex of $\mathbf{6}$, whereas the latter species remains unchanged under the same conditions, indicating that it is the preferred complex at equilibrium (though perhaps when in its iminolate form).

Attempts to use the reaction with nitroethane/HCHO to form a stable macrocyclic species from the Cu(II) complex of $\mathbf{5}$ were, not unexpectedly,[15] unsuccessful in that the reaction product was rapidly broken down in dilute HCl solution.
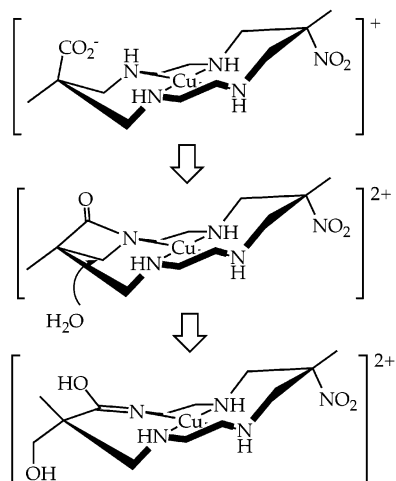
Figure 11. Positional interchange of macrocyclic substituent possible through reaction of an azetidinone intermediate.

The ultimate result of the present work is thus the establishment of simple synthetic pathways of moderate overall efficiency to new, cyclam-like macrocycles with amino, carboxylato, hydroxymethyl, and nitro substituents. It is presumed that full reduction of the complexes $[Cu(\mathbf{6})]^{2+}$ and $[Cu(\mathbf{7}H_{-1})]^{2+}$ would provide isomeric penta-amino-mono-ol ligands, viz., the cis and trans forms of 13-amino-4,13-dimethyl-4-hydroxymethyl cyclam. Even if only available in the case of $[Cu(\mathbf{6})]^{2+}$, however, the hydroxymethyl substituent should prove useful in further synthesis aimed at the production of multimacrocycles. Thus, oxidation to an aldehyde unit (stabilized against various reactions because of its attachment to a quaternary carbon) should allow Schiff base formation or reductive amination reactions to be used to link several cyclam units to a core.