Inorg. Chem. **2002**, *41*, 2892–2902

Inorganic Chemistry
Article

Crown Ether Appended Cyclam Receptors for Cationic Guests

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Received December 3, 2001

A series of crown ether appended macrocyclic amines has been prepared comprising benzo-12-crown-4, benzo-15-crown-5, or benzo-18-crown-6 attached to a diamino-substituted cyclam. The Co^{III} complexes of these three receptors have been prepared and characterized spectroscopically and structurally. Crystal structures of each receptor in complex with an alkali metal ion and structures of the benzo-12-crown-4 and benzo-15-crown-5-receptors without guest ions are reported. 2D NMR and molecular mechanics modeling have been used to examine conformational variations upon guest ion complexation. Addition of cations to these receptors results in an appreciable anodic shift in the $Co^{III/II}$ redox potential, even in aqueous solution, but little cation selectivity is observed. Evidence for complex formation has been corroborated by ^{23}Na and ^{7}Li NMR spectroscopy and electrospray mass spectrometry.

Introduction

The crown ethers comprise a well-known class of macrocyclic compound bearing mostly oxygen donors. They are known to bind alkali metal and alkaline earth cations within their cavities by electrostatic ion−dipole interactions, and their complexation properties have been studied extensively.[1] The interaction between crown ethers and cations may be considered in terms of an optimal spatial fit between the macrocyclic cavity size and the cationic radius imparting stability to the resulting complex. One of the issues to be addressed in the determination of cation−crown ether binding constants is signaling the host−guest interaction. A vast amount of research has been done with redox-active receptors for cationic species, which are sensitive to complexation of a guest ion through the electrostatic influence that this ion has on the redox potential of the host. Three commonly employed examples are ferrocenes,[2−8] nitrobenzenes,[9] and quinines,[10,11] and some examples are shown in Chart 1.

Cobalt amine complexes are also potentially useful signaling units if they can be stabilized in both the tri- and divalent oxidation states. Rendering the divalent oxidation state inert to substitution reactions requires the use of a macrocyclic ligand. In this case, simple one electron reductions of the Co^{III} center are uncomplicated by proton transfer in either aqueous or nonaqueous solution, unlike quinines and nitroaromatics. The tetraamine macrocycle cyclam (1,4,8,11-tetraazacyclotetradecane) is an effective ligand for Co^{III} and Co^{II}, and its electrochemistry is reversible under a variety of conditions. Functionality may be introduced into the ring with the diamino-sustituted cyclam *trans*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (L^5).[12] This ambidentate ligand forms stable tetradentate coordinated complexes with low spin d^8 and d^9 (square planar) metal ions with both pendent amines uncoordinated.[13,14] When bound to six-coordinate metal ions, one or both pendent amines of L^5 may coordinate, to give pentaamine[15] or hexaamine[16] complexes. Recently, we have been investigat-

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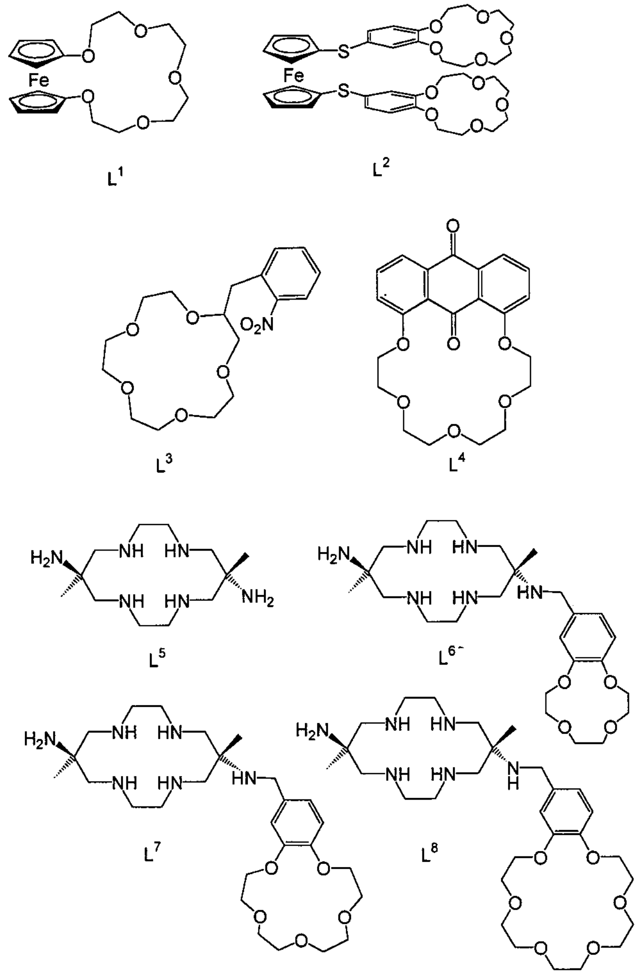
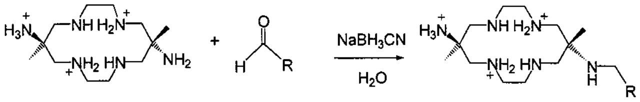
10.1021/ic011232h CCC: $22.00

Chart 1



Scheme 1



ing the chemistry of L^5 derivatives by using the pendent amines as links to active functional groups through reductive alkylation reactions as shown in Scheme 1.

In this work, we describe the synthesis and X-ray crystal structures of a new series of crown ether appended cyclams (L^6-L^8) and their Co^{III} complexes as redox-active cation receptors. Communication between metals coordinated to the azamacrocyclic and crown ether subunits is likely to be through-space (electrostatic),[2] and on this basis, the divalent form of the complex should bind cations more strongly (K_{red}) than the oxidized form (K_{ox}). It is necessary that K_{red} and K_{ox} differ for any effect of substrate binding to be apparent. Very large differences between K_{red} and K_{ox} (and large absolute values) result in two distinct voltammetric responses, for both the complexed and uncomplexed forms of the receptor with the current of each response indicative of the amount of free and complexed receptor.[17] However, more common is shifting voltammetric behavior, in which a gradual change in the apparent redox potential of the receptor is observed with increasing concentration of substrate. Complementary to these electrochemical studies, multinuclear (^{7}Li and ^{23}Na) NMR and mass spectrometry have been used to verify independently host−guest complexation in solution.

Experimental

Safety Note. Perchlorate salts are potentially explosive. Although no problems were experienced with the compounds synthesized, they should only be handled in small quantities, never scraped from sintered glass frits, nor heated in the solid state. Solutions containing sodium cyanoborohydride liberate toxic HCN gas when acidified and should only be used in a well ventilated fume hood.

Syntheses. Published preparations were employed for *trans*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine hydrochloride (L^5·HCl),[12] its free base (L^5),[18] benzo-15-crown-5,[19] 4′-formylbenzo-15-crown-5,[20] and $Na_3[Co(CO_3)_3]\cdot 3H_2O$.[21] 4′-Formylbenzo-12-crown-4 was synthesized according to a slightly modified literature procedure.[22] The crude product (an oil) was extracted with warm di-isopropyl ether and precipitated from the ether layer by cooling. 4′-Formylbenzo-18-crown-6 was synthesized in a similar manner. MeCN and DMF for electrochemistry experiments were freshly distilled before use. All other chemicals were used as purchased.

(6-(4′-Aminomethyl-benzo-12-crown-4)-6,13-dimethyl-1,4,8,11-tetraazacyclotetra-decan-13-amine)aquacobalt(III) Perchlorate Hydrate, $[CoL^6(OH_2)](ClO_4)_3\cdot H_2O$. L^5 (1.20 g, 4.64 mmol) was dissolved in 300 mL of ethanol (90%), and the pH was adjusted to 6.3 using 3 M HCl. Sodium cyanoborohydride (1.02 g, 16.2 mmol) and 4′-formyl-benzo-12-crown-4 (1.45 g, 4.9 mmol) were added, and the reaction was left to stir for 16 h. The pH was maintained at 6.3 by periodic addition of 3 M HCl. Water (150 mL) was then added to the reaction and the pH adjusted to 12, using concentrated NaOH, before extraction with two 50 mL portions of $CHCl_3$. The yellow oil remaining after evaporation of $CHCl_3$ was taken up in ethanol/water. $Na_3[Co(CO_3)_3]\cdot 3H_2O$ (2.03 g, 5.6 mmol) was added and the mixture heated at 80 °C for 2 h. The resulting solution was filtered, to remove a black precipitate, diluted, and charged onto Sephadex C-25 cation-exchange resin (Na^+ form). Only one major band was observed, and this eluted with 0.3 M $NaClO_4$. The orange solution was concentrated on a rotary evaporator to afford a solid, which was collected by filtration and air-dried (0.38 g, 14%). X-ray quality crystals formed from the filtrate upon standing. Calcd for $C_{25}H_{50}Cl_3CoN_6O_{18}$: C, 33.81; H, 5.68; N, 9.46. Found: C, 33.41; H, 5.64; N, 9.41%. Electronic spectrum (MeOH): λ_{max} 498 nm (ϵ 113 M^{-1} cm^{-1}), 278 nm (ϵ 6677 M^{-1} cm^{-1}). ^{1}H NMR (DMSO-d_6): δ (ppm) hydroxo ligand −3.79 (s, br, 1H); methyl groups 1.20 (s, 3H), 1.26 (s, 3H); amino methylenes (AB mult, 4H each) 2.32 and 2.97, 2.45 and 3.15, 2.66 and 2.79, 2.95 and 3.15; benzyl methylene 3.89 (s, 2H), crown ether methylenes (overlapping mult) 3.70, 4.09, 4.18; aromatics 6.97 (dd, 1H), 7.04 (dd, 1H), 7.26 (d, 1H); amines 1.96 (s, br, 1H), 4.85 (s, br, 2H), 6.40 (s, br, 2H). ^{13}C NMR (DMSO-d_6): δ (ppm) 19.1, 22.9, 44.3, 50.3, 51.4, 55.6, 56.7, 59.2, 62.5, 68.9, 68.9, 70.1, 70.3, 70.7, 71.8, 117.9 (2 peaks), 121.7,

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135.2, 148.8, 150.1. Infrared: $\bar{\nu}$ (cm^{-1}) 3088, 2920, 1626, 1505, 1454, 1270, 1118, 1077, 918, 837, 628.

Potassium Bis{(6-(4′-aminomethyl-benzo-12-crown-4)-6,13-dimethyl-1,4,8,11-tetra-azacyclotetradecan-13-amine)hydroxocobalt(III) Perchlorate Hydrate, K{[CoL^6(OH)]}$_2$(ClO$_4$)$_5$·8H$_2$O. Crystals of the K$^+$ complex were grown from a basic aqueous solution of $[CoL^6(OH_2)](ClO_4)_3 \cdot H_2O$ containing 35% DMF and 5 equiv of $KClO_4$.

(6-(4′-Aminomethyl)-benzo-15-crown-5)-6,13-dimethyl-1,4,8,11-tetraazacyclo-tetradecan-13-amine)aquacobalt(III) Perchlorate Pentahydrate, [CoL^7(OH$_2$)](ClO$_4$)$_3$·5H$_2$O. This complex was synthesized in a manner similar to the benzo-12-crown-4 analogue, except 4′-formylbenzo-15-crown-5 was used. One major band was observed during cation exchange chromatography, and this eluted with 0.3 M $NaClO_4$. The orange solution was concentrated on a rotary evaporator, to afford a solid, which was collected by filtration and air-dried (0.39 g, 8.5%). X-ray quality crystals of the protonated derivative $[Co(HL^7)(OH_2)](ClO_4)_4$ grew from the filtrate upon standing. Calcd for $C_{27}H_{60}Cl_3CoN_6O_{22}$: C, 32.88; H, 6.13; N, 8.52. Found: C, 32.81; H, 6.68; N, 8.48%. Electronic spectrum (MeOH): λ_{max} 495 nm (ϵ 131 M^{-1} cm^{-1}), 281 nm (ϵ 7271). ^{1}H NMR (DMSO-d_6): δ (ppm) hydroxo ligand −3.79 (s, br, 1H), methyl groups 1.136 (s, 3H), 1.143 (s, 3H); macrocyclic amino methylenes (AB mult, 4H each) 2.30 and 2.80, 2.45 and 3.20, 2.65 and 2.95, 2.90 and 3.10; benzyl methylene 3.69 (d, 2H); crown ether methylenes (overlapping mult) 3.64, 3.80, 3.90, 4.06, 4.17; aromatics 6.91 (d, 1H), 6.98 (dd, 1H), 7.22 (d, 1H); amines 1.95 (s, br, 1H), 4.84 (s, br, 2H), 6.52 (s, br, 2H). ^{13}C NMR (DMSO-d_6): δ (ppm) 19.1, 21.2, 44.5, 50.3, 51.4, 55.6, 56.8, 59.2, 62.5, 68.2, 68.8, 69.7, 70.3, 113.8, 114.4, 120.4, 133.9, 147.3, 148.5. Infrared: $\bar{\nu}$ (cm^{-1}) 3098, 2918, 1620, 1515, 1457, 1254, 1117, 1085, 943, 851, 786, 629.

Sodium *trans*-(6-(4′-Aminomethyl-benzo-15-crown-5)-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecan-13-amine)cyanocobalt(III) Perchlorate Hydrate, Na[CoL^7(CN)](ClO$_4$)$_3$·H$_2$O. $L^5 \cdot HCl$ (2.42 g, 5 mmol) was dissolved in 300 mL of 2:1 MeOH/H_2O. The pH of the solution was adjusted to pH 6.3 with sodium bicarbonate, and 4′-formylbenzo-15-crown-5 (3.00 g, 10 mmol) was added. Sodium cyanoborohydride (2.5 g) was added, and the mixture stirred at room temperature for 20 h. Methanol was removed, and the residue was taken up in 150 mL of water (final pH ∼ 9) and was washed with three 50 mL portions of $CHCl_3$ to remove 4-hydroxymethyl-benzo-15-crown-5. To the aqueous fraction was added $Na_3[Co(CO_3)_3] \cdot 3H_2O$ (1.98 g, 5.5 mmol) dissolved in 50 mL of water. The solution was stirred under reflux for 3 h, diluted to 2 L, filtered, and charged onto a Sephadex C-25 cation-exchange resin (Na$^+$ form). The yellow product (λ_{max} 432 nm) eluted first, with 0.15 M $NaClO_4$, followed by $[CoL^5]^{3+}$. Concentration of the first band to ∼30 mL produced yellow crystals upon standing. These were collected by filtration, washed with EtOH, and air-dried (0.66 g, 18%). Calcd for $C_{28}H_{52}Cl_3CoN_7O_{18}Na$: C, 34.92; H, 5.44; N, 10.18. Found: C, 34.01; H, 5.47; N, 10.00%. Electronic spectrum (H_2O): λ_{max} 428 nm (ϵ 105 M^{-1} cm^{-1}), 276 nm (ϵ 4136 M^{-1} cm^{-1}). ^{1}H NMR (D_2O): δ (ppm) methyl groups 1.25 (s, 3H), 1.38 (s, 3H), amino methylenes 2.28−2.97 (16H, mult), benzyl methylene 3.38 (s, 2H), crown ether methylenes (mult, 16H) 3.75−4.27, aromatics (overlapping mult, 3H) 7.04−7.26. ^{13}C NMR (D_2O): δ (ppm) 20.9, 23.5, 47.5, 54.1−66.6, 70.8−72.5, 116.3, 116.5, 124.4, 137.1, 149.8, 150.8. Infrared: $\bar{\nu}$ (cm^{-1}) 2909, 2137, 2024, 1543, 1513, 1459, 1266, 1236, 1157, 987, 941, 725.

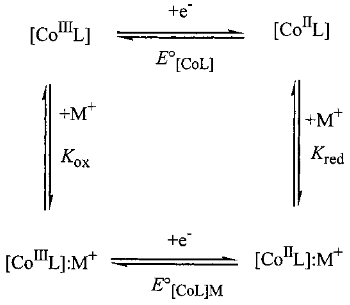
***trans*-(6-(4′-Ammoniomethyl)-benzo-18-crown-6)-6,13-dimethyl-1,4,8,11-tetraaza-cyclotetradecan-13-amine)aquacobalt(III) Perchlorate Trihydrate, [Co(HL^8)(OH$_2$)](ClO$_4$)$_4$·3H$_2$O.** This complex was synthesized in a manner similar to the benzo-15-crown-5 analogue, using 4′-formylbenzo-18-crown-6. Free Co_{aq}^{2+} eluted from the column first, followed by an indistinct orange band, which eluted slowly with 0.2 M $NaClO_4$. The third and major band was eluted with 0.4 M sodium perchlorate. A following yellow band of unsubstituted $[CoL^5]^{3+}$ was discarded. The major band was concentrated on a rotary evaporator, to produce an orange solid, which was collected by filtration and air-dried (0.12 g, 3.9%). Calcd for $C_{29}H_{62}Cl_4CoN_6O_{26}$: C, 31.33; H, 5.62, N, 7.56. Found: C, 31.70, H, 5.44, N, 7.49%. Electronic spectrum (MeOH): λ_{max} 495 nm (ϵ 124 M^{-1} cm^{-1}), 280 nm (ϵ 7418). ^{1}H NMR (MeCN-d_3): δ (ppm) hydroxo ligand −3.8 (s, br, 1H), methyl groups 1.250 (s, 3H), 1.254 (s, 3H); amino methylenes (AB mult, 4H each) 2.40 and 2.90, 2.51 and 3.15, 2.65 and 3.00, 3.05 and 3.10; benzyl methylene 3.75 (d, 2H); crown ether methylenes (overlapping mult) 3.57, 3.60, 3.64, 3.84, 4.09, 4.22; aromatics 6.85 (d, 1H), 7.00 (dd, 1H), 7.12 (d, 1H); amines 1.69 (s, br, 1H), 4.67 (s, br, 2H), 7.07 (s, br, 2H). ^{13}C NMR (MeCN-d_3): δ (ppm) 19.5, 22.2, 45.4, 52.1, 53.0, 57.4, 58.0, 60.6, 64.9, 67.5, 67.6, 69.5, 69.6, 70.1, 70.2, 70.6 ppm. Infrared: $\bar{\nu}$ (cm^{-1}) 2915, 1558, 1516, 1472, 1456, 1428, 1354, 1146, 1118, 1080, 956, 946, 785, 637.

Sodium {*trans*-(6-(4′-Aminomethyl-benzo-18-crown-6)-6,13-dimethyl-1,4,8,11-tetra-azacyclotetradecane-13-amine)hydroxocobalt(III) perchlorate hydrate, Na[Co(L^8)(OH)](ClO$_4$)$_3$·2.5H$_2$O. X-ray quality crystals of this compound were grown from a basic 35% aqueous DMF solution of $[Co(HL^8)(OH_2)](ClO_4)_4 \cdot 3H_2O$ and 5 equiv of $NaClO_4$.

Physical Methods. Routine ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 200 MHz spectrometer. High-field 1D NMR, COSY (correlated spectroscopy), HSQC (heteronuclear multiple quantum coherence), HMBC (heteronuclear multiple bond connectivity), ROESY (rotational nuclear Overhauser effect spectroscopY), and ^{23}Na and ^{7}Li NMR spectra were recorded with a Bruker AMX400 MHz spectrometer. ^{1}H and ^{13}C chemical shifts measured in deuterated acetonitrile and DMSO were referenced with the residual hydrogen resonance and ^{13}C resonance of the solvent peak and cited relative to tetramethylsilane, whereas ^{1}H and ^{13}C spectra measured in D_2O were referenced to the methyl resonance of sodium 3-(trimethylsilyl)propanesulfonate. ^{23}Na and ^{7}Li complexation titrations were performed on 0.6 mL of a 0.025 M solution of alkali metal perchlorate in CD_3CN. Cobalt complexes were added in 50 μL aliquots of a 0.03 M solution in CD_3CN, although in the case of $[CoL^6(OH)]^{2+}$ and $[CoL^8(OH)]^{2+}$, solutions contained approximately 15% DMF, to assist dissolution, and the chemical shift was measured after each addition. The systems were referenced to uncomplexed alkali metal perchlorate in MeCN. The reference was checked several times during the course of the titration.

Cyclic voltammetry and square wave voltammetry were performed with a BAS 100B/W analyzer using a Princeton Applied Research 303 static drop Hg working electrode, with a Ag/AgCl reference electrode and a platinum wire counter electrode. Potentials are cited versus the Ag/AgCl electrode. Differential pulse polarography was performed on the same instrument. All solutions were 0.1 M in Et_4NClO_4 and were purged with N_2 before measurement. The stoichiometry of each electron-transfer process was established by wave-height comparisons with known one electron redox processes. For the electrochemical substrate binding titrations, the equilibria may be represented by a redox square (Scheme 2). Experimentally, aliquots of a standard alkali metal perchlorate solution were added incrementally to a 5 mL sample of 5 mM cobalt complex, and cyclic voltammograms were measured after each addition. $[CoL^6(OH_2)]^{3+}$ and $[CoL^8(OH_2)]^{3+}$ were sufficiently

Scheme 2



soluble in pure water, but $[CoL^7(OH_2)]^{3+}$ required 35% DMF to effect dissolution, so measurements were performed for all complexes in this solvent system. All measurements were made at pH of 11.5−12.0, by the addition of Et_3N to the solutions before analysis. The shift in $Co^{III/II}$ redox potential (ΔE) is related to the cation concentration ($[M^+]$) and the Co^{II} and Co^{III} substrate binding constants (K_{red} and K_{ox}) by eq 1:

$$\Delta E = \frac{RT}{F} \ln\left[\frac{1 + K_{red}[M^+]}{1 + K_{ox}[M^+]}\right] \qquad (1)$$

Solution UV−vis spectra were measured on a Perkin-Elmer Lambda 40 spectrophotometer. Infrared spectra of compounds dispersed as KBr disks were measured on a Perkin-Elmer series 1600 FT-IR instrument. Molecular mechanics calculations were performed with MOMEC,[23] using a published force field.[24] The only additional parameters were the Na−O parameters, which were r_o 2.30 Å and k_r 0.3 mdyn Å^{-1}. No axial water molecules were included in the Na^+ coordination sphere. Electrospray ionization mass spectrometry was performed on a Finnigan MAT900XL-TRAP spectrometer.

Crystallography. Cell constants were determined by a least-squares fit to the setting parameters of 25 independent reflections measured on an Enraf-Nonius CAD4 four-circle diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å) and operating in the $\omega-2\theta$ scan mode within the range $2° < 2\theta < 50°$. Data reduction and empirical absorption corrections (ψ-scans) were performed with the WINGX[25] suite of programs. Structures were solved by heavy-atom methods with SHELXS86[26] and refined by full-matrix least-squares analysis with SHELXL97.[27] Most non-H atoms were refined with anisotropic thermal parameters, except for disordered perchlorate O-atoms, and, in some instances, atoms in the crown ether rings. Disordered atoms were refined with complementary occupancies and isotropic thermal parameters. In some cases, tetrahedral restraints were applied to disordered ClO_4^- ions and to uncomplexed crown ether ring atoms. A complete data set (to $2\theta = 50°$) for $[Co(HL^7)(OH_2)](ClO_4)_4$ could not be collected because of crystal instability, and isotropic refinement of the data was performed. Noncoordinated water H-atoms were not modeled in any structure. Drawings of molecules were produced with the program ORTEP.[28] Crystal data appear in Table 1, and selected bond lengths and angles are given in Table 2.

Results

Ligand Syntheses. Syntheses of the ditopic ligands L^6, L^7, and L^8 were accomplished in an identical manner by reductive alkylation of the L^5 precursor with the appropriate aldehyde. NMR spectroscopy showed the reaction mixture to contain impurities such as unreacted amine and reduced aldehyde, so purification of each ligand was achieved as its Co^{III} complex. Imidazolidines are possible byproducts if the intermediate imine undergoes intramolecular nucleophilic attack by a macrocyclic secondary amine, but this was not observed in the present system. The pH of the reaction appears to be quite important, where protonation and intramolecular H-bonding protect the macrocyclic amines from nucleophilic attack by the imine intermediate (Scheme 1).

Cobalt(III) Complexes. The cobalt(III) complexes of the macrocycles L^6, L^7, and L^8 were prepared and characterized. It was found previously that the unsubstituted parent ligand L^5 may bind to Co^{III} as a hexadentate, pentadentate, or tetradentate, depending on the reaction conditions.[12,29] In this case, pentadentate coordination has been observed exclusively, with the substituted pendent amine remaining uncoordinated. Electronic spectroscopy of each complex $[CoL^n(OH_2)]^{3+}$ ($n = 6-8$) was characteristic of a $Co^{III}N_5O$ chromophore, with a single broad visible maximum around 495 nm comprising low-symmetry components of the $^1T_{1g} \leftarrow {}^1A_{1g}$ (O_h) transition. The anticipated higher energy d−d maximum ($^1T_{2g} \leftarrow {}^1A_{1g}$ (O_h)) was obscured by intense maxima from the benzo-crown ether unit in the near UV. In the case of $[CoL^7(CN)]^{2+}$, which resulted from decomposition of excess sodium cyanoborohydride in the presence of the cobalt complex, unresolved components of the $^1T_{1g} \leftarrow {}^1A_{1g}$ (O_h) transition appeared at 428 nm, because of the influence of the strong field cyano ligand.

Crystal Structures: $[CoL^6(OH)](ClO_4)_2 \cdot H_2O$. The structure in Figure 1 shows the $[CoL^6(OH)]^{2+}$ receptor, in the absence of a guest. The structure comprises the complex cation, two disordered perchlorates (one at half occupancy), and a water molecule each on general sites, and another disordered ClO_4^- on a 2-fold axis. The amine macrocycle coordinates to Co as a pentadentate, with the unsubstituted primary amine coordinated in an axial position perpendicular to the macrocyclic secondary amines. Co−N bond lengths (Table 2) are not unusual.[29] The sixth coordination site is occupied by a hydroxo ligand. The macrocyclic ring adopts the so-called trans-I (*RSRS*) configuration,[30] where the four macrocyclic amine protons are on the same side of the ring and cis to the substituted pendant amine. This configuration is typical of pentadentate coordinated complexes of the parent ligand L.[5 14,15,29] Conformations of cyclam complexes (in a

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Table 1. Crystal Data

	$[CoL^6(OH)]$-$(ClO_4)_2{\cdot}H_2O$	$K\{[CoL^6(OH)]\}_2$-$(ClO_4)_5{\cdot}7H_2O$	$[Co(HL^7)(OH_2)]$-$(ClO_4)_4$	$Na[CoL^7(CN)]$-$(ClO_4)_3{\cdot}H_2O$	$Na[CoL^8(OH)]$-$(ClO_4)_3{\cdot}2.5H_2O$
formula	$C_{25}H_{49}Cl_2CoN_6O_{14}$	$C_{50}H_{108}Cl_5Co_2KN_{12}O_{37}$	$C_{27}H_{53}Cl_4CoN_6O_{22}$	$C_{28}H_{52}Cl_3CoN_6NaO_{18}$	$C_{29}H_{60}Cl_3CoN_6NaO_{21.5}$
fw	787.53	1803.69	1014.48	963.04	1025.1
space group	$C2/c$ (No. 15)	$P2/n$ (No. 13)[a]	$P2_1/n$ (No. 14)[b]	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)
a, Å	28.664(2)	11.363(1)	11.580(3)	11.584(1)	10.755(5)
b, Å	14.036(9)	14.3133(9)	14.604(1)	13.495(2)	10.948(2)
c, Å	18.187(2)	24.073(4)	25.965(7)	15.434(4)	20.690(3)
α, deg				64.02(2)	104.52(1)
β, deg	90.17(1)	97.13(1)	97.36(1)	77.46(1)	97.42(2)
γ, deg				75.203(9)	106.05(2)
V, Å^3	7317(5)	3885.0(8)	4354.9(2)	2081.6(6)	2214.3(1)
Z	8	2	4	2	2
T, °C	23	23	23	23	23
λ, Å	0.71073	0.71073	0.71073	0.71073	0.71073
μ, cm^{-1}	6.84	7.49	7.25	6.95	6.64
ρ_{calcd}, g cm^{-3}	1.430	1.542	1.547	1.536	1.537
$R(F_o)$[c]	0.0999	0.0863	0.1556	0.0642	0.0978
$wR2(F_o^2)$[d]	0.2738	0.2291	0.3639	0.1488	0.2371

[a] Variant of $P2/c$. [b] Variant of $P2_1/c$. [c] $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$. [d] $wR2(F_o^2) = (\sum w(F_o^2 - F_c^2)/\sum wF_o^2)^{1/2}$.

Table 2. Selected Bond Lengths (Å) and Bond Angles (deg) and Torsional Angles (deg) for Complex Cations

	$[CoL^6(OH)]^{2+}$	$\{K[CoL^6(OH)]_2\}^{5+}$	$[Co(HL^7)(OH_2)]^{4+}$	$\{Na[CoL^7(CN)]\}^{3+}$	$\{Na[CoL^8(OH)]\}^{3+}$
Co−N1	1.948(8)	1.949(7)	1.87(2)	1.962(6)	1.92(1)
Co−N2	1.927(9)	1.945(7)	1.98(2)	1.954(6)	1.963(9)
Co−N3	1.936(9)	1.950(8)	1.91(2)	1.948(6)	1.94(1)
Co−N4	1.949(9)	1.934(7)	1.97(2)	1.947(6)	1.951(9)
Co−N5	1.958(9)	1.954(7)	1.90(2)	2.001(5)	1.961(9)
Co−O (or C)	1.883(6)	1.893(6)	1.87(2)	1.894(8)	1.896(7)
range Na^+−O (ether)				2.314(7)−2.395(7)	2.65(1)−3.00(2)
range K^+−O (ether)		2.82(1)−2.95(1)			
N1−Co−N2	88.4(4)	88.4(3)	87.9(9)	88.3(3)	87.1(4)
N1−Co−N3	176.8(4)	176.5(3)	176(1)	176.1(3)	175.5(4)
N1−Co−N4	95.4(4)	95.4(3)	97.1(9)	94.7(2)	97.4(3)
N1−Co−N5	95.3(4)	94.1(3)	95(1)	94.0(2)	96.0(4)
N1−Co−O (or C)	91.3(3)	91.5(3)	89.6(9)	91.7(3)	87.1(4)
(H_3)C−**C**−**N6**−C(H_2) (ω_1)	46.5	42.1	59.3	48.0	51.2
C−**N6**−**C(H₂)**−C(Ar) (ω_2)	−166.5	−161.2	−161.4	−175.0	171.0
N6−**C(H₂)**−**C(Ar)**−C(H) (ω_3)	−76.0	−36.2	−45.3	−68.5	43.0

trans configuration) typically find the two six-membered chelate rings in chair conformations with the two gauche five-membered chelate rings. The pentadentate coordinated ligand L^6 has one of the six-membered chelate rings in a boat conformation, which is necessary in order for the primary amine (N5) to coordinate. The oxygen donors are distinctly nonplanar. Examination of O−CH_2−CH_2−O torsion angles shows the angle between O(1) and O(2) to be >90°. For guest binding, all of these torsional angles must be gauche, generally in the range 65°−75°.[31] The distortion of the small crown ether ring is in part an attempt to minimize electrostatic interactions between the electronegative oxygen atoms. A similar lack of planarity is exhibited by benzo-12-crown-4,[32] dibenzo-12-crown-4,[33] and benzo-13-crown-4[34] in their metal-free conformations.

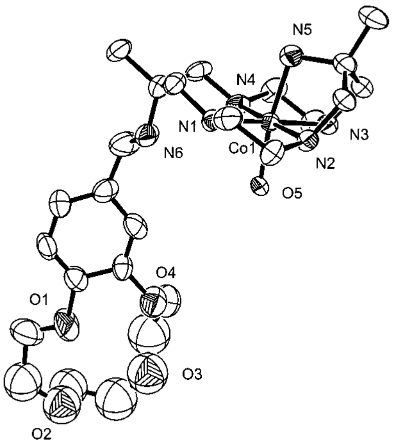

Figure 1. ORTEP view (30% ellipsoids) of the $[CoL^6(OH)]^{2+}$ cation. H-atoms omitted.

$K\{[CoL^6(OH)]\}_2(ClO_4)_5{\cdot}H_2O$. The structure in Figure 2 shows a K^+ complex of the receptor, where two crown ether units have bound to potassium to give a 2-fold symmetric trimetallic complex. The coordination environment of the Co^{III} center is identical to that of the guest-free receptor. The K^+ ion adopts a ten-coordinate distorted pentagonal prismatic geometry, comprising the bidentate ClO_4^- anion and two tetradentate coordinated benzo-12-crown-4 units. The Co···K separation is 10.92 Å, and the Co···Co distance is 17.58 Å. By comparison with the crystal structure of the guest-free receptor $[CoL^6(OH)]^{2+}$, the conformation of the crown ether

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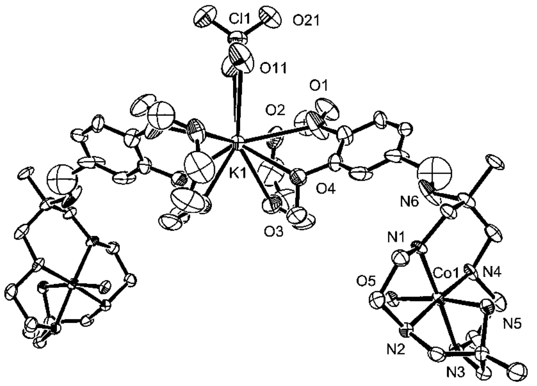

Figure 2. ORTEP view (30% ellipsoids) of the $\{K[CoL^6(OH)]_2\}(ClO_4)^{4+}$ cation. H-atoms omitted.

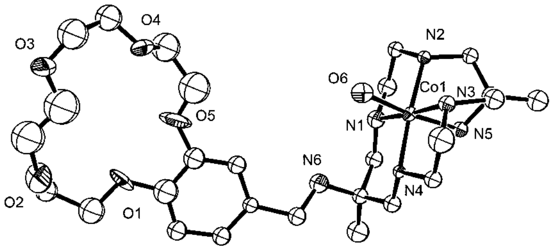

Figure 3. ORTEP view (30% ellipsoids) of the $[Co(HL^7)(OH_2)]^{4+}$ cation. H-atoms omitted.

ring is more highly ordered because of the effect of the coordinated ion, but the relative dispositions of the crown ether with respect to the Co macrocyclic amine moiety are very similar in both structures.

$[Co(HL^7)(OH_2)](ClO_4)_4$. Although the data for this structure were weak and incomplete because of crystal instability, the structure could still be solved, but refinement was restricted to isotropic thermal parameters, which resulted in a relatively imprecise result. Nevertheless, the conformation of the guest-free protonated receptor $[Co(HL^7)(OH_2)]^{4+}$ is well defined and illustrated in Figure 3. The geometry of the Co amine unit is the same as that seen in the two structures of the ligand L^6 described previously except an aqua ligand is present rather than hydroxo, and no disorder in the uncomplexed crown ether ring was identified. The tetrapositive charge results from protonation of the free amine (N6).

$Na[CoL^7(CN)](ClO_4)_3 \cdot H_2O$. The cyano-substituted analogue $[CoL^7(CN)]^{2+}$ was crystallized with a Na^+ guest ion bound in the benzo-15-crown-5 site. The structure of the complex is shown in Figure 4. Apart from CN^- coordination in the site trans to the pendant amine, the trans-I isomeric form of the Co amine moiety is again conserved. The Co−CN coordinate bond is the shortest, as expected. The pentadentate crown ether binds the Na^+ guest ion, which is also coordinated to a bidentate ClO_4^-. The crown ether−Na^+ coordinate bonds are ~0.2 Å shorter than those made with the ClO_4^- anion, and the Na^+ ion is displaced by ~0.66 Å from the least squares O_5 plane of the crown ether toward the anion. This is expected on the basis of the preferred hole size of benzo-15-crown-5, which is too small to completely encircle Na^+.

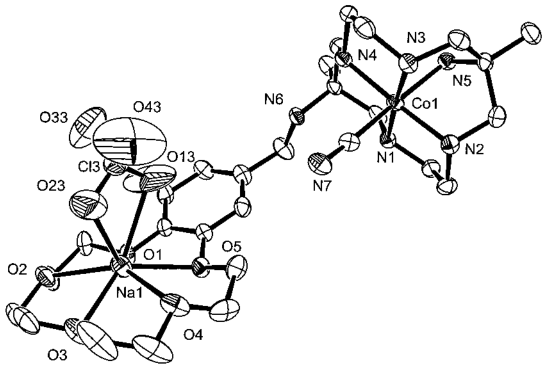

Figure 4. ORTEP view (30% ellipsoids) of the $Na[CoL^7(CN)]^{3+}$ cation. H-atoms omitted.

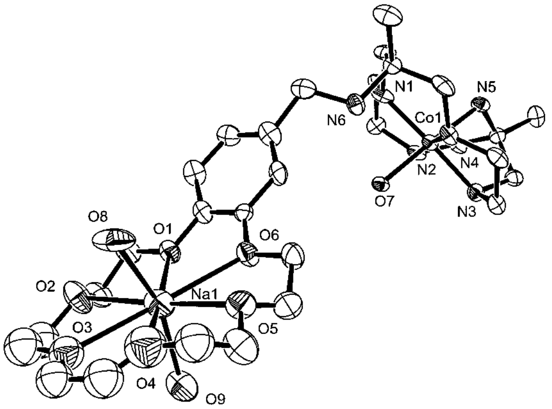

Figure 5. ORTEP view (30% ellipsoids) of the $Na[CoL^8(OH)]^{3+}$ cation. H-atoms omitted.

$Na[CoL^8(OH)](ClO_4)_3 \cdot 2.5H_2O$. The Na^+-bound receptor bearing an 18-crown-6 binding unit was also crystallized, and its structure is shown in Figure 5. The conformation of the Co^{III} amine moiety is identical with those found in the other four structures, and a hydroxo ligand occupies the sixth coordination site. The Na^+ ion is eight coordinate: bound to the hexadentate crown ether and a pair of trans axially coordinated aqua ligands. It is notable that the Na−O4 bond is 0.3 Å longer than the other crown ether−Na coordinate bonds, which reflects the size mismatch between the guest ion and the 18-membered ring.

Solution Conformation. The relative orientations of the crown ether rings and Co amine subunits were of interest. Because of its solubility and straightforward complexation properties, that is, no sandwich complex formation being possible, we focused on the $[CoL^8(OH)]^{2+}$ system as our model for the complexes investigated here. Across the series, L^6, L^7, and L^8 enlargement of the crown ether ring has little steric effect on the environment of the aminomethylene "bridge" between the azamacrocycle and crown ether subunits, so we assume that our observations for this system are representative of the entire series. A comprehensive assignment of both the ^1H and ^{13}C NMR resonances of $[CoL^8(OH)]^{2+}$ was accomplished using a variety of 2D experiments including COSY ($^1H-^1H$ coupling), HSQC ($^1H-^{13}C$ coupling, directly attached), and HMBC ($^1H-^{13}C$ coupling, separated by more than one bond). This information was used to enable a series of NOE experiments. There is a crossover between NOE signal enhancement for small molecules and signal attenuation for very large molecules,[35] with compounds in the intermediate molecular weight range 300−1000 g mol^{-1} tending to fall through the gap. For this reason, ROESY experiments, which are unaffected by molecular rotational frequencies, and hence molecular weight, were performed of the $[CoL^8(OH)]^{2+}$ system in the absence and presence of guest Na^+ ions. There are many cross-peaks of varying intensity (Figure S1, Supporting Information). Strong peaks are observed for pairs of protons in proximity (separation $r \sim 2-3$ Å), with intensities proportional to r^{-6}. Of most interest were the cross-peaks involving the aromatic protons in the 2- (7.12 ppm), 5- (7.00), and 6-positions (6.85). Although there are many peaks common to both spectra in the absence and presence of Na^+ ions, there are some significant differences. In the absence of added guest, H2 and H6 exhibit coupling with the pendent methyl group protons. Upon addition of Na^+, the $H2\cdots H_3C$ and $H6\cdots H_3C$ coupling vanishes and is replaced by a peak due to H2···HN−Co coupling. The trans-I stereochemistry of the coordinated macrocycle dictates that the methyl group and the secondary amine protons are trans with respect to the six-membered chelate ring to which they are attached. The changeover from methyl to amine proton coupling indicates that the crown ether undergoes a significant change in its disposition with respect to the Co amine subunit upon complexation of Na^+.

There are three saturated C−C or C−N bonds linking the azamacrocyclic and crown ether subunits, and the three torsional angles defined by these bonds are given in Table 2 and labeled ω_1, ω_2, and ω_3 in Figure 6. In principle, there are 54 ($6(sp^2-sp^3) \times 3(sp^3-sp^3) \times 3(sp^3-sp^3)$) torsional minima, if the crown ether and the Co amine units are treated as rigid bodies. In practice, there are relatively few stable, nondegenerate conformers when symmetry and steric effects are considered. The pseudo-mirror-plane symmetry of the Co amine unit makes one-third of the conformers ($\omega_1 \sim 60°$) degenerate with another third ($\omega_1 \sim -60°$). Furthermore, all conformers where ω_1 is anti ($\sim\pm180°$) may be ruled out on the basis of steric repulsion between the methylene and adjacent secondary amine protons. Turning to the ω_2 angle, inspection of molecular models shows that the anti rotamer and only one of the two gauche rotamers are possible, with the remaining gauche rotamer resulting in severe clashing between the crown ether and Co amine subunits. An sp^2-sp^3 C−C bond (ω_3) will have six torsional minima at ±30, ±90, and ±150°. Given the constraints that $\omega_1 \sim 60°$ and $\omega_2 \sim \pm180°$, this leaves only 12 possible nondegenerate conformers based on the ω_2 and ω_3 torsional angles. The torsional angles obtained from the crystal structure geometries are given in Table 2. Consistent with the preceding discussion, the ω_1 torsional angles are all close to the expected local minimum of ∼60°, and the ω_2 angles are around ±180°. The ω_3 torsional angles of $[CoL^6(OH)]^{2+}$ and $Na[CoL^7(CN)]^{3+}$ are close to the −90° minimum, and the $K\{[CoL^6(OH)]\}_2{}^{5+}$ and $[Co(HL^7)(OH_2)]^{3+}$ complexes exhibit torsional angles around the −30° minimum, while the same ω_3 torsion angle in structure of $Na[CoL^8(OH)]^{3+}$ is approximately 30°.

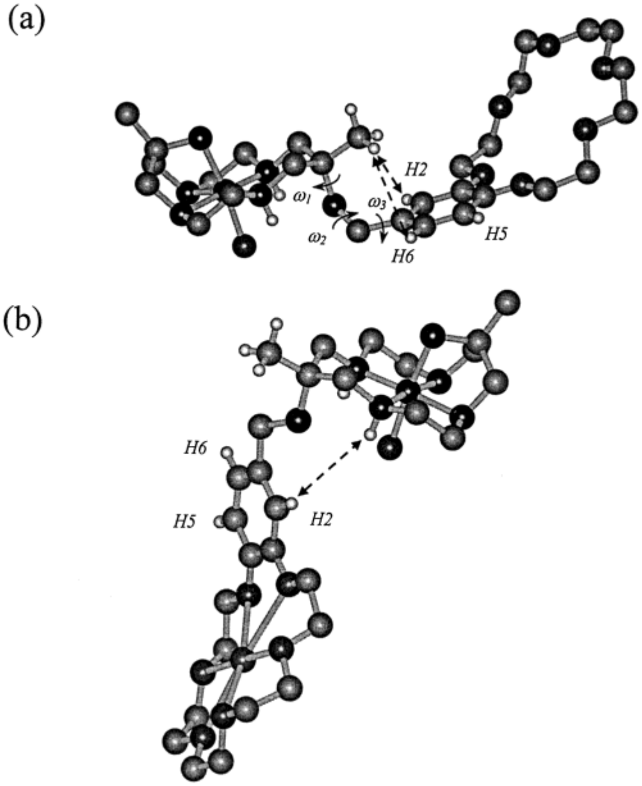

Figure 6. Molecular mechanics calculated structures of (a) $[CoL^8(OH)]^{2+}$ and (b) $Na[CoL^8(OH)]^{3+}$ consistent with their NMR spectra. Important H···H coupling highlighted.

We have employed molecular mechanics (MM) modeling to assist us in the assignment of solution conformations of $[CoL^8(OH)]^{2+}$ in the presence and absence of Na^+. MM calculations led to the assignment of the two conformers in Figure 6 as being the most likely ones for $[CoL^8(OH)]^{2+}$ and $Na[CoL^8(OH)]^{3+}$ on the basis of the NMR experiments. The calculated structure of the Na^+ complex (Figure 6b) is essentially the same as that found in the crystal structure (Figure 5). The substrate free conformation is distinctly different, with the crown ether group almost parallel with and oriented well away from the aza-macrocyclic cobalt subunit. The proximity of the methyl group and the aromatic protons has been highlighted in Figure 6a.

Electrochemical Titrations. As dissolved, the three Co complexes gave solution pH values around 8.5−9.0, but this resulted in irreversible voltammetric responses. At high pH (11−12), each receptor exists as a dipositively charged hydroxo complex where the pendant amine is not protonated, and reversible $Co^{III/II}$ couples were obtained around −0.7 V versus Ag/AgCl. At pH 3, the potentials shifted to −0.35 V versus Ag/AgCl. This anodic shift compared to the value at higher pH is consistent with protonation of both the hydroxo ligand and the pendant amine to give a tetrapositively charged species, that is, $[Co(HL^n)(OH_2)]^{4+}$. However, at this pH, the $Co^{III/II}$ potentials were unresponsive to the addition of cations. Figure 7 shows the gradual anodic shift of the $Co^{III/II}$ redox

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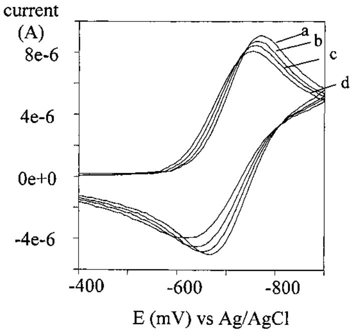

Figure 7. Cyclic voltammograms of $[CoL^7(OH)]^{2+}$ upon addition of Na^+: (a) 0 equiv Na^+ added, (b) 0.5 equiv, (c) 1.0 equiv, (d) 2.5 equiv.

Table 3. Electrochemically Determined Binding Constants for $[CoL^6(OH)]^{2+}$, $[CoL^7(OH)]^{2+}$ and $[CoL^8(OH)]^{2+}$ (Measured in H_2O Containing 35 % DMF)

		Li^+	Na^+	K^+
$[CoL^6(OH)]^{2+}$	$\log K_{red}$	2.5(1)	2.5(1)	2.5(1)
	$\log K_{ox}$	*a*	1.9(2)	1.4(3)
	$\Delta E_{1/2}$ (mV)	62	24.5	41
$[CoL^7(OH)]^{2+}$	$\log K_{red}$	2.4(1)	2.4(1)	2.3(1)
	$\log K_{ox}$	*a*	1.1(6)	*a*
	$\Delta E_{1/2}$ (mV)	41	42	30.5
$[CoL^8(OH)]^{2+}$	$\log K_{red}$	2.5(1)	2.6(1)	2.7(1)
	$\log K_{ox}$	1.6(5)	2.0(1)	*a*
	$\Delta E_{1/2}$ (mV)	34	29.5	48

[a] Values too small to be determined electrochemically.

couple in $[CoL^7(OH)]^{2+}$ upon addition of Na^+, which is representative of all of the titrations performed and demonstrates the shifting behavior of the cyclic voltammograms. The titration curves of $[CoL^6(OH)]^{2+}$, $[CoL^7(OH)]^{2+}$, and $[CoL^8(OH)]^{2+}$ with each of the monovalent cations Li^+, Na^+, and K^+ appear in the Supporting Information (Figure S2). Table 3 lists the stability constants determined for the three receptors in their oxidized and reduced forms with Li^+, Na^+, and K^+. In each case, $\log K_{red}$ is small ($\sim 10^2$) and only 1−2 orders of magnitude greater than K_{ox}, which is consistent with the observed shifting behavior. In some systems, K_{ox} values were too small to be determined.

Multinuclear NMR Titrations. ^7Li and ^{23}Na NMR spectroscopy was used to investigate receptor/substrate binding. In all cases, a single broad peak was observed as expected for rapid exchange between complexed and uncomplexed alkali metal ion at 302 K. The ^{23}Na NMR spectra in the presence of $[CoL^7(OH)]^{2+}$ are shown in Figure S3 of the Supporting Information. ^{23}Na and ^7Li NMR titration curves for $[CoL^6(OH)]^{2+}$, $[CoL^7(OH)]^{2+}$, and $[CoL^8(OH)]^{2+}$ also appear in the Supporting Information (Figure S4). In most cases, the sodium and lithium resonances shifted downfield with an increase in receptor concentration. Curiously, the benzo-18-crown-6 analogue, $[CoL^8(OH)]^{2+}$, causes an upfield shift of the ^{23}Na resonance, although this phenomenon been observed previously for receptors of this type.[36] Dilution of a sample of $NaClO_4$ showed that the ^{23}Na shift changed negligibly with concentration. The titration curves indicate only partial (weak) complex formation in all instances, because a gradual shift is observed that does not approach a saturating value within the concentration range investigated.[71] Limited solubility of the receptors prohibited the use of higher concentrations that might have led to a meaningful fit to the titration data,[37] so the data provide qualitative evidence only of complexation.

Electrospray Ionization Mass Spectrometry. A series of measurements were undertaken on $[CoL^6(OH)]^{2+}$, $[CoL^7(OH)]^{2+}$, and $[CoL^8(OH)]^{2+}$ with 1 equiv of Li^+, Na^+, and K^+ in methanol, and these results can be seen in Table 4. It should be noted that, particularly for $[CoL^7(OH)]^{2+}$ and $[CoL^8(OH)]^{2+}$, complexes with Na^+ and K^+ can be seen even without the addition of these cations. These ions are common trace impurities in the instrument line and glassware but, and in this case, they were present at easily detectable levels. No quantitative conclusions have been drawn from these experiments, but they do demonstrate that substrate binding occurs in the gas phase, as a complement to solid state (crystallography) and in solution (electrochemistry and NMR) studies.

Several patterns are obvious for all three receptors. For $[CoL^6(OH)]^{2+}$, a peak at 551, corresponding to $[Co(L^6) - 2H^+]^+$, suggests that the crown ether coordinates in the coordination site vacated by the dissociated OH^- ligand. Peaks at 587, 627, and 651 correspond to the ions $[Co(L^6)(2H_2O) - 2H^+]^+$, $[Co^{III}(L^6)(3H_2O)(Na^+) - 3H^+]^+$, and $[Co^{III}(L^6)(ClO_4\text{-}) - H^+]^+$, respectively. The aqua and/or perchlorato ligands most likely complete the cobalt coordination sphere, with extra water molecules and cations associated with the crown ether. Similar ions are seen in the spectra of $[CoL^7(OH)]^{2+}$ and $[CoL^8(OH)]^{2+}$, except that they are successively 44 mass units larger, because of the crown ether ring expansion by one (or two) ethyleneoxy (CH_2CH_2O) group(s). Common to all three receptors are peaks corresponding to the dipositively charged ion, appearing at 276, 298, and 320 for $[Co(L^6) - H^+]^{2+}$, $[Co(L^7) - H^+]^{2+}$, and $[Co(L^8) - H^+]^{2+}$, respectively. The $[CoL^6(OH)]^{2+}$ receptor appears to bind very few cations in a 1:1 ratio. Sodium and potassium both give some evidence of forming 2:1 sandwich type complexes, but these peaks are very small. The $[CoL^7(OH)]^{2+}$ receptor, with a benzo-15-crown-5 moiety, exhibits more selectivity. As mentioned previously, all spectra also exhibit peaks due to (adventitious) sodium and potassium complexes. In the cases where these solutions have been spiked with the appropriate cation, an increase in peak intensity is observed. Upon addition of lithium, peaks can be seen at 800, 816, and 832, corresponding to the Li^+, Na^+, and K^+ complexes, with two perchlorate anions present. Addition of sodium cations leads to the disappearance of the lithium signal, and a change of intensities of Na/K to approximately 6:1. Addition of potassium cations leads to a reversal of this ratio, with intensities now 4:5. Similar results were obtained with $[CoL^8(OH)]^{2+}$ (Table 4).

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Table 4. Observed ESI-MS Peaks

		$[CoL^6(OH)]^{2+}$	$[CoL^7(OH)]^{2+}$	$[CoL^8(OH)]^{2+}$
uncomplexed receptor		276, 551, 587, 651	298, 595, 631, 671, 695	320, 639, 675, 715, 739
+ 1 equiv Li^+	$\{[CoL^n](2ClO_4) + (Li^+) - H^+\}^{1+}$		800 (30)	845 (10)
	$\{[CoL^n](2ClO_4) + (Na^+) - H^+\}^{1+}$		816 (100)	861 (100)
	$\{[CoL^n](2ClO_4) + (K^+) - H^+\}^{1+}$		832 (30)	877 (25)
+ 1 equiv Na^+	$\{[CoL^n](2ClO_4) + (Na^+) - H^+\}^{1+}$	627	816 (100)	861 (100)
	$\{[CoL^n](2ClO_4) + (K^+) - H^+\}^{1+}$		832 (16)	877 (35)
+ 1 equiv K^+	$\{[CoL^n](2ClO_4)+(Na^+)\text{-}H^+\}^{1+}$		816 (80)	861 (50)
	$\{[CoL^n](2ClO_4)+(K^+)\text{-}H^+\}^{1+}$		832 (100)	877 (100)

Discussion

Pendant amines of L^5 are well suited to reductive alkylation (Scheme 1). Substituents such as methyl,[38] carboxymethyl,[39] carboxyphenylmethyl,[40] anthrylmethyl,[41] naphthylmethyl,[42] and ferrocenylmethyl[18] have been attached to L^5 without altering the donor properties of the secondary macrocyclic N-donors. In this sense, the amine complex subunit retains the spectroscopic and electrochemical properties of the unsubstituted precursor. By contrast, direct functionalization of the coordinating amines can be problematic through the possibility of N-based diastereomers and decreased binding strength going from a secondary to a tertiary amine. In this work, we have adapted this approach to the synthesis of benzo-crown ether-substituted amines by using the formyl derivatives of benzo-12-crown-4, benzo-15-crown-5, and benzo-18-crown-6. It is possible for side reactions to occur. The coordinated imine intermediate may undergo intramolecular nucleophilic attack by an adjacent secondary amine in the macrocyclic ring. The result is an imidazolidine, or cyclic aminal, and such compounds are relatively stable except in the presence of aqueous acids, where they are hydrolyzed. Previously, tetraaza-macrocycles with imidazolidine rings have been synthesized by reacting $[CuL^5]^{2+}$ and formaldehyde in aqueous solution.[43] The substituted macrocycles have reduced conformational flexibility and significantly different spectroscopic and electrochemical properties. More recently, a similar phenomenon has been observed in metal-free condensations of L^5 and its analogues with 4-carboxybenzaldehyde and glyoxylic acid,[44] and 2-naphthaldehyde.[42]

The conformational flexibility inherent to benzo-crown ethers is illustrated by the crystal structures shown in Figures 1−5. The conformational changes within large crown ethers upon complexation are apparent by comparing the structures of $[Co(HL^7)(OH_2)]^{4+}$ with $Na[CoL^7(CN)]^{3+}$. The most significant indicators of these conformational changes are the O−C−C−O dihedral angles within the ring. If any of these are greater than 90°, then at least one of the O-donors must adopt an exo orientation where the O atom is inappropriately oriented for metal ion coordination. In the structure of $[Co(HL^7)(OH_2)]^{4+}$, the O2−C22−C23−O3 angle is 173.8°, and O3 adopts an exo conformation. By comparison, the conformation of the smaller, less flexible crown ether within L^6 is less affected by metal ion coordination; that is, it is better preorganized for complexation than the larger cyclic ethers. Although we have no crystal structure of $[CoL^8(OH)]^{2+}$ in its guest-free form, the structures of benzo-18-crown-6 derivatives in the absence of guests are generally quite distorted, with some O-donors adopting an exo conformation while the methylene groups rotate inward to fill the cavity.[45] Upon complexation of a K^+ ion, an ion well matched to the cavity size of benzo-18-crown-6, the molecule assumes a highly symmetrical conformation.[46] In the crystal structure of [K(benzo-18-crown-6)](SCN), all K−O bond lengths are equal, and the five-membered chelate rings adopt energetically favorable gauche conformations.[47]

Many structures exist where crown ethers have complexed cations that are considered either too large or too small for the cavity. A common occurrence in instances where cations are too large for a cavity is the formation of sandwich complexes, in which the cation is sandwiched between two ligands. This is observed for complexes of benzo-15-crown-5 and K^+,[48] which as well as being too small, also provides too few oxygen donors for the potassium ion's coordination sphere. A similar situation exists for 12-crown-4 in complex with Na^+ or K^+.[49] In this case, we have observed a similar example with the crystallization of $K\{[CoL^6(OH)]\}_2(ClO_4)_5$. Complexes of 18-crown-6 and cesium tend to result in half-sandwich structures, with bridging anions, because the crown ether can almost satisfy the coordination number of the cation, but the metal is still too large for the cavity.[50] Crown ethers can complex cations that are too small by constricting their cavities, as seen in the structure of the sodium complex of 18-crown-6.[51] The structure is quite similar to that of the potassium complex; however, the Na−O bond lengths are slightly shorter, as expected. Although five O-donors are in

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a planar disposition with respect to the metal ion, the macrocycle folds in order that the sixth O-donor may coordinate, and ligand strain is increased as a result. In the present work, the complex $Na[CoL^8(OH)]^{3+}$ finds the Na^+ guest in a similar situation, with the ion being too small to bind to all six O-donors with equal strength. The excessively long Na−O4 contact (∼3.00 Å) reflects this size mismatch. It is also not unusual for large crown ethers to complex two cations. A well-known example is that of dibenzo-24-crown-8, which binds two sodium ions in its cavity.[52]

The solution NMR analysis of $[CoL^8(OH)]^{2+}$ in the absence and presence of Na^+ indicated a significant conformational change upon complexation. In terms of the torsional angles discussed previously, ω_2 must be gauche in the absence of bound guest ion if NOE peaks between the aromatic protons and the methyl group are to be observed. By contrast, the Ar−**H**···**H**−N−Co NOE peaks seen in the spectrum of $[CoL^8(OH)]^{2+}$ in complex with Na^+ are consistent with the MM-calculated conformation shown in Figure 6b and essentially the same conformation found in the crystal structure of $Na[CoL^8(OH)](ClO_4)_3$ (Figure 5). The origins of the substrate-induced conformational change remain unclear. Electrostatic repulsion between the two positively charged metal ions can be ruled out as the crown ether moves closer to the cobalt ion upon binding Na^+. The picture presented in Figure 6 is a very simplified one. Second-sphere coordination by solvent molecules is not included in the analysis, and this may have a bearing on the observed structures, but further speculation is not warranted. Nevertheless, the conformational change is marked, and our NMR experiments have been important in identifying this feature.

Cursory examinations of the electrochemically determined K_{red} values (Table 3) show that the receptor molecules exhibit very little selectivity, with all log K_{red} values reported being of the order 2 regardless of cavity size and ionic radius compatibility. This is similar to early work on anthraquinone-based receptors, which showed very little selectivity upon reduction.[10,53−55] Although size compatibility between the cationic substrate and the crown ether ring size is important, it is not necessarily dominant. A large number of factors, some of which include electrostatic effects, anions, solvation, and chelate ring size, may be equally important.[56,57] Also, the number of donor atoms that a crown ether ring can provide is critical. By formation of sandwich complexes, macrocycle folding,[58] or incorporation of solvent or anion molecules, crown ethers can bind a range of ill-fitting cations.

The azamacrocyclic cobalt(III) subunit in these systems may be considered as a substituent on the crown-ether-fused phenyl ring. It has been shown that substituent groups can have a considerable effect on stability constants.[59,60] In some cases, these effects can be larger than the ring size effect. The influence of aromatic substituents is most likely reflected in the Lewis basicity of the two aromatic ether oxygens on each receptor. The stability constants of benzo crown ethers are already known to be lower than those of aliphatic crown ethers, by virtue of their increased rigidity and also the decreased basicity of the oxygens due to their conjugation with the aromatic ring. The Co^{III} amine macrocycle is a large, positively charged group, which on the whole should draw electron density away from the crown ether. The observed 1−2 orders of magnitude changes in binding constant upon reduction reflect a significant effect of the Co amine subunit. However, whether this is a through-space or through bond effect is uncertain.

Another consideration is pH, which leads to the presence of an OH^- ligand in the sixth coordination site of the Co^{III} complex. Upon protonation of both the hydroxo ligand and the free secondary amine, the tetrapositively charged complexes are ineffective receptors through the increase in electrostatic repulsion of their substrates. The potentially bridging hydroxo ligand may also have an attractive effect toward a substrate cation. The crown ether moiety is syn to the hydroxo ligand, and the flexibility of the sidearm linking the two subunits is sufficient to allow conformational rearrangement of the molecule. Evidence is provided by NOE NMR experiments for a change in position of the aromatic protons upon cation addition, consistent with movement of the crown ether syn to the hydroxo ligand.

It was important to independently demonstrate metal ion binding in these systems with more than one physical method. NMR spectroscopy is a commonly used technique for the determination of binding constants.[61−65] It depends on chemical shift or line width differences between complexed and uncomplexed species and may be used when such differences can be detected in either the receptor or the substrate. ^{13}C and ^1H NMR spectroscopy are frequently used, with resonances of the atoms in the crown ether being monitored. The changes observed in proton spectra are typically very small, generally around 0.1−0.2 ppm shift, and up to about 0.5 ppm in some specially designed

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sandwich-type complexes.[66,67] ^{13}C spectra offer changes of the order 2−3 ppm.[66,68,69]

Another common tactic is to monitor the NMR spectrum of the substrate cation.^{23}Na and ^{7}Li have nuclear spin $1^1/_2$ and high abundances of 100% and 92.58%, respectively, making them attractive nuclei for NMR titrations.[70−74] Chemical shift variations were observed because of changes in the cation solvation shell, as solvent molecules are replaced by crown ether oxygens in the complexation process. Although significant shifts in the ^{7}Li and ^{23}Na NMR resonances were observed (Figure S4), stability constants could not be reliably obtained by nonlinear least-squares methods as discussed in the Results section. Nevertheless, the results are indicative of the complexation, implying that the solvation environment of the metal cation is perturbed significantly upon addition of receptor. This is important, given the similarity of electrochemically determined values and the possibility of other factors influencing the potential shift.

Electrospray mass spectrometry is a low energy, soft ionization technique, which results in little or no fragmentation of ions, and as such lends itself well to the study of weakly bonded systems. It has been proven useful in the study of hydrogen-bonded aggregates,[75−77] and has been widely used in the study of coordination compounds, including the crown ethers.[78] It is a particularly useful technique for determining the stoichiometry of complexation, and binding constants have even been determined by comparison of peak heights.[79] It also offers several advantages over other techniques, in that very little sample is required, and it is compatible with a large range of solvent systems. However, information obtained for gaseous phase behavior does not necessarily correlate with that found in solution. Factors such as pH, solvation, and solvent polarity may result in different responses for different complexes.[80] Solvation is particularly important, because ions that are easily desolvated generate larger signals, and this may have an effect on quantitative results. ESI-MS has proven useful in this instance as further evidence of association, but quantitative statements cannot be made. The most significant conclusions to be drawn from the MS experiments were that 1:1 binding stoichiometry of $[CoL^7(OH)]^{2+}$ and $[CoL^8(OH)]^{2+}$ with sodium and potassium was preferred to Li complexation and to 2:1 receptor/substrate (sandwich) complex formation, which is consistent with crystallographic and electrochemical studies.

Conclusions

In this work, we have synthesized and characterized a new series of receptors based on a common pentaaminehydroxocobalt(III) unit covalently linked to a crown ether binding unit. We have studied the solution binding properties of this series using electrochemical, NMR, and mass spectrometric techniques, and the formation of receptor/substrate complexes has been established in each case. A significant degree of communication between binding and signaling subunits has been demonstrated, although without selectivity.

Acknowledgment. We wish to thank Ms. Lynette Lambert and Mr. Graham MacFarlane for technical assistance with the multinuclear NMR spectroscopy and mass spectrometry experiments, respectively. Financial support of the University of Queensland and the Australian Research Council is also gratefully acknowledged.

Supporting Information Available: Crystallographic data in CIF format; ROESY NMR spectra, electrochemical titration curves, ^{23}Na NMR spectra in the presence of $[CoL^7(OH)]^{2+}$, and all NMR titration curves (Figures S1−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

IC011232H

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