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Synthesis and Characterization of Water-Operative Cationic and Anionic Metal-Ion Activated Molecular Receptors for Aromatic Anions

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Two new, octadentate, water-soluble, macrocyclic ligands, 1,4,7,10-tetrakis((2*S*)-(–)-2-hydroxy-3-[3′-(*N,N,N*-trimethylammonium)-phenoxy]-propyl)-1,4,7,10-tetraazacyclododecane tetratriflate, ((*S*)-tmappc12 triflate, **L^1 triflate**) and 1,4,7,10-tetrakis((2*S*)-(–)-2-hydroxy-3-[2′-sulfo-4′-methylphenoxy]-propyl)-1,4,7,10-tetraazacyclododecane, ((*S*)-sthmppc12, **L^2H_4**) have been prepared with a view to using them to study anion sequestration in aqueous solution. Their pK_a and metal-ion binding constant values with a range of alkaline earth, transition, and post-transition metals are reported. The eight-coordinate, water-soluble Cd(II) complexes of **$(L^1)^{4+}$** and **$(L^2)^{4-}$**, [Cd**L^1**]$(CF_3SO_3)_6$ and $(NH_4)_2$-[Cd**L^2**], the former cationic and the latter anionic, have both been shown to be capable of acting as anion receptors in aqueous solution. The binding constant values (log(K/M^{-1}) given in parentheses) for binding by the cationic receptor to a range of aromatic anions in water are *p*-nitrophenolate (1.7), *p*-formylphenolate (2.1), *p*-nitrobenzoate (3.0), *p*-aminobenzoate (4.5), *p*-dimethylaminobenzoate (>4.5), D- and L-tryptophanate (1.6, 2.2), phenoxyacetate (2.1), and acetate (2.3). With the anionic receptor, nonzero binding constants were only measurable for *p*-nitrobenzoate (∼0.4), *p*-aminobenzoate (2.0), and *p*-dimethylaminobenzoate (1.8). By reference to the X-ray determined structures of related, but water-insoluble inclusion complexes, anion retention is thought to occur within a hydrophobic cavity, with four convergent hydroxy groups at its base, which develops in **$(L^1)^{4+}$** and **$(L^2)^{4-}$** through the juxtapositioning of aromatic rings that occurs as a consequence of octadentate coordination.

Introduction

Sequestration of anions from the aqueous environment into the confines of a synthetic molecular receptor is a challenging problem compared to accomplishing the same operation in an organic solvent. This arises from the large magnitude of the solvation (hydration) energy associated with the anion, as well as its intended binding site, in water compared to that in solvents of lower dielectric constant. Because of this, there is a tendency for the net enthalpy gain, achieved when the exothermic host−guest interaction energy delivered at the binding site is offset against the endothermic desolvation energy, to be negligibly small.[1] Naturally occurring anion receptors that operate in the aqueous environment overcome this problem by employing convergent anion−dipole binding groups that are situated within a binding cavity, located within the structure of a protein, that is well shielded from the surrounding solvent.[1] One can envisage that the binding cavity, if at least partially hydrophobic, serves to draw partially hydrophobic anions into its confines, with concomitant desolvation. Once the anion has locked onto the binding groups within the interior, the competition with the solvent is to some extent eliminated by the walls of the cavity. In earlier work,[2−4] we have demonstrated the feasibility of constructing anion receptors in which a partially hydrophobic cavity with convergent binding groups at its base exists. The cavity assembles as a structural feature of an octadentate, pendant-armed macrocyclic ligand in re-

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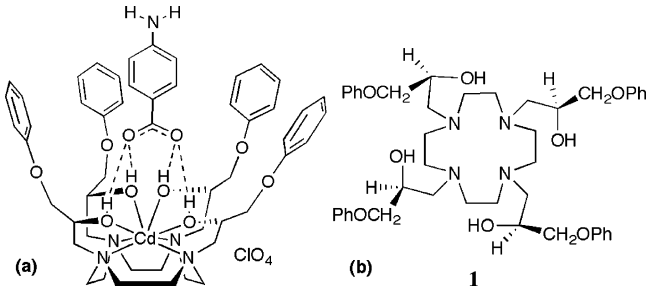

Figure 1. (a) Structural characteristics of *p*-aminobenzoate inclusion within the host−guest complex formed from the Cd(II) complex of the receptor ligand **1**, shown as (b).

sponse to metal ion coordination. Located at its base are four hydroxy groups capable of acting as hydrogen-bond donors to an incoming anion. A number of these receptor complexes containing bound anions have been structurally characterized by X-ray crystallography,[2−4] with the one displayed schematically in Figure 1a being typical. Here *p*-aminobenzoate is the guest anion and Cd(II) is the eight-coordinating metal ion responsible for activating, or pre-assembling, the receptor ligand **1**, Figure 1b, into the appropriate conical conformation, with all of the O−H bonds directed into the anion-binding cavity.

We have pursued this work to date principally using receptor ligand **1**, as shown. This is a homochiral, octadentate, pendant-donor macrocyclic ligand derived from cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) which has a phenyoxymethylene moiety attached to each of four coordinating pendant arms. Cyclen derivatives of this type are well known for their ability to complex in such a way that all four arms project in the same direction;[5] thus, the attachment of a phenyoxymethylene group to each arm provides a means by which octadentate coordination causes the receptor ligand to erect a framework of juxtaposed phenyl rings that define a substantial, partially hydrophobic cavity in the resulting receptor complex. By analogy with calix[4]-arene,[6] this amounts to metal ion coordination causing the ligand to adopt a cone conformation. A shortcoming of this approach has been that the presence of four phenoxymethylene groups causes the receptor to be insoluble in water, and so it has not been possible to test the capability of this type of anion receptor to operate in water, even though structural considerations make it look promising and binding constants as high as $10^{7.5}$ have been measured in 20% aqueous 1,4-dioxane on a related ligand that carries a fluorescent probe.[7] The objective of the present work was to ascertain whether this type of metal-ion activated anion receptor could be successfully employed in water by introducing ionic groups that would render it sufficiently hydrophilic to dissolve in water at usefully high concentrations. Preferably, these ionic groups should be cationic to enhance the electrostatic attraction of the incoming, and subsequently retained, anion, but for comparison, we also investigated the consequences of using an anionic group. Accordingly, we have modified **1** by attaching to each of the four aromatic rings either a cationic trimethylammonium group or an anionic sulfonate group to produce two new receptor ligands (*S*)-tmappc12, and (*S*)-sthmppc12, respectively (Figure 2). It is on the synthesis and metal ion complexation of these two receptor ligands, as well as the anion binding properties of the two Cd(II) receptor complexes derived from them, that we now report.

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Experimental Section

General Information. Ligand and metal complex syntheses were all performed under dry nitrogen gas. Solvents were purified using literature methods.[8] Microanalyses were conducted at the University of Otago, New Zealand. Melting points were measured using a Reichert hot-stage microscope and are uncorrected. NMR data were collected using a Varian Gemini 300 spectrometer operating at 300.075 MHz for protons and 75.462 MHz for ^{13}C. ^{1}H NMR chemical shifts were referenced to the residual protonated solvent peak taken as 7.26 ppm for $CDCl_3$ or 3.31 ppm for CD_3OD. In the case of D_2O, acetonitrile, $\delta = 2.06$ ppm, or 1,4-dioxane, $\delta = 3.75$ ppm, was added as an internal reference. For ^{13}C NMR spectra, chemical shifts were referenced to the central resonance of the solvent multiplet peak taken as 77.00 ppm for $CDCl_3$ or 49.00 ppm for CD_3OD. For solutions in D_2O, either acetonitrile was added as an internal reference and the peak from the methyl group at 1.47 ppm was used or the 1,4-dioxane peak at 67.19 ppm was used. Optical rotations were measured at ambient temperature using a PolAAr automatic polarimeter. Flash chromatography was carried out using the method of Still.[9] Silica gel from Merck Kieselgel with a particle size of 230−400 mesh was used as the stationary phase. Cadmium(II) triflate sesquihydrate was prepared by the literature method.[10]

Syntheses. (2*S*)-(+)-[3′-(*N*,*N*-Dimethylamino)phenoxy]-1,2-epoxypropane. *N*,*N*-dimethyl-3-aminophenol (1.372 g, 10 mmol) in dry DMF (10 mL) was added dropwise over 10 min to a stirring suspension of oil-free sodium hydride (240 mg, 10 mmol) in dry DMF (10 mL) at room temperature. Hydrogen gas was released during the reaction, and the mixture became a light brown solution. The solution was kept stirring for 1 h, and then (2*S*)-(+)-glycidyl tosylate (2.210 g, 9.7 mmol) in dry DMF (10 mL) was added dropwise over 15 min. The reaction mixture was allowed to stir for 24 h, by which time TLC indicated the disappearance of the glycidyl tosylate. The DMF was then evaporated, and water (50 mL) was added to dissolve the sodium tosylate. The product was extracted using diethyl ether (4 × 100 mL) giving a brown oil. This was purified by flash chromatography on a silica gel column (20 cm × 3 cm), using dichloromethane as the eluent, to afford the pure product as a colorless oil. Yield 0.87 g, 46%. ^{1}H NMR ($CDCl_3$) δ 7.20 (1H, t, $J = 8.6$ Hz, ArH), 6.35 (3H, m, ArH), 4.23 (1H, dd, $J = 3.2$, 12.0 Hz, CH_2OAr), 3.93 (1H, dd, $J = 6.0$, 12.0 Hz), 3.36 (1H, m, CH), 2.95 (6H, s, CH_3), 2.88 (1H, t, $J = 5.4$ Hz, CH_2O), 2.73 (1H, dd, $J = 2.7$, 10.0 Hz, CH_2O). ^{13}C NMR ($CDCl_3$) δ 159.2 (1C, ipso), 151.6 (1C, ipso), 129.3 (1C, ArH), 105.7 (1C, ArH), 101.5 (1C, ArH), 99.3 (1C, ArH), 68.3 (1C, CH_2OAr), 49.8 (1C, CH), 44.2 (1C, CH_2), 40.0 (2C, CH_3). (Found C, 68.67; H, 7.64; N, 7.16. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%). $[\alpha]_D^{298} = +5.98°$ (*c* 10.5, $CHCl_3$).

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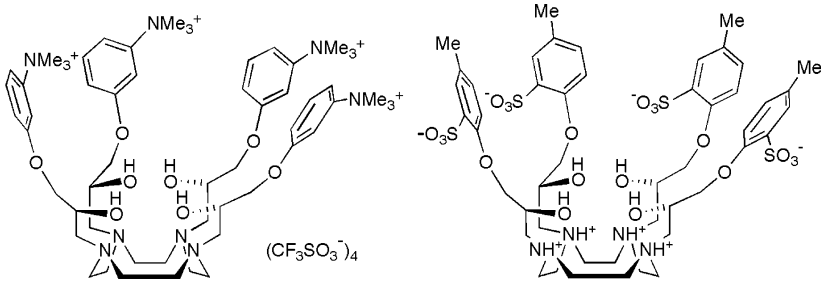


(*S*)-tmappc12 **L[1] triflate** (*S*)-sthmppc12 **L[2]H[4]**

Figure 2. Water-soluble anion receptor ligands discussed in this work.

(2*S*)-(+)-[3′-(*N,N,N*-Trimethylammonium)phenoxy]-1,2-epoxypropane Iodide. (2*S*)-(+)-[3′-(*N,N*-dimethylamino)phenoxy]-1,2-epoxypropane (2.02 g, 10.5 mmol) was dissolved in dry dichloromethane (5 mL). Excess methyl iodide (15 g, 100 mmol) was added dropwise, while stirring, to form a yellow solution. After 30 min, a white solid started to form. The reaction was left overnight to come to completion. The solid was separated by filtration, washed with dichloromethane (3 × 5 mL), and dried. Recrystallization from methanol gave the pure product as off-white needles, mp 160−163 °C. Yield 2.42 g, 69%. ^{1}H NMR (D_2O) δ 7.56 (1H, t, J = 8.2 Hz, ArH), 7.47−7.15 (3H, m, ArH), 4.57 (1H, dd, J = 2.0, 11.8 Hz, CH_2OAr), 4.02 (1H, dd, J = 6.3, 11.6 Hz, CH_2OAr), 3.65 (9H, s, CH_3), 3.55 (1H, m, CH), 3.04 (1H, t, J = 4.4 Hz, CH_2O), 2.95 (1H, dd, J = 3.0, 4.4 Hz, CH_2O). ^{13}C NMR (D_2O) δ 159.5 (1C, ipso), 148.0 (1C, ipso), 132.0 (1C, ArH), 116.9 (1C, ArH), 112.9 (1C, ArH), 107.9 (1C, ArH), 69.5 (1C, *CH*$_2$−O−Ar), 57.5 (3C, CH_3), 51.4 (1C, CH), 45.5 (1C, CH_2). (Found C, 42.95; H, 5.38; N, 4.09. $C_{12}H_{18}INO_2$ requires C, 43.00; H, 5.41; N, 4.18%). $[\alpha]_D^{298}$ = +5.53° (*c* 4.74, CH_3OH).

(2*S*)-(+)-[3′-(*N,N,N*-Trimethylammmonium)phenoxy]-1,2-epoxypropane Triflate. A solution of silver(I) triflate (84 mg, 0.18 mmol) in dry methanol (5 mL) was added dropwise to a solution of (2*S*)-(+)-[3′-(*N,N,N*-trimethylammmonium)phenoxy]-1,2-epoxypropane iodide (122 mg, 0.36 mmol) in dry methanol (10 mL) at 50 °C. On completion of the addition, the precipitated silver iodide was filtered off while the solution was still hot. On cooling the filtrate to room temperature, the pure product slowly crystallized as white needles, which were filtered off and dried under vacuum, mp 58−59 °C. Yield 61 mg, 54%. ^{1}H NMR (CD_3OD) δ 7.6−7.1 (4H, m, ArH), 4.51 (1H, dd, J = 2.2, 11.4 Hz, CH_2OAr), 3.95 (1H, dd, J = 6.6, 11.6 Hz, CH_2OAr), 3.68 (9H, s, CH_3), 3.39 (1H, m, CH) 2.91 (1H, t, J = 4.6 Hz, CH_2O), 2.81 (1H, dd, J = 2.7, 5.0 Hz, CH_2O). ^{13}C NMR (CD_3OD) δ 161.1 (1C, ipso), 149.4 (1C, ipso), 132.4 (1C, ArH), 121.8 (1C triflate, q, J = 319 Hz), 117.7 (1C, ArH), 113.1 (1C, ArH), 108.1 (1C, ArH), 71.0 (1C, CH_2OAr), 57.7 (3C, CH_3), 51.1 (1C, CH), 44.8 (1C, CH_2). (Found C, 43.79; H, 5.02; N, 4.13.$C_{13}H_{18}F_3NO_5S$ requires C, 43.70; H, 5.08; N, 3.92%). $[\alpha]_D^{298}$ = +4.82° (*c* 5.19, CH_3OH).

1,4,7,10-Tetrakis((2*S*)-(−)-2-hydroxy-3-[3′-(*N,N,N*-trimethylammonium)-phenoxy]-propyl)-1,4,7,10-tetraazacyclododecane Tetratriflate, (*S*)-tmappc12 triflate (L[1] triflate). (2*S*)-(+)-[3′-(*N,N,N*-Trimethylammmonium)phenoxy]-1,2-epoxypropane triflate (103 mg, 0.34 mmol) was dissolved in dry ethanol (10 mL) at 80 °C. A solution of cyclen (14.4 mg, 0.084 mmol) in dry ethanol (2 mL) was added to it. The mixture was then heated at 80 °C and left for 15 h. At this point, the solution was allowed to cool. Slow evaporation of the solution to dryness gave the pure product as a white powder, mp 98−100 °C. Yield quantitative. ^{1}H NMR (CD_3-OD) δ 7.6−7.1 (16H, m, ArH), 4.26 (4H, s, C*H*OH), 4.11 (8H, m, br, CH_2OAr), 3.63 (36H, s, CH_3), 3.1 (8H, m, br, CH_2N), 2.9−2.3 (16H, m, br, $N(CH_2)_2N$). ^{13}C NMR (CD_3OD) δ 161.6 (4C, ipso), 149.5 (4C, ipso), 132.4 (4C, ArH), 121.8 (C triflate, q, J = 319 Hz), 117.8 (4C, ArH), 112.9 (4C, ArH), 108.2 (4C, ArH), 72.3 (4C, CH_2OAr), 67.8 (4C, CHOH), 58.7 (4C, CH_2N), 57.7 (12C, CH_3), 52.8 (8C, $N(CH_2)_2N$). (Found C, 43.41; H, 5.87; N, 6.80. $C_{60}H_{92}$ $F_{12}N_8O_{20}$ S_4·$3H_2O$ requires C, 43.53; H, 5.97; N, 6.77%). $[\alpha]_D^{298}$ = −42.69° (*c* 12.58, CH_3OH).

[Cd((*S*)-tmappc12)](CF$_3$SO$_3$)$_6$·4H$_2$O, [CdL[1]](CF$_3$SO$_3$)$_6$. A solution of (*S*)-tmappc12 triflate (801 mg, 0.4 mmol) in methanol (10 mL) was added dropwise to a stirred supension of solid cadmium(II) triflate·$1.5H_2O$ (215 mg, 0.4 mmol) in methanol (5 mL) at 60 °C over a period of 10 min. Heating and stirring were continued for 2 h, over which time the suspended solid gradually dissolved forming a pink solution. The solution was kept stirring for a further 1 h and then cooled to room temperature. The solution was then slowly evaporated to yield a hygroscopic pink solid which was dried under high vacuum giving the analytically pure product without further purification, mp 170−174 °C. Quantitative yield. ^{1}H NMR (CD_3OD) δ 7.6−7.1 (16H, m, ArH), 4.6 (4H, br, C*H*OH), 4.2 (8H, br, CH_2O), 3.62 (36H, s, CH_3), 3.5−2.5 (24H, m, br, CH_2N, $N(CH_2)_2N$). ^{13}C NMR (CD_3OD) δ 161.2 (4C, ipso), 149.5 (4C, ipso), 132.5 (4C, ArH), 121.8 (C triflate, q, J = 319 Hz), 117.9 (4C, ArH), 113.3 (4C, ArH), 108.4 (4C, ArH), 71.7 (4C, CH_2O), 66.6 (4C, CHOH), 57.7 (12C, CH_3), 56.5 (4C, CH_2N), 51.5 (4C, $N(CH_2)_2N$), 50.4 (4C, $N(CH_2)_2N$). (Found C, 35.62; H, 4.65; N, 5.54. $C_{62}H_{92}CdF_{18}O_{26}N_8S_6$·$4H_2O$ requires C, 35.73; H, 4.84; N, 5.38%).

(2*S*)-(+)-3-[4′-Methylphenoxy]-1,2-epoxypropane. *p*-Cresol (1.622 g, 15 mmol) in dry DMF (10 mL) was added dropwise over 10 min to a stirred suspension of oil-free sodium hydride (360 mg, 15 mmol) in dry DMF (10 mL) at room temperature. During this period, hydrogen gas was released and the mixture became clear. The solution was stirred for 1 h, and then (2*S*)-(+)-glycidyl tosylate (3.400 g, 14.9 mmol) in dry DMF (10 mL) was added over 15 min. The reaction mixture was then stirred for 24 h. Following this, the DMF was evaporated and water (25 mL) was added to the residue to dissolve the sodium tosylate. The crude product was isolated as a pale yellow oil by diethyl ether extraction (4 × 50 mL). It was then purified by flash chromatography on a silica gel column (20 cm × 3 cm) using dichloromethane as the eluent to give the pure product as a colorless oil. Yield 1.68 g, 70%. ^{1}H NMR ($CDCl_3$) δ 7.08 (2H, d, J = 8.6 Hz, ArH), 6.80 (2H, d, J = 8.6 Hz, ArH), 4.18 (1H, dd, J = 3.3, 11.1 Hz, CH_2OAr), 3.94 (1H, dd, J = 5.4, 11.1 Hz, CH_2OAr), 3.33 (1H, m, CHO), 2.90 (1H, t, J = 4.6 Hz, CH_2O), 2.75 (1H, dd, J = 2.8, 5.2 Hz, CH_2O), 2.28 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.4 (1C, ipso), 130.5 (1C,

ipso), 129.9 (2C, ArH), 114.5 (2C, ArH); 68.8 (1C, CH_2−O−Ar), 50.2 (1C, CH), 44.7 (1C, CH_2), 20.4 (1C, CH_3). $[\alpha]_D^{298} = +2.24°$ (*c* 3.12, $CHCl_3$).

1,4,7,10-Tetrakis((2*S*)-(−)-2-hydroxy-3-[4′-methylphenoxy]-propyl)-1,4,7,10-tetraazacyclododecane, (2). (2*S*)-(+)-3-[4′-Methylphenoxy]-1,2-epoxypropane (1.189 g, 7.2 mmol) in dry ethanol (10 mL) was added dropwise over 10 min to a gently refluxing solution of cyclen (304 mg, 1.76 mmol) in dry ethanol (10 mL). The reaction mixture was kept stirring for 15 h by which time the completion of the reaction had been indicated by the disappearance of the epoxide during TLC monitoring. The product precipitated as a white solid (mp 121−123 °C) as the solution cooled to room temperature, and was filtered off. Yield 1.4 g, 96%. ^{1}H NMR ($CDCl_3$) δ 7.04 (8H, d, $J = 8.6$ Hz, ArH), 6.80 (8H, d, $J = 8.6$ Hz, ArH), 5.34 (4H, OH), 4.19 (4H, m, br, C*H*OH), 4.04 (4H, dd, $J =$ 4.3, 9.4 Hz, CH_2O), 3.87 (4H, dd, $J = 6.4$, 9.4 Hz, CH_2O), 3.0 (8H, d, $J = 10.0$ Hz, CH_2N), 2.7−2.1 (16H, m, $N(CH_2)_2N$ ring), 2.3 (12H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.8 (4C, ipso), 129.9 (4C, ipso), 129.8 (8C, ArH), 114.5 (8C, ArH), 70.1 (4C, CH_2OAr), 66.0 (4C, CHOH), 59.0 (4C, CH_2N), 51.6 (8C, $N(CH_2)_2N$ ring) 20.4 (4C, CH_3). (Found C, 69.48; H, 8.48; N, 6.81. $C_{48}H_{68}N_4O_8$ requires C, 69.54; H, 8.27; N, 6.76%). $[\alpha]_D^{298} = -124°$ (*c* 2, $CHCl_3$).

1,4,7,10-Tetrakis((2*S*)-(−)-2-hydroxy-3-[2′-sulfo-4′-methylphenoxy]-propyl)-1,4,7,10-tetraazacyclododecane, (*S*)-sthmppc12 (L^2H_4). Chlorosulfonic acid (7.4 g, 63 mmol) was added dropwise over 10 min to a well-stirred solution of 1,4,7,10-tetrakis((2*S*)-(−)-2-hydroxy-3-[4′-methylphenoxy]-propyl)-1,4,7,10-tetraazacyclododecane (1.3 g, 1.57 mmol) in dry dichloromethane (5 mL) which had been cooled to −10 °C in an ice−salt bath. The temperature of the reaction mixture was maintained well below 10 °C during the addition. A sticky, lumpy white precipitate formed immediately after the first drop of chlorosulfonic acid reached the solution, but this then gradually turned into a light brown layer. The reaction mixture was stirred for 8 h at room temperature. At the conclusion of the reaction, the mixture was cooled in an ice bath and a mixture of ice and water (10 mL) was poured into the mixture. A sticky solid formed immediately. The solid was washed with cold water several times, until the washing water was at pH 3−4, to remove most of the excess acid. Demineralized water (10 mL) was then added to the solid and the mixture was heated at 80 °C for 2 h in a water bath. The solid dissolved after 15 min of heating. The water was then removed by evaporation. Acetone (15 mL) was added to the solid remaining in the flask, and the white solid was then recovered by filtration. Further purification was conducted by washing the solid with acetone (3 × 10 mL) giving a fine white solid, mp 254−258 °C. Yield 1.55 g, 86%. ^{1}H NMR (D_2O) δ 7.60 (4H, s, ArH), 7.25 (4H, d, $J = 8.6$ Hz, ArH), 6.95 (4H, d, $J = 8.6$ Hz, ArH), 4.40 (4H, m, C*H*OH), 4.05 (8H, m, CH_2OAr), 3.8−2.8 (24H, m, br, CH_2N, $N(CH_2)_2N$ ring), 2.27 (12H, s, CH_3). ^{13}C NMR (D_2O) δ 153.7 (4C, ipso), 134.3 (4C, ArH), 131.5 (4C, ipso), 130.9 (4C, ipso), 129.1 (4C, ArH), 114.7 (4C, ArH), 70.9 (4C, CH_2OAr), 65.3 (4C, CHOH), 56.0 (4C, CH_2N), 50.6 (8C, br, $N(CH_2)_2N$ ring), 20.2 (4C, CH_3). (Found C, 48.30; H, 5.98; N, 4.75. $C_{48}H_{68}N_4O_{20}S_4 \cdot 2H_2O$ requires C, 48.64; H, 6.12; N, 4.73%). $[\alpha]_D^{298} = -76.13°$ (*c* 3.726, H_2O).

Cd[Cd((*S*)-sthmppc12)]·10H_2O, Cd[CdL^2]. A solution of (*S*)-sthmppc12 (505 mg, 0.425 mmol) in water (10 mL) was added dropwise to a suspension of solid cadmium(II) carbonate (147 mg, 0.85 mmol) in water (5 mL) at 80 °C. Carbon dioxide gas was immediately released from the reaction mixture, and the suspension turned to a clear solution by the end of addition. The mixture was stirred for 2 h and then acetonitrile was added until the solution turned cloudy. Cooling this suspension gave a copious white precipitate of the pure product, which was collected by filtration, washed with acetonitrile (3 × 5 mL), and then dried under vacuum, mp 282−286 °C (dec). Yield 472 mg, 71%. ^{1}H NMR (D_2O) δ 7.59 (4H, s, ArH), 7.23 (4H, d, $J = 8.6$ Hz, ArH), 7.02 (4H, d, $J = 8.6$ Hz, ArH), 4.35 (4H, broad, C*H*OH), 4.2−4.0 (8H, broad, CH_2O), 3.3−2.4 (24H, broad, CH_2N, $N(CH_2)_2N$), 2.22 (12H, s, CH_3). ^{13}C NMR (D_2O) δ 153.7 (4C ipso), 134.3 (4C, ArH), 131.4 (4C, ipso), 131.2 (4C, ipso), 129.1 (4C, ArH), 115.0 (4C, ArH), 71.2 (4C, CH_2-OAr), 65.6 (4C, CHOH), 55.4 (4C, CH_2N), 50.4 (4C, $N(CH_2)_2N$ ring), 49.4 (4C, $N(CH_2)_2N$ ring), 20.2 (4C, CH_3). (Found C, 37.06; H, 5.39; N, 3.73. $C_{48}H_{64}Cd_2O_{20}N_4S_4 \cdot 10H_2O$ requires C, 37.14; H, 5.58; N, 3.61%).

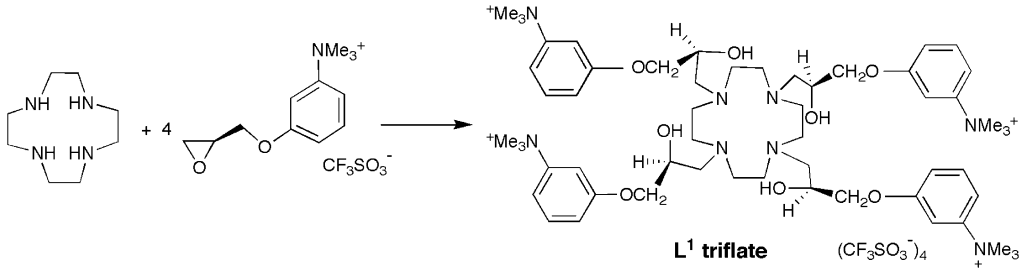
Potentiometric Titrations. The potentiometric titrations used to determine ligand pK_a values and metal−ligand binding constants were carried out under an atmosphere of water-saturated argon in a water-jacketed vessel maintained at 298.2 K. Data were obtained from 10 cm^3 aliquots of solution containing 0.005 M $HClO_4$, 0.100 M NEt_4ClO_4, and the appropriate ligand at ca. 0.001 M, titrated with 0.100 M, carbon dioxide free, NEt_4OH. Potassium hydrogen phthalate (0.005 M) was used as the primary standard against which the base concentration was initially determined by titration. The acid concentration was then accurately determined by titration against the standardized base. A Metrohm E665 Dosimat autoburet equipped with a 5 cm^3 buret was used to deliver the titrant and the potential measured by an Orion Ross Sure Flow 81-72BN combination electrode connected to an Orion SA 720 pH meter. The autoburet and pH meter were interfaced to a personal computer, which controlled the addition of titrant, using a program written by Drs A. Arnold and P. Duckworth, so that successive additions of titrant caused a decrease of 4 mV in the potential reading. The electrode $E°$ value was redetermined daily using data from a strong acid−strong base titration.

The pK_a and formation constants were determined from the titration curve using the program SUPERQUAD.[11] Formation constant data were gathered from solutions to which 0.1 M metal perchlorate solution was added so as to give metal-to-ligand ratios in the range 0.5:1−2:1. At least three titrations were performed for each ligand or ligand−metal ion combination unless precipitation intervened. The constants from each titration were averaged and are reported with an uncertainty corresponding to one-half of the range of the values. The criterion used to assess whether a satisfactory match between the theoretical titration curve and the experimental titration curve had been achieved was that χ^2 was below 12.6 at the 95% confidence level.

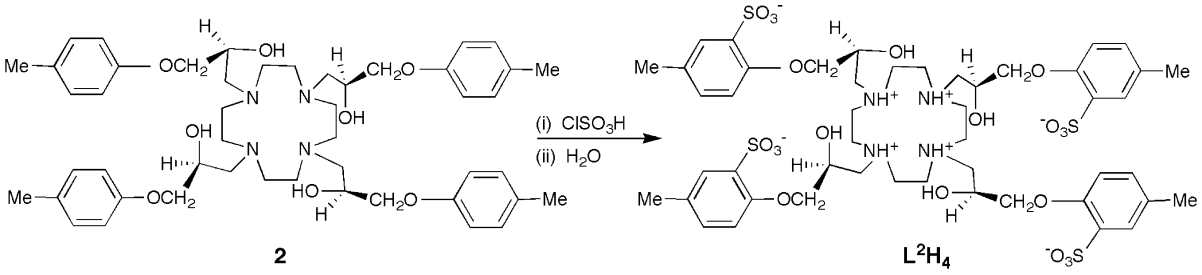
NMR Titrations. Titrations of a solution of the guest anion with a solution of the host molecule, during which the ^{1}H NMR spectrum of the guest was monitored, were used as a means of determining the binding constants for particular host−guest interactions. These were conducted in D_2O (0.1 M in $NaNO_3$) at either the natural pD of the guest salt solution, ca. 7.7, or in the case of phenolates, at pD 10.4, established by the addition of 0.5 M NaOH. The guest/host ratios were in the range 1:0−1:20, and in all cases, at least 15 experimental points were used to define the titration curve. The concentration of the guest in the NMR tube was maintained at 10^{-3} M, for titrations involving $(\mathbf{L^1})^{4+}$, or 5×10^{-3} M for titrations involving $(\mathbf{L^2})^{4-}$, by utilizing 50 μL of a 14 or 70 mM stock solution. The main stock solution for the host was also 14 or 70 mM, but some of the $[Cd(\mathbf{L^1})](CF_3SO_3)_6$ solution was diluted to make a secondary stock solution with a concentration of 1.4 mM.

(11) Gans, P.; Sabatini, A.; Vacca. A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195.

Scheme 1



Scheme 2



The secondary stock solution was used to make up solutions in which the guest/host ratios were in the lower range of 1:0.1−1:0.5, so that the aliquots taken lay in the range 50−250 μL. After combining the appropriate aliquots of guest and host solutions, the volume was made up to 0.7 mL and the ^{1}H NMR spectrum recorded at 294 K.

Binding constants ($\log(K/M^{-1})$) were obtained through analysis of the guest ^{1}H NMR chemical shift, versus host concentration, titration curves using a locally written nonlinear regression procedure.[3]

Guest anions were employed as sodium salts. They were produced by reacting an ethanolic solution of the neutral guest with a stoichiometric amount of sodium hydroxide dissolved in ethanol. The crude products were isolated by evaporation of the solvent. Purification was achieved by recrystallization from either methanol or ethanol.

Results and Discussion

Syntheses of the Receptor Ligands and Complexes. The cationic receptor ligand (*S*)-tmappc12 tetratriflate (hereafter **L^1 triflate**) was prepared in quantitative yield by the reaction of cyclen with (2*S*)-(+)-[3′-(*N*,*N*,*N*-trimethylammmonium)-phenoxy]-1,2-epoxypropane triflate in ethanol, as shown in Scheme 1. The use of enatiomerically pure 3′-(*N*,*N*,*N*-trimethylammmonium)phenoxy-1,2-epoxypropane triflate is necessary to ensure that only the homochiral diastereomer of the ligand is formed. The epoxide salt was synthesized from commercially available (2*S*)-glycidyl tosylate and 3-dimethylaminophenol according to the method of Klunder,[12] followed by treatment of the product with methyl iodide and then metathesis of the resulting iodide salt with silver triflate. The triflate salt of the Cd(II) complex, which was to act as the cationic water soluble anion receptor, was formed as the tetrahydrate by the reaction of cadmium(II) triflate sesquihydrate with **L^1 triflate** in refluxing methanol. It has a solubility in H_2O at 295 K and pH 7.0 of >0.02 M.

(12) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

Table 1. Stepwise Acid Dissociation Constants at 298.2 K for Protonated $(L^1)^{4+}$ and $(L^2)^{4-}$ [a] (Data Compared with that for thec12, Taken from Ref 17[b])

ligand	$(L^1)^{4+}$	$(L^2)^{4-}$	thec12
pK_{a1}[c]	9.87 ± 0.03	11.01 ± 0.03	9.78
pK_{a2}	6.94 ± 0.06	8.48 ± 0.05	8.01
pK_{a3}	<2.0	2.0 ± 0.2	2.3
pK_{a4}	<2.0	1.7 ± 0.1	<2.3

[a] I = 0.1 mol dm^{-3} Et_4NClO_4, pK_w = 13.73. [b] I = 0.1 mol dm^{-3} $NaNO_3$. [c] The stepwise equilibrium constants K_{a1}, K_{a2} etc. refer to the equations $HL^+ \rightleftharpoons L + H^+$, $H_2L^{2+} \rightleftharpoons HL^+ + H^+$, etc. (in these equations, for simplicity, the charge due to the aromatic substituent is being ignored), where p$K_a = -\log K_a$.

The receptor ligand (*S*)-sthmppc12 (hereafter **L^{2}H$_4$**), was prepared in 86% yield by regiospecific sulfonation of the homochiral receptor ligand, **2** shown in Scheme 2, using chlorosulfonic acid.[13,14] Initially, this procedure forms the water-insoluble tetra(sulfonyl chloride), which when subjected to heating in water, without isolation, readily hydrolyzes to the water-soluble zwitterionic product, as shown. Microanalysis and ^{13}C NMR spectroscopy indicated that monosulfonation of each aromatic ring had occurred exclusively, in accordance with the earlier experimental findings with *p*-cresol by Cerfontain et al.[15] The point of sulfonation was shown to be ortho to the phenoxy group by the ^{1}H NOESY NMR spectrum which displayed a strong cross-peak between the methyl resonance and the unique aromatic singlet resonance. Ligand **2** was prepared by a method similar to **L^1 triflate**, but starting from (2*S*)-(+)-3-[4′-methylphenoxy]-1,2-epoxypropane, prepared using Klunder's method.[12] The Cd(II) complex, $Cd[Cd\mathbf{L}^2]\cdot 10H_2O$, was formed in 71% yield by the reaction of cadmium(II) carbonate with **L^{2}H$_4$** in hot water. It has a solubility in H_2O at 295 K and pH 7.0 of >0.1 M.

(13) Makha, M.; Raston, C. L. *Tetrahedron Lett.* **2001**, 6215.
(14) Makha, M.; McKinnon, I. R.; Raston C. L. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1801.
(15) Cerfontain, H.; Lambrechts, H. J. A.; Schaasberg-Nienhuis, Z. R. H.; Coombes, R. G.; Hadjigeorgiou, P.; Tucker, G. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 659.

Table 2. Formation Constants at 298.2 K for Metal Complexes of $(\mathbf{L^1})^{4+}$ and $(\mathbf{L^2})^{4-}$, Together with pK_a Values for the Pendant Hydroxyl Group[a] (Data Compared with That for thec12,[b] Taken from Refs 17 and 18)

		log K								
reaction[c]	ligand	Co^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
$M + LH \rightleftharpoons MLH$	$(\mathbf{L^2})^{4-}$	6.9 ± 0.4	7.7 ± 0.1	5.9 ± 0.2	8.6 ± 0.1	9.7 ± 0.1	[d]	[d]	[d]	[d]
	thec12	5.8	3.5	4.0	5.2	3.1	[d]	[d]	[d]	[d]
$M + L \rightleftharpoons ML$	$(\mathbf{L^1})^{4+}$	[e]	10.3 ± 0.2	7.3 ± 0.2	12.4 ± 0.2	[e]	<2.0	4.1 ± 0.2	[e]	[e]
	$(\mathbf{L^2})^{4-}$	10.4 ± 0.2	14.3 ± 0.2	10.5 ± 0.2	14.1 ± 0.2	16.8 ± 0.2	4.5 ± 0.3	7.9 ± 0.1	7.6 ± 0.1	6.7 ± 0.1
	thec12	6.0	15.2	12.8	14.6	15.3	2.86	7.41	6.47	4.84
$M + L \rightleftharpoons ML_{-H} + H$	$(\mathbf{L^2})^{4-}$	2.4 ± 0.1	4.5 ± 0.2	1.8 ± 0.2	4.2 ± 0.1	6.9 ± 0.1	-5.5 ± 0.6	2.19 ± 0.04	2.68 ± 0.08	3.63 ± 0.05
	thec12	-2.5	5.9	4.5	4.9	4.2	[d]	[d]	[d]	[d]
$M + L \rightleftharpoons ML_{-2H} + 2H$	$(\mathbf{L^2})^{4-}$	[d]	[d]	-8.4 ± 0.2	[d]	[d]	[d]	[d]	[d]	[d]

		pK_a ML								
reaction	ligand	Co^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
pK_{a1}	$(\mathbf{L^2})^{4-}$	8.0 ± 0.3	9.8 ± 0.4	8.7 ± 0.4	9.9 ± 0.3	9.9 ± 0.3	10.0 ± 0.9	10.1 ± 0.1	10.3 ± 0.2	10.3 ± 0.2
$ML \rightleftharpoons ML_{-H} + H$	**thec12**	8.5	9.3	8.3	9.7	11.1	[d]	[d]	[d]	[d]
pK_{a2}	$(\mathbf{L^2})^{4-}$	[d]	[d]	10.2 ± 0.4	[d]	[d]	[d]	[d]	[d]	[d]
$ML_{-H} \rightleftharpoons ML_{-2H} + H$	**thec12**	[d]	12.0	[d]	11.5	[d]	[d]	[d]	[d]	[d]

[a] $I = 0.1$ mol dm^{-3} Et_4NClO_4, p$K_w = 13.73$. [b] $I = 0.1$ mol dm^{-3} $NaNO_3$. [c] For simplification, the charges are omitted. [d] Not observed. [e] Precipitation occurred early in the titration.

Receptor Ligand pK_a's and Metal Binding Constants. The protonated tertiary amine pK_a values for $(\mathbf{L^1})^{4+}$ and $(\mathbf{L^2})^{4-}$ were determined by potentiometric titration with NEt_4-OH ($I = 0.1$ M, NEt_4ClO_4) and are given in Table 1 along with the values for thec12 for comparison. Thec12 is analogous to $(\mathbf{L^1})^{4+}$ and $(\mathbf{L^2})^{4-}$ but has H in place of the substituted phenoxymethylene appendage. The pK_a values follow the usual pattern for cyclen derivatives of indicating high basicity for the first two protonated tertiary amines (pK_{a1} and pK_{a2}) followed by considerably reduced basicity for the subsequently protonated tertiary amines (pK_{a3} and pK_{a4}).[16] Overall, the relative basicity of the three ligands in Table 1, in the form in which they will generate metal complexes with all four nitrogen atoms coordinated, is best gauged by the sum of pK_{a1} and pK_{a2}. As expected, this summation shows that anionic $(\mathbf{L^2})^{4-}$ (19.49) is more basic than neutral thec12 (17.79), which is more basic than cationic $(\mathbf{L^1})^{4+}$ (16.81). The presence of the negatively charged sulfonates on $(\mathbf{L^2})^{4-}$ increases its basicity to the point where pK_{a3} and pK_{a4} can be measured within the pH limitations of glass electrode potentiometry (pH range = 2−12) whereas for the positively charged $(\mathbf{L^1})^{4+}$ neither of these pK_a values can be measured since the triprotonated and tetraprotonated macrocycles do not occur to a significant extent above pH 2. For thec12, pK_{a3}, but not pK_{a4}, can be measured.[17]

Identical potentiometric titration of the protonated ligands to that described above, but in the presence of the divalent alkaline earth, transition, and post-transition metal ions listed in Table 2, revealed the formation of only an $[ML]^{6+}$ species in the case of $(\mathbf{L^1})^{4+}$, whereas the more basic $(\mathbf{L^2})^{4-}$ showed a much richer chemistry with evidence of $[MLH]^{-}$, $[ML]^{2-}$, and $[ML_{-H}]^{3-}$ with all M(II) studied and in addition an $[ML_{-2H}]^{4-}$ species when M(II) = Zn(II). The protonated species presumably arise because of the inherently high basicity of $(\mathbf{L^2})^{4-}$ which allows it to bind with one amine protonated. The deprotonated species, containing L_{-H} or L_{-2H}, have previously been associated with deprotonation of one or more of the coordinated hydroxy groups, facilitated by the polarizing effect of the metal ion, although deprotonation of a coordinated water molecule cannot be excluded.[19] Speciation diagrams for the Cd(II) complexation of $(\mathbf{L^1})^{4+}$ and $(\mathbf{L^2})^{4-}$, which are of significance in the context of the Cd(II) activation of each ligand toward behavior as an anion receptor complex, are shown as Figures 3 and 4. If the stability of the ML species, $[M\mathbf{L^1}]^{6+}$ and $[M\mathbf{L^2}]^{2-}$, are compared to that of $[M(thec12)]^{2+}$, it is evident that the most basic ligand, $(\mathbf{L^2})^{4-}$, does not always produce the most stable complex. This only occurs for the alkaline earth elements, Co(II), and Pb(II). In the case of Pb(II), this may be an instance of an increased number of oxygen atoms on the pendant arms promoting enhanced stability, as has been noted previously.[20] On the other hand, the least basic ligand, $(\mathbf{L^1})^{4+}$, for all M(II) where it has been possible to make a measurement, does produce the least stable complex. It should be noted, however, that the stability of the Cd(II) complexes is still sufficiently high for it to be taken advantage of as the potentially eight-coordinate metal ion most suitable for assembling both $(\mathbf{L^1})^{4+}$ and $(\mathbf{L^2})^{4-}$ into the conical conformation necessary for anion sequestration.

Behavior of the Cationic Anion Receptor Complex $[Cd\mathbf{L^1}]^{6+}$. The solubility of $[Cd\mathbf{L^1}](CF_3SO_3)_6$ in water permitted an investigation of its ability to retain anionic guests under aqueous conditions. This was performed by titration of a 10^{-3} M D_2O solution (0.1 M in $NaNO_3$) of the guest molecule with a solution containing the host, during which the changing chemical shift of an appropriate ^1H NMR resonance from the guest, taken to be indicative of molecular inclusion, was monitored. The pD of the solutions was checked using a pH meter and normally found to be on the

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(17) Turonek, M. L.; Duckworth, P. A.; Laurence, G. S.; Lincoln, S. F.; Wainwright, K. P. *Inorg. Chim. Acta* **1995**, *230*, 51.
(18) Dhillon, R.; Lincoln, S. F.; Madbak, S.; Stephens, A. K. W.; Wainwright, K. P.; Whitbread, S. L. *Inorg. Chem.* **2000**, *39*, 1855.
(19) Hay, R. W.; Pujari, M. P.; Moodie, W. T.; Craig, S.; Richens, D. T.; Perotti, A.; Ungaretti, L. *J. Chem. Soc., Dalton Trans.* **1987**, 2605.
(20) Hancock, R. D. *Acc. Chem. Res.* **1990**, *23*, 253.

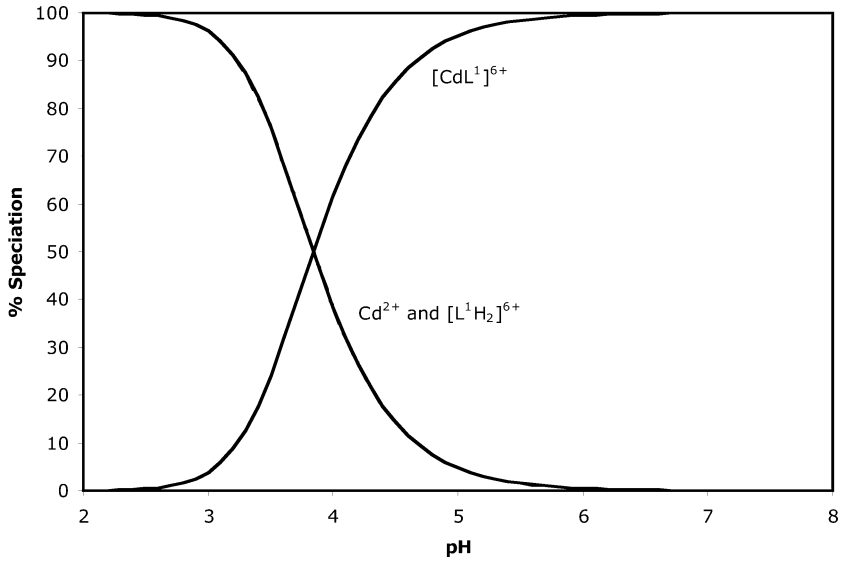

Figure 3. Speciation for 10^{-3} M $(\mathbf{L^1})^{4+}$ plus 10^{-3} M Cd^{2+} as a function of pH at 298 K with $I = 0.1$ M (NEt_4ClO_4).

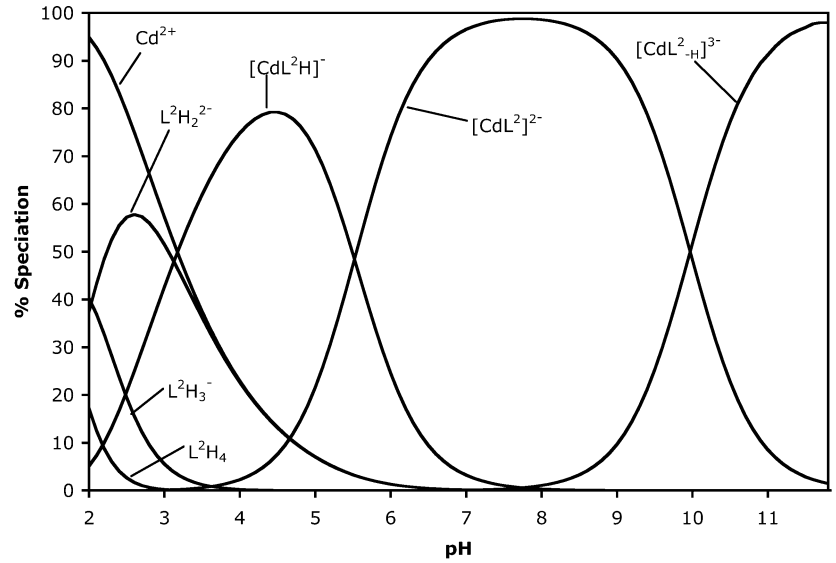

Figure 4. Speciation for 10^{-3} M $(\mathbf{L^2})^{4-}$ plus 10^{-3} M Cd^{2+} as a function of pH at 298 K with $I = 0.1$ M (NEt_4ClO_4).

order of 7.7 ± 0.3, which, being well above the pK_a of the benzoates and carboxylates used and within the pH range where the concentration of $[Cd\mathbf{L^1}]^{6+}$ is maximized (>6.1, Figure 3), was not adjusted. Where phenolates were under investigation to ensure complete deprotonation of the phenol, the pD was adjusted to ca. 10.4 using 0.5 M sodium hydroxide.

The guest anions that were studied in conjunction with $[Cd\mathbf{L^1}]^{6+}$ are listed in Table 3 along with their binding constant ($\log(K/M^{-1})$) values, deduced by nonlinear least squares regression analysis of the titration curves. These anions were chosen since they were the same or similar to those that had been identified in earlier work with $[Cd(\mathbf{1})]^{2+}$, in nonaqueous solvents, as either giving isolable host−guest complexes[2] or displaying log K values in DMSO in the range $3 \rightarrow 4.5$.[3] Where comparisons are possible with the earlier DMSO work we note that the absolute value of the binding constant has diminished by between 1 (acetate) and 3 orders of magnitude (phenoxyacetate). A typical titration curve involving $[Cd\mathbf{L^1}]^{6+}$, that with L-tryptophanate, is shown in Figure 5 and the remainder are shown in the Supporting Information as Figures S1−S8. Before these curves were

Table 3. $\log(K/M^{-1})$ Values for Anion Binding with $[Cd\mathbf{L^1}]^{6+}$ in D_2O (0.1 M in $NaNO_3$) at pD = 7.7, unless Otherwise Stated, Determined at [anion] = 10^{-3} M, $[[Cd\mathbf{L^1}]^{6+}] = 0-10^{-2}$ M, unless Otherwise Stated, at 294 K

anion	NMR chemical shift change[a]	$\Delta\delta$[b]	log K[c]
p-nitrophenolate (pK_a = 7.14)	6.508−7.165[e]	0.657	1.7 ± 0.2[d]
p-formylphenolate (pK_a = 7.66)	9.412−9.363[f]	−0.049	2.1 ± 0.1[d]
p-nitrobenzoate (pK_a = 3.44)	8.287−8.050	−0.237	3.0 ± 0.1
p-aminobenzoate (pK_a = 4.92)	7.741−7.609	−0.132	4.5 ± 0.2
p-dimethylaminobenzoate (pK_a = 5.03)	7.809−7.679[g]	−0.130	> 4.5
D-tryptophanate (pK_a = 2.38)	7.737−7.705[g]	−0.032	1.6 ± 0.1
L-tryptophanate (pK_a= 2.38)	7.737−7.701[g]	−0.036	2.2 ± 0.1
phenoxyacetate (pK_a = 3.60)	6.940−6.843[g]	−0.097	2.1 ± 0.04
acetate (pK_a = 4.76)	1.715−1.843[h]	0.128	2.3 ± 0.1

[a] Free guest given first. [b] Negative value corresponds to upfield shifting. [c] Uncertainties given as 1 standard deviation. [d] Measured at pD 10.4. [e] $[Host]_{max}$ was 1.6×10^{-2} M (16 equiv). [f] $[Host]_{max}$ was 1.2×10^{-2} M (12 equiv). [g] $[Host]_{max}$ was 1.5×10^{-2} M (15 equiv). [h] $[Host]_{max}$ was 2.0×10^{-2} M (20 equiv).

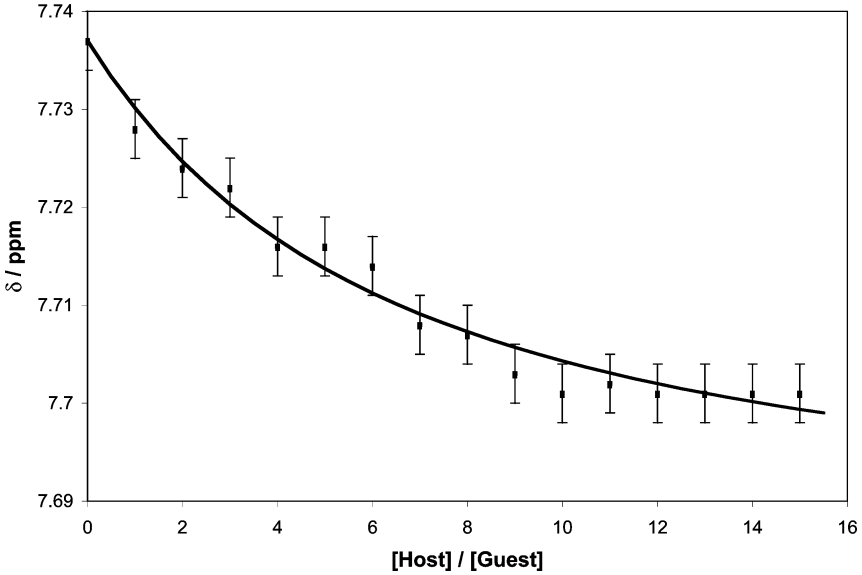

Figure 5. ^{1}H NMR chemical shift changes in D_2O (0.1 M in $NaNO_3$) for the most downfield resonance of 10^{-3} M sodium (L)-tryptophanate as it is titrated with [Cd**L**$^{\mathbf{1}}$]$(CF_3SO_3)_6$ (host) as a function of [host] at 294 K. Squares indicate the experimental data points and the curve indicates the theoretical δ values for the calculated values of K and $\delta_{\text{host-guest}}$. Error bars correspond to $\pm$0.003 ppm.

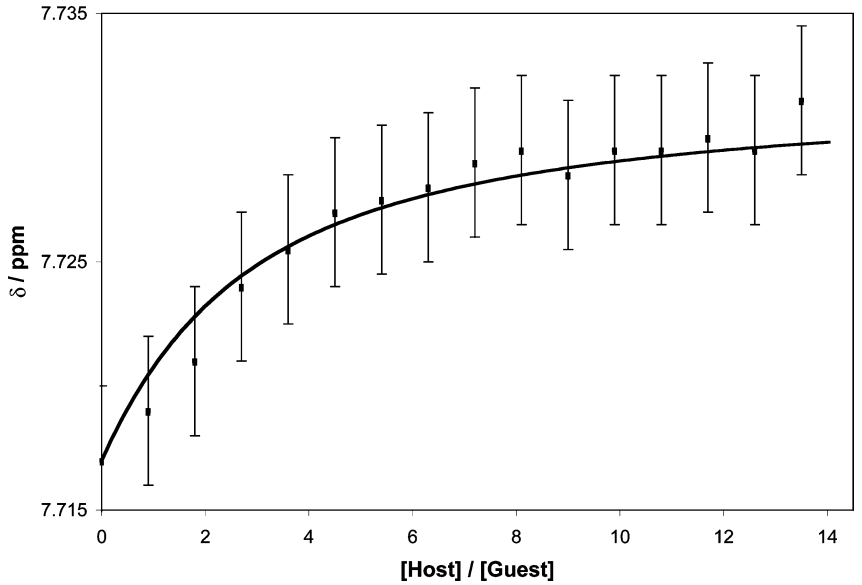

Figure 6. ^{1}H NMR chemical shift changes in D_2O (0.1 M in $NaNO_3$) for the most downfield resonance of 5×10^{-3} M sodium *p*-aminobenzoate as it is titrated with $(NH_4)_2$[Cd**L**$^{\mathbf{2}}$] (host) as a function of [host] at 294 K. Squares indicate the experimental data points and the curve indicates the theoretical δ values for the calculated values of K and $\delta_{\text{host-guest}}$. Error bars correspond to $\pm$0.003 ppm.

accepted as being indicative of the anion binding within the binding cavity of [Cd**L**$^{\mathbf{1}}$]$^{6+}$, blank titrations were performed using tetraethylammonium perchlorate instead of [Cd**L**$^{\mathbf{1}}$]$^{6+}$ to check that the observed changes in ^{1}H NMR chemical shift were not simply due to ion pairing between the tetraalkylammonium groups of [Cd**L**$^{\mathbf{1}}$]$^{6+}$ and the guest anion. These blank titrations demonstrated no systematic alteration in the anion ^{1}H NMR chemical shift values, and all values were within $\pm$0.002 ppm of the starting value.

Generally, the log K values can be seen to increase, within any one class of anion, in accordance with increasing basicity of the anion (pK_a given in Table 3). The increase in binding constant with increasing pK_a is consistent with the anions acting as hydrogen-bond acceptors with the four convergent O−H hydrogen-bond donors at the base of the binding cavity. In previous work, aromatic carboxylates have been shown by X-ray crystallography to hydrogen bond within the binding cavity in such a way that each carboxylate oxygen atom acts as a hydrogen-bond acceptor to two cis-hydroxy groups;[3] phenolates, on the other hand, bind to one pair of cis-hydroxy groups, which manifests itself here by the lower binding constants. The lower log K values shown by the two acetates, compared to the benzoates, is suggestive of a certain degree of stabilization for the benzoate guests afforded by $\pi-\pi$ interaction with the aromatic rings forming the cavity. The aromatic ring of phenoxyacetate is likely to lie well beyond the confines of the aromatic cavity, and its binding fails to be strengthened in this way. The difference in log K value between the two enantiomers of tryptophanate

Table 4. log K Values for Aromatic Anion Binding with $(NH_4)_2[Cd\mathbf{L^2}]$ in D_2O (0.1 M in $NaNO_3$) Performed at [anion] = 5×10^{-3} M, $[(NH_4)_2[Cd\mathbf{L^2}]] = 0-6.75 \times 10^{-2}$ M (13.5 equiv), at 294 K

anion	NMR chemical shift change[a]	$\Delta\delta$[b]	log K[c]
p-nitrobenzoate	8.285−8.266	−0.019	∼0.4
p-aminobenzoate	7.717−7.732	0.015	2.0 ± 0.4
p-dimethylaminobenzoate	6.921−6.898	−0.023	1.8 ± 0.2

[a] Free guest given first. [b] Negative values corresponds to upfield shifting. [c] Uncertainty given as 1 standard deviation.

indicates slight thermodynamic, chiral discrimination, in favor of the L-form, by the chiral cavity.

Behavior of the Anionic Anion Receptor Complex $[Cd\mathbf{L^2}]^{2-}$. Before commencing similar titration studies of anion binding with $[Cd\mathbf{L^2}]^{2-}$, $Cd[Cd\mathbf{L^2}]\cdot 10H_2O$ was converted to $(NH_4)_2[Cd\mathbf{L^2}]\cdot 8H_2O$ by precipitation of the ionic Cd(II) as $Cd(OH)_2$ using aqueous ammonia. In this way, interference by coordination of the intended guest anion to free Cd(II) was avoided. Since it was anticipated that log K values would be lower with the anionic host than with the cationic host, the titrations were conducted using the higher guest anion concentration of 0.005 M to promote discernible association at accessible host concentrations, but in other respects, the titrations were identical to those described above. The titration curve for *p*-aminobenzoate with $[Cd\mathbf{L^2}]^{2-}$ is shown in Figure 6 as a typical example and the remainder in Figures S9 and S10 of the Supporting Information. Blank titrations in which the guest anion was titrated with ammonium nitrate instead of $(NH_4)_2[Cd\mathbf{L^2}]$ were conducted to establish whether the ^{1}H NMR resonance chemical shift perturbation that was seen might simply be arising from ion pairing with the ammonium ion, but no perturbation of more than ± 0.002 ppm was observed in these experiments.

The limited number of binding constants that were able to be measured using $[Cd\mathbf{L^2}]^{2-}$ are given in Table 4. By way of explanation of the limited number it should be noted that, as far as we are aware, these are the first anion binding constants measured in water using an anionic receptor. It is unfortunate that, because of the small value of the ^{1}H NMR chemical shift perturbation, the uncertainty is significant. A recent review has pointed to the difficulty of achieving discernible anion binding in water even with a neutral receptor, for the reasons given in the Introduction, and cites the example of the bacterial sulfate binding protein (SBP) as perhaps the only presently known example of this.[1a] Thus, the observation of any form of anion binding with an anionic variant of this class of anion receptor identifies the class as having unique characteristics. In part, this may derive from the fact that, although $[Cd\mathbf{L^2}]^{2-}$ as a whole is negatively charged, it does have a positive center, in the form of the Cd(II) ion. Related crystal structures show that this is likely to be located ca. 4.0 Å away from retained benzoate oxygen atoms,[3,21] thereby contributing a slight stabilizing effect to the anion association in addition to that derived from hydrogen bonding. From the three binding constants that we have determined, it is noteworthy that the anticipated reduction in stability due to the overall anionic character of the receptor amounts to ∼3 orders of magnitude. Compared to the values measured with the cationic receptor, the relative ordering (within experimental error) is unchanged. The other guest anions listed in Table 3 were also investigated but were found to give no systematic ^{1}H NMR resonance chemical-shift perturbation that could be made use of to evaluate a binding constant. This is consistent with their binding constants with $[Cd\mathbf{L^2}]^{2-}$ being below that of *p*-nitrobenzoate, just as they are with $[Cd\mathbf{L^1}]^{6+}$.

Conclusion

We have been able to demonstrate through this study that the anion-binding properties of $[Cd(\mathbf{1})]^{2+}$ (Figure 1), initially discovered in DMSO,[3] can be maintained in water, providing that a cationic hydrophilic group is used to achieve water solubility. The stability of the host−guest complex in water is typically about 2 orders of magnitude lower than it is in DMSO when the water solubility of the receptor complex is achieved using the trimethylammonium moiety. If the anionic hydrophilic group, sulfonate, is used to do this, although the water solubility is greater, the strength of the anion binding reduces to a negligibly low level for all but the most strongly bound anions, which in this study were *p*-amino- and *p*-dimethylaminobenzoate.

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Supporting Information Available: Figures S1−S10 showing the titration curves used to evaluate anion binding constants that are not already shown in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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