Synthesis and Characterization of Cobalt-Cage Complexes with Pendant Phenol Groups

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Received December 15, 1995[⊗]

The synthesis and characterization of four compounds formed from the reductive amination of *m*- and *o*-hydroxybenzaldehyde to (1,8-diamino-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)cobalt(III) are presented. These compounds are the mono- and dialkylated derivatives of the starting cobalt complex. The X-ray crystal structures of each compound, as its fully protonated chloride salt, have been obtained and are reported. The pK_a's of the compounds were determined by nonlinear least-squares analysis of data from potentiometric titrations and UV/vis spectrophotometry. The K_a's of the phenol groups of the compounds are reduced by roughly 1 order of magnitude compared to their analogous organic phenols. In the solid state, the compounds with one pendant phenol group (**2**, **4**) are yellow and adopt the ob_3 conformation of their ethylene diamine rings in their crystal structures, while the compounds with two pendant phenol groups (**3**, **5**) are orange and have the lel_3 conformation in their crystal structures. Solid-state reflectance UV/vis spectroscopy confirms these structural differences. In water, all four compounds form orange solutions and adopt the lel_3 conformation, as indicated by comparison of UV/vis spectroscopy and cyclic voltammetry properties with the literature.

Introduction

In catalysis by metal complexes, the complex usually binds substrates in the inner coordination sphere, which requires one or more vacant or labile coordination sites about the metal center. In biology, one important catalytic process is the hydrolysis of phosphate esters, such as in RNA and DNA. Metal ions are cofactors in many enzymes that hydrolyze nucleic acids. There are many reports of labile metal complexes that hydrolyze nucleic acid substrates.[1−7] However, for applications of such catalysts in biological systems, e.g. antiviral chemotherapy, the lability of such complexes is a potential drawback, because demetalation reactions can occur *in vivo* at a labile coordination site, rendering the catalyst ineffective.

The commonly proposed roles for metal ions in phosphate ester hydrolysis are Lewis acid activation of the phosphate ester and provision of an activated hydroxide, which is derived from water binding to the Lewis acidic metal center.[8] However, ribonuclease H (RNase H), a magnesium-dependent enzyme that cleaves the RNA strand of RNA−DNA hybrids, has been shown to retain considerable activity when incubated with kinetically inert cobalt(III) complexes.[9] This introduces a new role, outer-sphere in nature, for metal complexes in the hydrolysis of nucleic acids, e.g. providing electrostatic relief during the attack of nucleophiles on the anionic RNA substrate.

Among the work of our research group to develop new species for the hydrolysis of RNA,[10−13] one route involves the preparation of kinetically inert, highly charged metal complexes that deliver reactive functional groups to RNA. These compounds potentially combine the most desirable properties of both inorganic and organic catalysts. Such complexes with pendant catalytic groups may bind to RNA and afford catalytic activity at specific sites. Toward this end, we report a series of Co(III)-hexaamine complexes which contain pendant, nucleophilic phenol groups. Hydroxybenzaldehydes were coupled to (1,8-diamino-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)-cobalt(III) by reductive amination. The synthesis, characterization, X-ray crystal structures, and thermodynamic studies of these compounds are herein presented.

Abbreviations. Because of the length of the IUPAC names for the compounds described in this study, we have used an adapted version of the original nonsystematic nomenclature[14] which represents these Co−hexaamine cage complexes by "M-(X,Ysar)", where "sar" represents the parent hexaazabicyclo-[6.6.6]eicosane, or "sarcophagine", and X and Y are the substituents in the 1- and 8-positions of the cage. Our nomenclature refers to the number and form of the phenol groups attached to the cage; the presence of the 1- and 8-ammonium groups is implicit for all of the product compounds. Illustrations of the starting material (**1**) and the four product compounds (**2**−**5**) are given in Scheme 1, and their abbreviations are listed below.

Tris(ethylenediamine)cobalt(III) = $Co(en)_3$. (1,8-Diamino-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)cobalt(III) tris-(tetraphenylborate) = "Co(diaminosarcophagine)"$(BPh_4)_3$ = Co(diAMsar)$(BPh_4)_3$[14] (**1**). ((1-(*m*-Hydroxybenzyl)ammonio)-8-ammonio-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)-cobalt(III) pentachloride = "Co(monometaphenol)sar"$(Cl)_5$ = "Co(MMP)sar"$(Cl)_5$ (**2**). (1,8-Bis(*m*-hydroxybenzyl)ammonio)-

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⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

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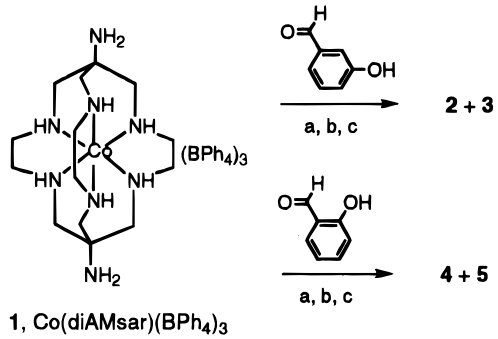
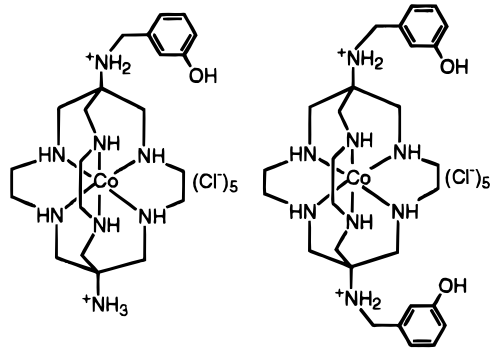
S0020-1669(95)01610-7 CCC: $12.00

Scheme 1. Structures, Nonsystematic Nomenclature, and Summary of the Synthesis for the Co-Cage Phenol Complexes



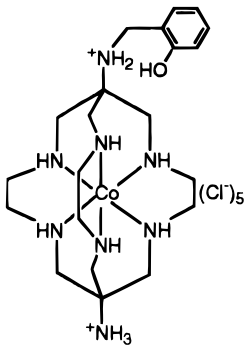
1, Co(diAMsar)(BPh$_4$)$_3$

a) MeOH, AcOH, Δ, 72 h
b) NaBH(OAc)$_3$, RT, 12 h
c) Isolation from HCl solution

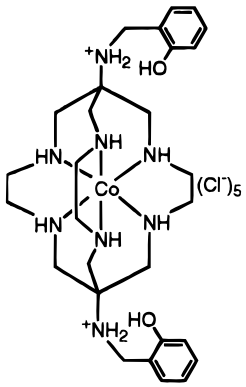


2, Co(MMP)sar(Cl)$_5$

3, Co(BMP)sar(Cl)$_5$



4, Co(MOP)sar(Cl)$_5$



5, Co(BOP)sar(Cl)$_5$

3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)cobalt(III) pentachloride = "Co(bismetaphenol)sar"(Cl)$_5$ = "Co(BMP)sar"(Cl)$_5$ (**3**). ((1-(*o*-Hydroxybenzyl)ammonio)-8-ammonio-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)cobalt(III) pentachloride = "Co(monoorthophenol)sar"(Cl)$_5$ = "Co(MOP)sar"(Cl)$_5$ (**4**). (1,8-Bis((*o*-hydroxybenzyl)ammonio)-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)cobalt(III) pentachloride = "Co(bisorthophenol)sar"(Cl)$_5$ = "Co(BOP)sar"(Cl)$_5$ (**5**).

Experimental Section

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Gemini 300 MHz spectrometer and a Varian 500 MHz spectrometer, with D_2O as the solvent at pD ≈ 3.0, and chemical shifts referenced externally to sodium 3-(trimethylsilyl)tetradeuteropropionate. Thin-layer chromatography (TLC) was performed on Baker-flex Silica Gel IB2-F plates, with 70% MeOH/30% ammonium acetate (NH_4OAc) as the eluting solvent (initial NH_4OAc stock concentration: 20% by weight). FAB-mass spectra were obtained from the Midwest Center for Mass Spectrometry, University of Nebraska—Lincoln, and from the Washington University Mass Spectrometry Resource. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Solid-phase diffuse reflectance and solution-phase UV/visible absorption spectra, and UV/visible spectrophotometric titration spectra were obtained on a Cary 1-E spectrophotometer. Potentiometric titration data were obtained with a Fisher Accumet 825 pH meter with a Fisher electrode and temperature compensation probe and were processed with the computer program PKAS.[15] X-ray crystal structures were obtained from the X-ray Crystallography Facility of the Department of Chemistry, Washington University. Cyclic voltammetry was performed on a Bioanalytical Systems 100B electrochemical analyzer.

Reagents. Co(diAMsar) was synthesized as the Cl_3 salt[16] and converted to the tetraphenylborate (BPh_4) salt by anion exchange of [Co(diAMsar)]Cl_3 with $NaBPh_4$ in aqueous solution. [Co(diAMsar)]-(BPh_4)$_3$ was isolated by vacuum filtration as a yellow-orange solid, dried under reduced pressure, protected from light, and used without further purification. Optically pure Co(en)$_3$ was not used in the Co(diAMsar) synthesis, and no resolution was performed, so that each coupling product is a racemic mixture.

3-Hydroxybenzaldehyde was obtained from Eastman Kodak, recrystallized from water,[17] and dried under reduced pressure. 2-Hydroxybenzaldehyde and sodium triacetoxyborohydride ($NaHB(OAc)_3$) were obtained from Aldrich. 2-Hydroxybenzaldehyde was used without further purification. MeOH was dried by distillation over 4 Å sieves under a N_2 atmosphere.

Coupling Reaction. [Co(diAMsar)](BPh_4)$_3$ (**1**, 20.0 g, 0.0150 mol) and each hydroxybenzaldehyde (*m*-hydroxybenzaldehyde, 5.50 g, 0.0450 mol; *o*-hydroxybenzaldehyde, 3.67 g, 0.0300 mol) were respectively refluxed in anhydrous MeOH (~40−100 mL), with 4.3 mL (0.060 equiv) of glacial acetic acid present, for 72 h under a N_2 atmosphere and shielded from visible light. The reaction mixture was allowed to cool to room temperature, $NaHB(OAc)_3$ (25.5 g, 0.12 mol) was added,[18] and the mixture was stirred overnight. The products were absorbed onto silica gel and initially purified by dry-packed flash column chromatography, using as the eluting solvent a mixture of 70% MeOH and 30% aqueous NH_4OAc solution (initial NH_4OAc stock solution: 20% by weight). The fractions were monitored by silica gel TLC. This initial column chromatography partially separated the bis-coupled Co-cage phenol and the mono-coupled Co-cage phenol from the Co(diAMsar) starting material. Each product was further purified by evaporating the MeOH, diluting the remaining aqueous solution ~80-fold, and chromatographing the solution on a Dowex 50-WX2 [H^+] cation exchange resin column. Co(MMP)sar and Co(MOP)sar were eluted from their respective columns with 2.0−2.5 M HCl and isolated in their fully protonated forms as their Cl_5 salts (**2** and **4**, respectively). Co(BMP)sar and Co(BOP)sar were eluted from their respective columns with 3.0−4.0 M HCl and isolated in their fully protonated forms as their Cl_5 salts (**3** and **5**, respectively). The HCl elutions were evaporated under reduced pressure to give a yellow solid for Co(MMP)sar(Cl)$_5$ (**2**) and Co(MOP)sar(Cl)$_5$ (**4**), and an orange solid for Co(BMP)sar-(Cl)$_5$ (**3**) and Co(BOP)sar(Cl)$_5$ (**5**). Crystals of each compound were grown by slow evaporation of a concentrated aqueous HCl solution of the compound.

^{1}H NMR and ^{13}C NMR assignments are made with reference to the carbon numbering schemes in Figure 1. Two-dimensional NMR data were obtained for Co(MMP)sar(Cl)$_5$ (**2**) only, and NMR assignments of compounds **3**−**5** were made with reference to the data for **2**.

Co(MMP)sar(Cl)$_5$ (2). ^{1}H NMR (300 MHz): δ 2.98−3.14 (m, 12 H), 3.47−3.63 (m, 12 H; H11, H21, H31, H13, H14, H23, H24, H33,

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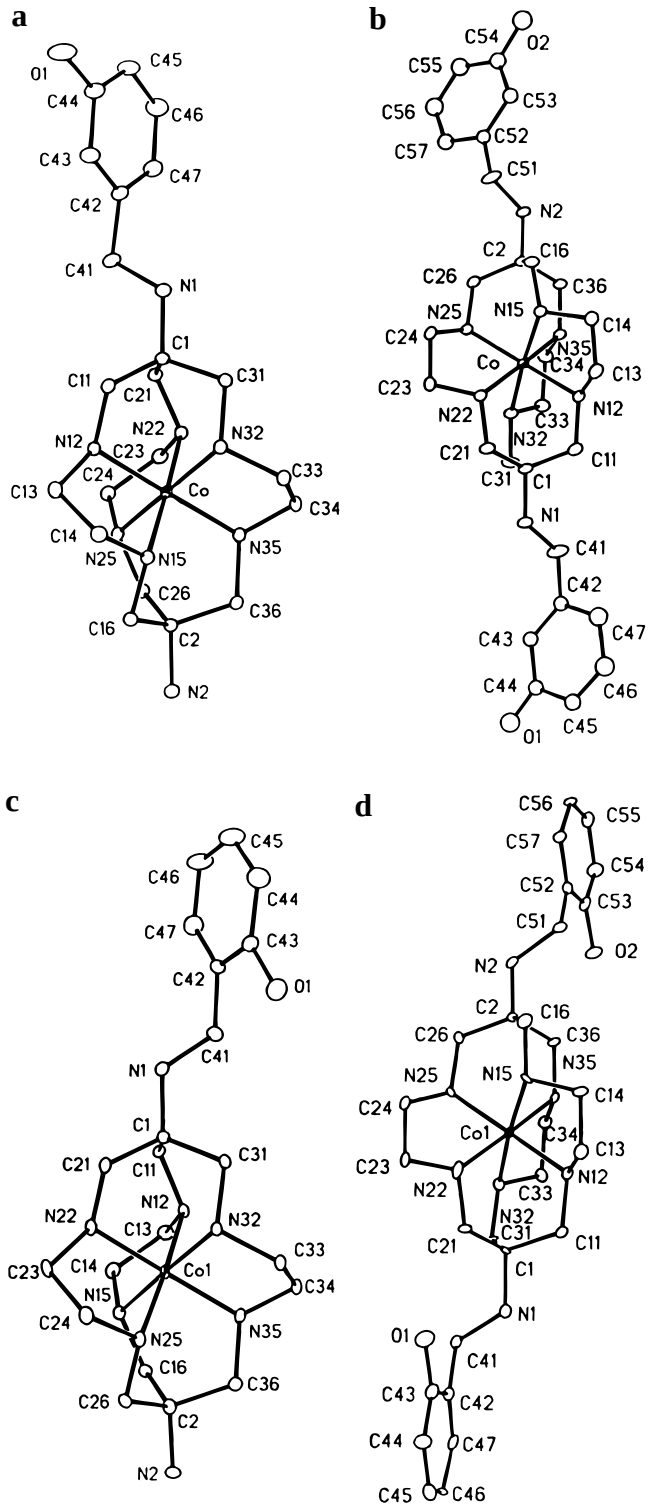

Figure 1. Thermal ellipsoid drawings: (a) the Co(MMP)sar cation, $\Lambda(\lambda\lambda\lambda)$ configuration; (b) the Co(BMP)sar cation, $\Lambda(\delta\delta\delta)$ configuration; (c) the Co(MOP)sar cation, $\Lambda(\lambda\lambda\lambda)$ configuration; (d) the Co(BOP)sar cation, $\Lambda(\delta\delta\delta)$ configuration. 20% thermal ellipsoids are shown for non-H atoms; H atoms are omitted for clarity.

H34, H16, H26, H36); 4.22 (s, 2 H; H41), 6.96−7.04 (m, 3 H; H43, H45, H47), 7.33−7.39 (dd, 1 H; H46). ^{13}C NMR (75 MHz): δ 49.33 (C41), 52.67 (C16, C26, C36), 53.94 (C11, C21, C31), 56.83 (C13, C14, C23, C24, C33, C34), 58.77 (C2), 63.90 (C1), 119.58 (C43), 119.87 (C45), 124.76 (C47), 133.76 (C46), 134.25 (C42), 158.93 (C44). $R_f = 0.24$. MS (FAB, $CoC_{21}H_{42}N_8OCl_5$ = M): *m/z* 549.4 ([M − 2HCl − Cl]$^+$, 7%), 514.3 ([M + e$^-$ − 2HCl − 2Cl]$^+$, 19%), 478.4 ([M + e$^-$ − 3HCl − 2Cl]$^+$, 100%). HR-FAB on $CoC_{21}H_{39}N_8O$ ([M + e$^-$ − 3HCl − 2Cl]$^+$), *m/z*: calculated, 478.2578; found, 478.2574. Anal. Calcd for $CoC_{21}H_{42}N_8OCl_5\cdot3.5H_2O$; Co, 8.16; C, 34.94; H, 6.84; N 15.52; Cl, 24.56. Found: Co, 8.12; C, 35.24; H, 6.89; N, 15.62; Cl, 24.33. Formula for the X-ray quality crystals: $CoC_{21}H_{42}N_8OCl_5\cdot4.5H_2O$.

Co(BMP)sar(Cl)$_5$ (3). ^{1}H NMR (300 MHz): δ 3.03, 3.21 (dd, 12 H), 3.58, 3.68 (dd, 12 H); (H11, H21, H31, H13, H14, H23, H24, H33, H34, H16, H26, H36), 4.25 (dd, 4 H; H41, H51), 6.91−7.00 (m, 6 H; H43, H45, H47, H53, H55, H57), 7.31 (dd, 2 H; H46, H56). ^{13}C NMR (75 MHz): δ 49.33 (C41, C51), 52.46, 55.74 (C11, C21, C31, C13, C14, C23, C24, C33, C34, C16, C26, C36), 63.46 (C1, C2), 119.58 (C43, C53), 119.91 (C45, C55), 124.75 (C47, C57), 133.73 (C46, C56), 133.83 (C42, C52), 158.90 (C44, C54). $R_f = 0.73$. MS (FAB, $CoC_{28}H_{48}N_8O_2Cl_5$ = M): *m/z* 655.5 ([M − 2HCl − Cl]$^+$, 10%): 620.5 ([M + e$^-$ − 2HCl − 2Cl]$^+$, 59%), 583.5 ([M − 4HCl − Cl]$^+$, 100%). HR-FAB on $CoC_{28}H_{44}N_8O_2$ ([M − 4HCl − Cl]$^+$), *m/z*: calculated, 583.2919; found, 583.2942. Anal. Calcd for $CoC_{28}H_{48}N_8O_2Cl_5\cdot2H_2O$; Co, 7.36; C, 41.99; H, 6.54; N 13.99; Cl, 22.13. Found: Co, 7.66; C, 42.04; H, 6.43; N, 14.06; Cl, 22.20. Formula for the X-ray quality crystals: $CoC_{28}H_{48}N_8O_2Cl_5\cdot4.5H_2O$.

Co(MOP)sar(Cl)$_5$ (4). ^{1}H NMR (300 MHz): δ 2.97−3.17 (m, 12 H), 3.47−3.67 (m, 12 H; H11, H21, H31, H13, H14, H23, H24, H33, H34, H16, H26, H36), 4.30 (s, 2 H; H41), 6.95−7.01 (m, 2 H), 7.34−7.39 (m, 2 H; H44, H45, H46, H47). ^{13}C NMR (75 MHz): δ 45.57 (C41), 52.52, 53.94 (C11, C21, C31, C16, C26, C36), 56.90 (C13, C14, C23, C24, C33, C34), 58.76 (C2), 63.89 (C1), 118.45, 119.21, 123.49 (C42, C44, C46), 134.49, 135.08 (C45, C47), 157.92 (C43). $R_f = 0.28$. MS (FAB, $CoC_{21}H_{42}N_8OCl_5$ = M): *m/z* 549.2 ([M − 2HCl − Cl]$^+$, 19%), 514.3 ([M + e$^-$ − 2HCl − 2 Cl]$^+$, 68%), 477.3 ([M − 4HCl − Cl]$^+$, 100%). HR-FAB on $CoC_{21}H_{38}N_8O$ ([M − 4HCl − Cl]$^+$), *m/z*: calculated, 477.2500; found, 477.2485. Anal. Calcd for $CoC_{21}H_{42}N_8OCl_5\cdot3.5H_2O$: Co, 8.16; C, 34.94; H, 6.84; N 15.52; Cl, 24.56. Found: Co, 8.31; C, 34.73; H, 6.79; N, 15.55; Cl, 24.30. Formula for the X-ray quality crystals: $CoC_{21}H_{42}N_8OCl_5\cdot5H_2O$.

Co(BOP)sar(Cl)$_5$ (5). ^{1}H NMR (300 MHz): δ 3.04−3.24 (dd, 12 H), 3.60−3.70 (dd, 12 H; H11, H21, H31, H13, H14, H23, H24, H33, H34, H16, H26, H36), 4.30 (dd, 4 H; H41, H51), 6.94−7.00 (m, 4 H), 7.33−7.40 (m, 4 H; H44, H45, H46, H47, H54, H55, H56, H57). ^{13}C NMR (75 MHz): δ 45.52 (C41, C51), 52.62, 56.02 (C11, C21, C31, C13, C14, C23, C24, C33, C34, C16, C26, C36), 63.56 (C1, C2), 118.46, 119.54, 123.50 (C42, C44, C46, C52, C54, C56), 134.44, 134.98 (C45, C47, C55, C57), 157.92 (C43, C53). $R_f = 0.72$. MS (FAB, $CoC_{28}H_{48}N_8O_2Cl_5$ = M): *m/z* 655.5 ([M − 2HCl − Cl]$^+$, 16%), 620.6 ([M + e$^-$ − 2HCl − 2Cl]$^+$, 64%), 583.6 ([M − 4HCl − Cl]$^+$, 100%). HR-FAB on $CoC_{28}H_{44}N_8O_2$ ([M − 4HCl − Cl]$^+$), *m/z*: calculated, 583.2919; found, 583.2903. Anal. Calcd for $CoC_{28}H_{48}N_8O_2Cl_5\cdot1.5H_2O$; Co, 7.44; C, 42.47; H, 6.49; N 14.15; Cl, 22.38. Found Co, 6.98; C, 42.78; H, 6.36; N, 14.22; Cl, 22.46. Formula for the X-ray quality crystals: $CoC_{28}H_{48}N_8O_2Cl_5\cdot7.5H_2O$.

Results

Synthesis. The Co−hexaamine complexes with the parent cage structure 3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane, or "sarcophagine," possess great thermodynamic stability and kinetic inertness.[14] The Co(III) ion is encapsulated in the hexaamine cage and requires relatively harsh conditions for its removal.[19] In Co(diAMsar), the primary amines at the 1- and 8-positions provide convenient points for attachment of functional groups to the cage. For these reasons, Co(diAMsar) was chosen as the parent species for the synthesis of compounds **2**−**5**.

Because of the electrostatic influence of the Co(III) center, the nucleophilicity of the primary amines of Co(diAMsar) is reduced compared to typical organic amines, and we thus expected formation of the intermediate iminium ion in reductive amination to be correspondingly difficult. To compensate for the reduced nucleophilicity, the initial coupling of the aldehyde to the amine was performed under dehydrating and refluxing

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Table 1. Product Yields (%)

compound	aldehyde/Co(diAMsar) starting ratio	combined isolated yield of mono-coupled/bis-coupled products	isolated yields
Co(MMP)sar(Cl)$_5$ (**2**)	3:1	46	26
Co(BMP)sar(Cl)$_5$ (**3**)			20
Co(MOP)sar(Cl)$_5$ (**4**)	2:1	44	32
Co(BOP)sar(Cl)$_5$ (**5**)			12

Table 2. X-ray Diffraction Structure Summary

	Co(MMP)sar(Cl)$_5$·4.5H$_2$O (**2**·4.5H$_2$O)	Co(BMP)sar(Cl)$_5$·4.5H$_2$O (**3**·4.5H$_2$O)	Co(MOP)sar(Cl)$_5$·5H$_2$O (**4**·5H$_2$O)	Co(BOP)sar(Cl)$_5$·7.5H$_2$O (**5**·7.5H$_2$O)
		Data Collection Summary		
formula	$CoC_{21}H_{51}Cl_5N_8O_{5.5}$	$CoC_{28}H_{57}Cl_5N_8O_{6.5}$	$CoC_{21}H_{52}Cl_5N_8O_6$	$CoC_{28}H_{63}Cl_5N_8O_{9.5}$
fw	739.9	846.0	748.9	900.0
diffractometer	Siemens R3m/V	Siemens R3m/V	Siemens P4	Siemens P4
cryst syst	monoclinic	triclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P\bar{1}$	$P2_1/n$	$P2_1/n$
a, Å	14.351(3)	10.479(2)	14.572(2)	14.052(3)
b, Å	14.283(3)	12.913(2)	14.1990(10)	16.8270(10)
c, Å	16.614(3)	14.879(2)	16.615(4)	18.066(2)
α, deg	90	95.29	90	90
β, deg	105.52(2)	93.86(2)	108.31(9)	110.370(10)
γ, deg	90	105.72(2)	90	90
V, Å^3	3281.5(10)	1920.8(5)	3261.4(9)	4004.9(10)
Z	4	2	4	4
cryst dimens, mm	0.40 × 0.66 × 0.61	0.81 × 0.52 × 0.33	0.43 × 0.52 × 0.97	0.26 × 0.61 × 0.34
cryst color and habit	yellow cube	orange prism	yellow prism	orange prism
d (calcd), g/cm^3	1.498	1.463	1.525	1.493
radiation, Å	Mo Kα	Mo Kα	Cu Kα	Cu Kα
wavelength, Å	0.710 73	0.710 73	1.541 78	1.541 78
scan type	$\theta-2\theta$	$\theta-2\theta$	$\theta-2\theta$	$\theta-2\theta$
scan rate, deg/min in ω	3.66−14.65	3.50−14.65	2.00−60.00	2.00−60.00
scan range (ω), deg	1.20	1.20	0.96	0.96
2θ range, deg	3.0−55.0	3.0−55.0	2.0−113.0	2.0−113.0
temp, K	295	295	295	295
		Refinement Summary		
data refinement software	SHELXL-93	SHELXL-93	SHELXL-93	SHELXL-93
no. of data collcd	9018	8958	5356	6516
no. of unique data	7546	7511	4293	5268
no. of data with I > 2σ(*I*)	5815	5617	3647	3502
abs coeff cm^{-1}	9.76	8.46	83.07	69.35
abs cor applied	semiempirical	semiempirical	semiempirical	semiempirical
data/param	18.4/1	20.9/1	10.4/1	11.1/1
R, % (*I* > 2σ(*I*))	4.66	6.01	5.38	7.05
wR2, % (*I* > 2σ(*I*))	12.55	16.07	13.72	18.19
goodness-of-fit	1.06	1.03	1.05	1.01

conditions for an extended period of time before adding the reducing agent. To remove the water produced in the formation of the iminium ion, a Dean−Stark trap containing 3 Å molecular sieves was employed. Our procedure differs from a recently published procedure for reductive amination with Co(diAMsar) which is performed at ambient temperature and involves reduction of the Co(diAMsar)$^{3+}$ to Co(diAMsar)$^{2+}$ with Zn metal.[20]

In the coupling reaction with each benzaldehyde, an excess of the aldehyde relative to Co(diAMsar) was used, which resulted in a mixture of mono- and dialkylated products with either one or two pendant phenol groups on the cage. Two different ratios were used in the two couplings (Table 1), and the overall yield of each pair of products was 44−46%.

Crystal Structure Solution and Refinement. The crystal data and data collection parameters for the four cage compounds are summarized in Table 2, and selected bond lengths and angles are presented in Table 3. Atomic coordinates and equivalent isotropic displacement coefficients for each cage cation are given in Tables 4−7. Parts a−d of Figure 1 show representative structures of each cage cation.

For Co(MMP)sar(Cl)$_5$·4.5 H$_2$O (**2**·4.5 H$_2$O) and Co(BMP)-sar(Cl)$_5$·4.5H$_2$O (**3**·4.5H$_2$O), single crystals were mounted in glass capillaries, and cell constants were determined by least-squares refinement of the setting angles of 25 independent reflections, measured and refined on a Siemens R3m/V diffractometer. Intensity data were collected at 295 K using graphite-monochromated Mo Kα radiation and the $\theta-2\theta$ scanning technique. Three standard reflections were measured after every 97 reflections, with no significant decay observed.

The data were reduced and refined using SHELXTL PLUS (VMS). The position of the cobalt atom was determined using heavy atom methods. The remaining non-hydrogen atoms were found by successive full-matrix least-squares refinements and difference Fourier map calculations. For both Co(MMP)sar-(Cl)$_5$·4.5H$_2$O (**2**·4.5H$_2$O) and Co(BMP)sar(Cl)$_5$·4.5H$_2$O (**3**·4.5H$_2$O), one water molecule refined with 50% occupancy. (The thermal parameter of each of these oxygen atoms was fixed to the average values of the full occupancy water oxygens, and the site occupancy was allowed to refine. The site occupancy factor refined to approximately 0.5, so occupancies were fixed at 50%, and the thermal parameters were then allowed to refine.)

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Table 3. Selected Bond Lengths and Angles

	Co(MMP)sar(Cl)$_5$·4.5H$_2$O (**2**·4.5H$_2$O)	Co(BMP)sar(Cl)$_5$·4.5H$_2$O (**3**·4.5H$_2$O)	Co(MOP)sar(Cl)$_5$·5H$_2$O (**4**·5H$_2$O)	Co(BOP)sar(Cl)$_5$·7.5H$_2$O (**5**·7.5H$_2$O)
		Bond Lengths (Å)		
av Co−N	1.962 (1.957−1.966)	1.974 (1.969−1.985)	1.960 (1.953−1.962)	1.974 (1.962−1.984)
N−H···Cl	3.15−3.17	3.08−3.23	3.14−3.21	3.07−3.32
N−H···O$_{water}$	2.71−2.92	2.69, 2.77	2.72−3.25	2.78, 3.49
O$_{water}$−H···Cl	3.08−3.44	3.08−3.33	3.13−3.38	3.06−3.38
O$_{water}$−H···O$_{water}$	2.78, 2.92	2.61−3.27	2.77−3.30	2.47−3.05
O$_{phenol}$−H···O$_{water}$	2.80	disordered		2.66, 3.08
O$_{phenol}$−H···Cl			3.09	3.10, 3.43
O$_{phenol}$···H−N			3.30	2.93, 3.08
		Angles (deg)		
av N−Co−N (intracap)[a]	86.9 (86.4−87.3)	86.2 (85.9−86.6)	86.6 (85.9−87.2)	86.5 (86.2−86.7)
av N−Co−N (intercap)[b]	91.4 (90.0−92.2)	90.6 (89.7−91.8)	91.4 (90.7−92.3)	90.4 (90.0−90.8)
av N−C−C−N torsion	44.0 (42.9−44.9)	54.5 (53.6−55.0)	43.8 (42.2−45.4)	56.2 (54.9−57.5)
av twist angle (ϕ)[38]	56.8	55.0	56.3	54.5

[a] 6-membered chelate rings. [b] 5-membered chelate rings.

Table 4. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients (Å^2 $\times$ 10^3) for the Co(MMP)sar Cation[a]

	x	*y*	*z*	*U*(eq)[b]
Co	5911(1)	653(1)	2928(1)	16(1)
N(1)	2942(2)	17(2)	1308(2)	25(1)
N(2)	8873(2)	1350(2)	4496(2)	27(1)
N(12)	5490(2)	−604(2)	2498(2)	20(1)
N(15)	6532(2)	48(2)	3994(2)	20(1)
N(22)	5327(2)	1235(2)	1840(2)	20(1)
N(25)	7094(2)	544(2)	2558(2)	20(1)
N(32)	4716(2)	805(2)	3270(2)	20(1)
N(35)	6296(2)	1896(2)	3411(2)	20(1)
O(1)	−88(2)	−2243(2)	−485(2)	59(1)
C(1)	3951(2)	202(2)	1851(2)	22(1)
C(2)	7876(2)	1124(2)	3975(2)	22(1)
C(11)	4418(2)	−722(2)	2237(2)	23(1)
C(13)	5998(2)	−1331(2)	3113(2)	27(1)
C(14)	6183(2)	−942(2)	3986(2)	26(1)
C(16)	7610(2)	147(2)	4238(2)	23(1)
C(21)	4532(2)	663(2)	1308(2)	22(1)
C(23)	6096(2)	1462(2)	1413(2)	25(1)
C(24)	6868(2)	725(2)	1641(2)	26(1)
C(26)	7898(2)	1132(2)	3054(2)	23(1)
C(31)	3843(2)	867(2)	2548(2)	22(1)
C(33)	4815(2)	1626(2)	3849(2)	25(1)
C(34)	5436(2)	2360(2)	3594(2)	25(1)
C(36)	7180(2)	1877(2)	4131(2)	23(1)
C(41)	2887(3)	−501(3)	505(2)	39(1)
C(42)	1866(2)	−559(3)	−35(2)	31(1)
C(43)	1329(3)	−1356(3)	−11(2)	36(1)
C(44)	403(3)	−1439(3)	−538(2)	36(1)
C(45)	24(3)	−733(3)	−1098(3)	45(1)
C(46)	567(3)	62(3)	−1125(3)	52(1)
C(47)	1487(3)	152(3)	−591(3)	42(1)

[a] Estimated standard deviations are given in parentheses. [b] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

All non-hydrogen atoms in Co(MMP)sar(Cl)$_5$·4.5H$_2$O were refined anisotropically. Hydrogen atoms were placed at idealized positions and refined isotropically using the riding model.[21]

Each pendant phenol group of Co(BMP)sar(Cl)$_5$·4.5H$_2$O (**3**·4.5H$_2$O) was found to exhibit a 2-fold lateral disorder. Two partial-occupancy phenyl rings were idealized geometrically and refined for each end of the molecule; one end refined to 60%/40% occupancy, while the other end refined to 55%/45% occupancy. Each phenol ring and a hydrogen-bonded water molecule associated with the ring were found to be cooperatively disordered. All non-hydrogen atoms were refined anisotropically, except for disordered atoms and associated water molecules. Hydrogen atoms were placed at idealized positions and refined isotropically using the riding model.

For Co(MOP)sar(Cl)$_5$·5H$_2$O (**4**·5H$_2$O) and Co(BOP)sar(Cl)$_5$·7.5H$_2$O (**5**·7.5H$_2$O), single crystals were mounted in glass capillaries, and cell constants were determined by least-squares refinement of the setting angles of 12 independent reflections, measured and refined on a Siemens P4 diffractometer. Intensity data were collected at 295 K using graphite-monochromated Cu Kα radiation and the $\theta-2\theta$ scanning technique. Three standard reflections were measured after every 97 reflections, with no significant decay observed.

The data were reduced and refined using SHELXTL PLUS (PC version). The position of the cobalt atom was determined using direct methods. The remaining non-hydrogen atoms were found by successive full-matrix least-squares refinements and difference Fourier map calculations. For Co(BOP)sar(Cl)$_5$·7.5H$_2$O (**5**·7.5H$_2$O), one of the associated water molecules was refined with 50% occupancy (see above for refinement procedure). All non-hydrogen atoms in Co(MOP)sar(Cl)$_5$·5H$_2$O and Co(BOP)sar(Cl)$_5$·7.5H$_2$O were refined anisotropically. Hydrogen atoms were placed at idealized positions and refined isotropically using the riding model.

pK_a determinations. The pK_a's for the ionizable groups of all of the compounds (Table 8) were determined by potentiometric titration and analysis with the program PKAS,[15] with the exception of the pK_a's for the phenol groups of Co(BOP)sar(Cl)$_5$ (**5**). Under concentrations used for potentiometric titration, Co(BOP)sar precipitated out of solution in a deprotonated form at pH $\approx$ 8.5. Thus the potentiometric data for Co(BOP)sar(Cl)$_5$ were sufficient to obtain pK_a values for only its cage capping amine groups. To determine the pK_a's of the phenol groups of Co(BOP)sar, UV/vis spectrophotometry was employed.[22] Formation of the phenolate anion at 237 ($\pm$1) nm was detected as the pH of the solution was increased. At the low concentration required for this technique, precipitation of the compound did not occur.

Because the concentration and ionic strength are different in the spectrophotometric and potentiometric analyses, the Co(BOP)sar phenol group pK_a's are not strictly comparable to those obtained by potentiometric titration. In fact, the analysis of the spectrophotometric data gave only one pK_a value for the Co(BOP)sar phenol groups. This is because as each phenol group was deprotonated to produce the phenolate anion, the same chromophore appeared and increased in intensity in the suc-

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Table 5. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$) for the Co(BMP)sar Cation[a]

	x	*y*	*z*	*U*(eq)[b]
Co	−7288(1)	−4865(1)	−2496(1)	24(1)
N(1)	−9573(4)	−8389(3)	−3407(3)	39(1)
N(2)	−5052(4)	−1339(2)	−1542(2)	33(1)
N(12)	−7383(3)	−6063(2)	−1747(2)	30(1)
N(15)	−5383(3)	−4352(2)	−2035(2)	28(1)
N(22)	−6943(3)	−5761(2)	−3545(2)	29(1)
N(25)	−7021(3)	−3682(2)	−3273(2)	29(1)
N(32)	−9230(3)	−5380(3)	−2869(2)	31(1)
N(35)	−7743(3)	−3940(2)	−1511(2)	28(1)
O(1)	−13695(8)	−12144(6)	−4706(5)	68(2)[c]
O(1A)	−13389(12)	−12442(9)	−4428(8)	68(2)[d]
O(2)	−1513(8)	2807(7)	−455(5)	72(2)[e]
O(2A)	−793(10)	2029(8)	−2(7)	72(2)[f]
C(1)	−8835(4)	−7216(3)	−3081(3)	33(1)
C(2)	−5758(4)	−2508(3)	−1890(3)	30(1)
C(11)	−8275(5)	−7157(3)	−2112(3)	44(1)
C(13)	−5994(4)	−6068(3)	−1464(3)	39(1)
C(14)	−5195(4)	−4913(3)	−1228(3)	37(1)
C(16)	−4734(4)	−3157(3)	−1878(3)	33(1)
C(21)	−7761(5)	−6918(3)	−3726(3)	42(1)
C(23)	−6964(5)	−5166(3)	−4355(3)	38(1)
C(24)	−6297(5)	−3988(3)	−4040(3)	39(1)
C(26)	−6424(5)	−2550(3)	−2844(3)	35(1)
C(31)	−9828(5)	−6554(3)	−3192(4)	44(1)
C(33)	−9940(4)	−4991(4)	−2132(3)	38(1)
C(34)	−9123(4)	−3863(3)	−1760(3)	37(1)
C(36)	−6781(4)	−2861(3)	−1212(3)	31(1)
C(41)	−10761	−8891	−2906	63(2)
C(42)	−11238(6)	−10104(3)	−3183(4)	37(1)[c]
C(43)	−12236(6)	−10549(4)	−3885(4)	40(1)[c]
C(44)	−12715(5)	−11667(4)	−4084(3)	41(2)[c]
C(45)	−12196(6)	−12340(3)	−3582(4)	45(2)[c]
C(46)	−11197(7)	−11896(4)	−2880(4)	63(2)[c]
C(47)	−10718(6)	−10778(4)	−2680(4)	58(2)[c]
C(42A)	−11043(10)	−10098(5)	−3001(6)	37(1)[d]
C(43A)	−11985(9)	−10660(6)	−3706(6)	40(1)[d]
C(44A)	−12381(8)	−11786(6)	−3809(5)	41(2)[d]
C(45A)	−11836(9)	−12349(5)	−3209(6)	45(2)[d]
C(46A)	−10893(10)	−11787(7)	−2504(6)	63(2)[d]
C(47A)	−10497(10)	−10662(7)	−2400(6)	58(2)[d]
C(51)	−3856	−786	−2019	60(2)
C(52)	−3551(6)	408(3)	−1857(4)	35(1)[e]
C(53)	−2682(6)	1071(4)	−1157(4)	43(2)[e]
C(54)	−2437(6)	2189(4)	−1106(4)	50(2)[e]
C(55)	−3061(8)	2644(3)	−1754(5)	61(2)[e]
C(56)	−3930(7)	1981(5)	−2454(4)	65(2)[e]
C(57)	−4175(6)	863(4)	−2506(4)	50(2)[e]
C(52A)	−3404(7)	413(4)	−1684(5)	35(1)[f]
C(53A)	−2367(7)	678(5)	−995(5)	43(2)[f]
C(54A)	−1769(7)	1756(6)	−665(5)	50(2)[f]
C(55A)	−2207(9)	2570(4)	−1024(6)	61(2)[f]
C(56A)	−3243(9)	2305(5)	−1713(6)	65(2)[f]
C(57A)	−3842(7)	1227(6)	−2043(5)	50(2)[f]

[a] Estimated standard deviations are given in parentheses. [b] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. [c] site occupancy factor (sof) = 0.60. [d] Sof = 0.40. [e] Sof = 0.55. [f] Sof = 0.45.

Table 6. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$) for the Co(MOP)sar Cation[a]

	x	*y*	*z*	*U*(eq)[b]
Co(1)	866(1)	662(1)	2930(1)	13(1)
N(1)	−2125(3)	−37(3)	1285(3)	22(1)
N(2)	3872(3)	1365(3)	4514(3)	22(1)
N(12)	447(3)	−608(3)	2503(2)	16(1)
N(15)	1537(3)	62(3)	4017(3)	17(1)
N(22)	−293(3)	826(3)	3267(3)	19(1)
N(25)	1275(3)	1908(3)	3418(2)	16(1)
N(32)	220(3)	1229(3)	1819(2)	14(1)
N(35)	2005(3)	558(3)	2545(3)	16(1)
O(1)	−2914(3)	655(3)	−707(3)	42(1)
C(1)	−1115(3)	175(3)	1836(3)	17(1)
C(2)	2860(4)	1143(3)	3989(3)	19(1)
C(11)	−615(3)	−741(3)	2251(3)	17(1)
C(13)	991(4)	−1328(3)	3131(3)	21(1)
C(14)	1199(4)	−942(3)	4005(3)	24(1)
C(16)	2610(4)	158(3)	4261(3)	20(1)
C(21)	−1198(4)	859(4)	2527(3)	20(1)
C(23)	−176(4)	1658(3)	3843(3)	23(1)
C(24)	443(4)	2389(3)	3602(3)	22(1)
C(26)	2179(4)	1894(3)	4149(3)	18(1)
C(31)	−572(4)	636(3)	1282(3)	17(1)
C(33)	955(4)	1477(3)	1395(3)	20(1)
C(34)	1732(4)	745(4)	1623(3)	21(1)
C(36)	2826(4)	1135(3)	3055(3)	19(1)
C(41)	−2210(4)	−687(4)	546(4)	31(1)
C(42)	−3212(4)	−733(4)	−60(3)	26(1)
C(43)	−3537(4)	−69(4)	−702(3)	27(1)
C(44)	−4425(5)	−159(5)	−1303(4)	47(2)
C(45)	−5009(5)	−923(6)	−1262(5)	59(2)
C(46)	−4705(5)	−1582(6)	−628(5)	57(2)
C(47)	−3804(5)	−1486(5)	−25(4)	44(2)

[a] Estimated standard deviations are given in parentheses. [b] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

cessive UV/vis spectra, at essentially the same wavelength. Thus it was not possible to distinguish the pK_a's of the two phenol groups from the spectrophotometric data. At high pH, Co(BMP)sar also precipitates from solution. However, this occured at a higher pH than for Co(BOP)sar, >9.5, and sufficient data were acquired from potentiometric titration to obtain satisfactory pK_a values for all four ionizable groups of Co(BMP)sar.

Discussion

Solid-State and Solution-State Structures. In the solid state, an immediately apparent difference among the compounds is that Co(MMP)sar$(Cl)_5$ (**2**) and Co(MOP)sar$(Cl)_5$ (**4**) are yellow, whereas Co(BMP)sar$(Cl)_5$ (**3**) and Co(BOP)sar$(Cl)_5$ (**5**) are orange. The crystal structures of the compounds further illustrate the distinction between these pairings of the complexes. The mono-alkylated compounds **2** and **4** have the ob_3 configuration of their ethylene diamine rings about the Co center, while the dialkylated compounds **3** and **5** have the lel_3 configuration. The *lel* and *ob* terms refer to the parallel and oblique orientation about the Co center of the ethylene-diamine rings with relation to the C_3 axis of the complex (Figure 2).[23] In Co(diAMsar) and compounds **2**−**5**, the C_3 axis runs through the Co center and the 1- and 8-amino groups of the complex. The solid-state diffuse reflectance UV/visible spectra (Table 9) provide further confirmation of this situation. The spectra for Co(BMP)sar$(Cl)_5$ and Co(BOP)sar$(Cl)_5$ have a peak at ∼475 nm, which is consistent with previously reported Co-cage complexes which have the lel_3 conformation.[24] By contrast, the diffuse reflectance spectra of Co(MMP)sar$(Cl)_5$ and Co(MOP)sar$(Cl)_5$ lack this peak at ∼475 nm.

In Co-sarcophagine complexes, the lel_3 configuration tends to be more common than the ob_3 configuration. Several of the ob_3 complexes[25,26] have sterically bulky substituents attached to the cage. Our observation that Co(MMP)sar and Co(MOP)sar adopt the ob_3 conformation in the solid state is consistent with these prior complexes, since each has a bulky phenol group

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Table 7. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients (Å^2 $\times$ 10^3) for the Co(BOP)sar Cation[a]

	x	*y*	*z*	*U*(eq)[b]
Co(1)	304(1)	4166(1)	2650(1)	15(1)
N(1)	−2633(5)	3002(4)	2663(4)	23(2)
N(2)	3239(5)	5344(4)	2690(4)	23(2)
N(12)	−78(6)	3052(4)	2384(4)	21(2)
N(15)	784(5)	4168(4)	1743(4)	18(2)
N(22)	−1066(6)	4516(4)	2006(4)	26(2)
N(25)	645(5)	5309(4)	2836(4)	18(2)
N(32)	−117(5)	4082(4)	3583(4)	20(2)
N(35)	1685(5)	3881(4)	3374(4)	15(2)
O(1)	−4271(5)	3742(4)	1377(4)	41(2)
O(2)	4945(5)	4461(4)	3993(4)	38(2)
C(1)	−1654(6)	3406(5)	2661(5)	15(2)
C(2)	2279(6)	4935(5)	2648(5)	17(2)
C(11)	−1014(6)	2748(5)	2502(5)	22(2)
C(13)	−106(7)	2919(5)	1559(5)	28(2)
C(14)	825(7)	3323(5)	1511(5)	24(2)
C(16)	1765(7)	4597(6)	1817(5)	30(2)
C(21)	−1957(6)	4014(5)	1993(5)	20(2)
C(23)	−1176(7)	5356(5)	2236(5)	26(2)
C(24)	−216(6)	5767(5)	2283(5)	26(2)
C(26)	1633(7)	5583(5)	2830(6)	26(2)
C(31)	−1160(6)	3786(5)	3475(5)	19(2)
C(33)	717(6)	3619(5)	4192(5)	24(2)
C(34)	1679(7)	3954(5)	4189(5)	23(2)
C(36)	2583(7)	4279(5)	3283(5)	23(2)
C(41)	−3371(7)	3505(5)	2936(5)	24(2)
C(42)	−4429(7)	3216(5)	2531(5)	25(2)
C(43)	−4865(7)	3356(5)	1723(5)	30(2)
C(44)	−5851(7)	3108(6)	1316(6)	35(2)
C(45)	−6402(8)	2746(6)	1734(7)	41(3)
C(46)	−6001(6)	2659(5)	2534(6)	29(2)
C(47)	−4985(7)	2877(5)	2937(6)	29(2)
C(51)	4012(7)	4873(5)	2424(5)	26(2)
C(52)	5074(7)	5130(5)	2883(5)	23(2)
C(53)	5508(8)	4896(5)	3665(5)	30(2)
C(54)	6515(8)	5071(6)	4097(6)	37(2)
C(55)	7088(8)	5493(5)	3738(6)	34(2)
C(56)	6660(7)	5731(5)	2962(6)	31(2)
C(57)	5643(7)	5542(5)	2544(6)	28(2)

[a] Estimated standard deviations are given in parentheses. [b] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

Table 8. pK_a Values[a]

compound	capping amine values	phenol group value(s)
Co(MMP)sar(Cl)$_5$ (**2**)	2.23 ± 0.07	9.02 ± 0.07
	2.95 ± 0.04	
Co(MOP)sar(Cl)$_5$ (**3**)	2.38 ± 0.02	9.22 ± 0.07
	3.01 ± 0.07	
Co(BMP)sar(Cl)$_5$ (**4**)	2.21 ± 0.01	8.84 ± 0.01
	2.46 ± 0.01	9.39 ± 0.01
Co(BOP)sar(Cl)$_5$ (**5**)	2.42 ± 0.03	9.04 ± 0.07[b]
	2.77 ± 0.02	

[a] pK_a's determined by potentiometric titration, analyzed with program PKAS,[15] [Co-cage solution] = 0.003−0.005 M, T = 25 °C. [b] pK_a determined by UV/visible spectrophotometry,[22] [Co-cage solution] = 6×10^{-5} M, T = 25 °C. Errors in all cases were reported as scatter.

substituent attached to the cage. On the basis of this trend, we expected the two bis-alkylated compounds to be even more sterically crowded than the mono-alkylated species, and to adopt the *ob*$_3$ conformation in the solid state as well. In fact, however, Co(BMP)sar and Co(BOP)sar adopt the *lel*$_3$ conformation in the solid state. Presumably, crystal packing forces favor the *ob*$_3$ conformation for Co(MMP)sar and Co(MOP)sar. Preliminary molecular mechanics calculations on the isolated cage cations *in vacuo* showed the *lel*$_3$ structure to be more stable than the *ob*$_3$ structure for both the mono- and bis-phenol cages.[27]

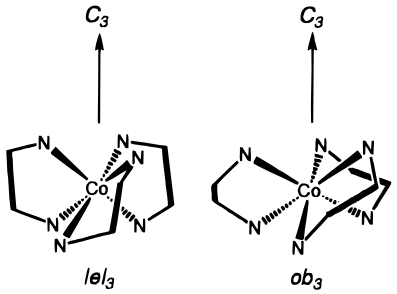

Figure 2. Illustrations of the *lel*$_3$ and *ob*$_3$ configurations of Δ-[Co(en)$_3$], viewed parallel to the C_3 axis. Ethylene diamine carbons are indicated by the bold C−C bond.

Table 9. UV−Visible Absorption Spectral Data

compound	solution absorption bands[a] λ_{max} (nm)	ϵ (M^{-1} cm^{-1})	solid-state reflectance bands (nm)
Co(MMP)sar(Cl)$_5$ (**2**)	475	149	369
	341	150	
	218	2.19×10^4	
Co(BMP)sar(Cl)$_5$ (**3**)	472	143	470
	334	177[b]	
	217	2.86×10^4	
Co(MOP)sar(Cl)$_5$ (**4**)	475	143	369
	342	140	
	217	2.05×10^4	
Co(BOP)sar(Cl)$_5$ (**5**)	472	138	474
	336	153	370
	216	2.69×10^4	

[a] Readings in 0.1 M HCl. [b] Estimate; peak appears as shoulder.

Table 10. Reduction Potentials [(Co-cage)$^{3+/2+}$][a]

compound	$E_{1/2}$ (V)	compound	$E_{1/2}$ (V)
CodiAMsar	−0.54	Co(MOP)sar	−0.52
Co(MMP)sar	−0.52	Co(BOP)sar	−0.51
Co(BMP)sar	−0.51		

[a] 0.10 M $NaClO_4$(aq) as the supporting electrolyte, pH 7.5 ± 0.2 (adjusted after dissolution of the complex), referenced to Ag/AgCl standard electrode. All solutions were degassed with Ar.

In the solution state, by contrast, all four of the compounds adopt the *lel*$_3$ conformation. This is deduced from the observations that all four compounds (a) produce an orange solution when dissolved in water or HCl solution, and (b) have their UV maxima of the lower-energy visible absorption band ($^1A_{1g} \rightarrow {}^1T_{1g}$) at 474 ± 2 nm (Table 9). This is consistent with other cobalt−sarcophagine complexes which have a variety of substituents attached to the cage and are in the *lel*$_3$ conformation in aqueous solution, yet whose $^1A_{1g} \rightarrow {}^1T_{1g}$ band remains around 472 ± 3 nm.[24] The Co(complex)$^{3+/2+}$ reduction potentials (Table 10) are also in the range expected for Co(III)−sarcophagine complexes which have the *lel*$_3$ conformation.[24,28] Co(MMP)sar and Co(MOP)sar therefore change their conformation upon crystallization.

pK_a Determinations. In the diaminosarcophagine ligand of Co(diAMsar), the acidity of its fully protonated primary amine groups is strikingly higher than that of the conjugated acids of typical organic amines, which is due to the electrostatic influence of the Co(III) center.[29,30] Co−sarcophagine compounds which

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have an imidazole moiety attached to the cage *via* the primary amines have been prepared in our group. In these complexes, the pK_a's of the imidazolium groups were lowered relative to imidazole itself, although these changes in pK_a were less extreme than those for the fully protonated parent primary amines of Co(diAMsar). This is because the imidazole is situated further from the Co center than the parent primary amine and is also a less rigidly bound part of the cage ligand.[30]

In keeping with these results, the pK_a's of the phenol groups should be reduced, compared to their analogous organic phenols, upon coupling to Co(diAMsar). As expected, the K_a's of the phenol groups in all four compounds were lowered compared to their analogous cresols[31] by roughly 1 order of magnitude, on average. From statistical arguments, the two phenol pK_a's in Co(BMP)sar and Co(BOP)sar were expected to differ by about 0.6.[32] This is evident for Co(BMP)sar$(Cl)_5$ (**3**), whose phenol pK_a's differ by 0.55 ± 0.02. As noted earlier, the UV/vis spectrophotometric analysis of Co(BOP)sar$(Cl)_5$ (**5**) did not provide pK_a values for both phenol groups. In light of the statistical argument noted above, the reported value for the Co(BOP)sar phenol pK_a's is assumed to represent the negative logarithm of the average of the two actual K_a values. By analogy with Co(BMP)sar and using the statistical argument, the pK_a values for the phenol groups of Co(BOP)sar should be approximately 8.74 and 9.34. Also, despite the different solution ionic strengths in the two methods, the calculated pK_a for the Co(BOP)sar phenol groups is generally in the range of the phenol pK_a's for the other compounds which were obtained by potentiometric titration.

In Co-cage compounds such as **2**−**5**, the Co(III) center may exert its effects on the proximal phenol groups by two general means: through-bond inductive and through-space Coulombic mechanisms. If the Co(III) center transmitted its effects to the phenol group through the σ-bond network of the ligand, the spectroscopic properties of these complexes should vary with the cage ligand.[24] In such an interaction, different ligands would provide different ligand fields about the Co(III) center. However, as Sargeson and co-workers have described, known *lel*$_3$ Co−sarcophagine complexes show no significant variation in ligand field strength, and retain their lower energy UV/vis chromophores around 472 ± 3 nm, even with a wide variety of cage ligands.[24] Thus the ligand field is generally not affected by functional groups in the outer coordination sphere. Since the UV/vis chromophores in **2**−**5** are in this same range, ∼473−474 nm, we conclude that the Co(III) exerts its influence on the outer-sphere phenol group *via* a through-space Coulombic, rather than a through-bond inductive, mechanism.

Conclusions

This general class of molecules has potential use as electrostatic delivery agents for reactive functional groups. The extreme stability of Co−sarcophagine complexes makes them appealing candidates for *in vivo* use, as has already been demonstrated.[20,33] In the context of our overall goal of developing new species to perform RNA hydrolysis, these compounds may be further derivatized (e.g. by nitration on the aromatic rings) to optimize the pK_a of the phenol groups to around physiological pH.

As pointed out by a reviewer, the juxtaposition of metal centers with other functional groups is of great importance in the active sites of metalloenzymes. In particular, these additional moieties may assist the metal in substrate binding and may promote bond breaking and formation through proton transfers. Such cooperation is seen, for example, in the active site of carboxypeptidase A.[34] As we develop the properties of the Co-sarcophagine complexes reported here, we hope to find substrate-binding and activation properties that are enhanced by combination of a highly charged metal center with proximal functional groups. We are presently examining the ability of these cage complexes to serve as cofactors for metalloenzymes, such as RNase H.

Co-hexaamine complexes are known to bind to and induce structural changes in different nucleic acid structures.[35−37] In general, electrostatics and hydrogen bonding contribute to the association of such coordinatively-saturated metal complexes to nucleic acids. Chirality is another recognition element for different nucleic acid conformations which metal complexes can provide. The two stereoisomers of $Co(en)_3$ have recently been shown to bind distinctly to left-handed and right-handed conformations of DNA.[37] The compounds described in this report can be prepared as their separate stereoisomers and may have distinct recognition properties toward nucleic acids.

Acknowledgment. We thank Prof. M. L. Gross and his staff for helpful discussions on interpreting the mass spectral data, Prof. K. D. Moeller and his group for advice on the CV studies and the use of their equipment, Dr. D. A. d'Avignon for assistance with obtaining and interpreting the NMR spectra, and Dr. L. A. Bass for helpful discussions. G.C.Y. thanks the U.S. Department of Education for financial support through the Graduate Assistance in Areas of National Need (GAANN) program (Grant No. P200A40147). This work was supported in part by NSF Grant CHE-9318581. Acknowledgment is also made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The Midwest Center for Mass Spectrometry received partial support from the National Science Foundation, Biology Division (Grant No. DIR9017262). The Washington University Mass Spectrometry Resource is an NIH Research Resource (Grant No. P41RR0954).

Supporting Information Available: For compounds **2**−**5**, packing diagrams and thermal ellipsoid drawings and tables of crystallographic data, hydrogen coordinates, thermal parameters, and bond distances and angles (47 pages). Ordering information is given on any current masthead page.

IC951610G

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