Synthesis and Complexation Properties of Poly(ethylene glycol)-Linked Mono- and Bis-dioxocyclams

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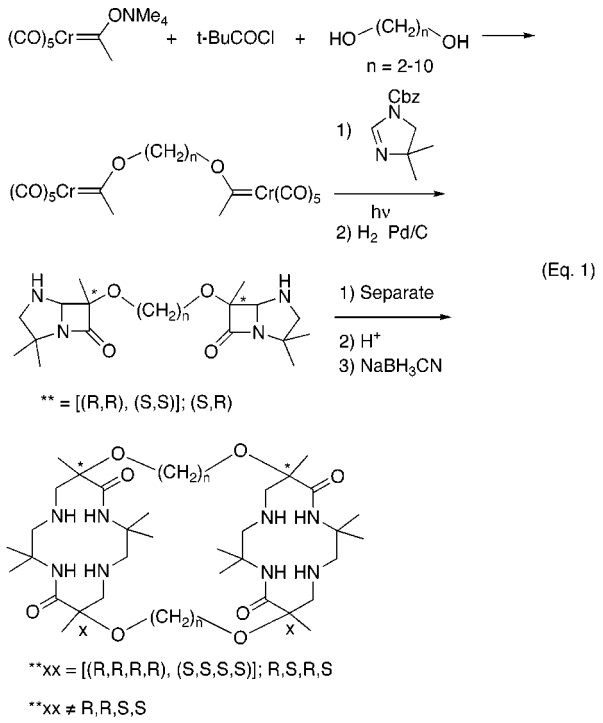
Both tri- and tetra(ethylene glycol) linked bis-chromium carbene complexes have been synthesized. These carbene complexes were photolyzed with N-protected imidazolines to give protected azapenams. These were transformed into polyether-linked basket dioxocyclams **4a**,**b** and bis-dioxocyclams **5a**,**b**. These compounds have cavities for the complexation of both "hard" and "soft" metal ions. The complexes of Ni, Ba, and Gd were synthesized.

Introduction

The synthesis and complexation properties of macrocyclic ligands having coordination sites for both "soft" transition metals and "hard" alkaline and alkaline earth metals has been an active area of research for well over a decade.[1] Although quite diverse, these systems usually have polyamine sites for coordination of the transition metal, and polyether linkages for complexation of the "hard" cations. Complexation of the polyether portions of these types of ligands has been used to organize two transition metal centers at short distances in macrocyclic ligands,[2] to hydrogen bond to neutral guests already coordinated to the transition metal,[3] to aid in cooperative binding of potassium and lipophilic substrates,[4] to reversibly alter the dihedral angle in bipyridines both intra[5] and intermolecularly,[6] to manipulate photoexcited states,[7] and to generate switchable porphyrin arrays.[8] Most of these applications rely on the considerable contractions polyethers experience when they coordinate to hard cations.

Recently an unconventional synthesis of dioxocyclams was reported from these laboratories.[9] It involves photolysis of chromium carbene complexes with protected imidazolines to produce protected azapenams. Removal of the protecting group and acid-catalyzed cleavage and dimerization, followed by reduction, produced dioxocyclams in excellent yield. When bis-carbene complexes were used with achiral imidazolines, separable mixtures of diastereoisomeric bis-azapenams were prepared. Acid-catalyzed cleavage/dimerization produced bis-dioxocyclams in excellent yield, with high selectivity for forming homo dimers (centers of like configuration undergoing dimerization) (eq 1).[10] The structures of the metal



(Eq. 1)

complexes of the two diastereoisomers differed substantially, with the meso complexes having the two planar metal-cyclam rings strictly face-to-face and eclipsed, while the D,L pair had the rings at an angle of ≈70° (like an open book) and gauche. This chemistry offers a short, efficient synthesis of functionalized, complex bis-macrocycles. Its application to polyether-linked bis-dioxocyclams is presented below.

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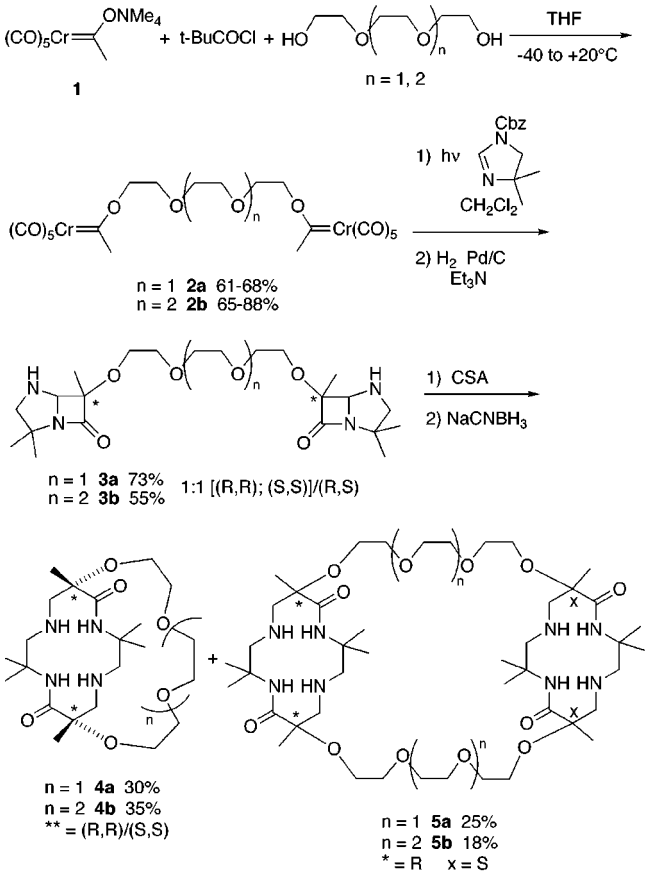
Scheme 1



Results and Discussion

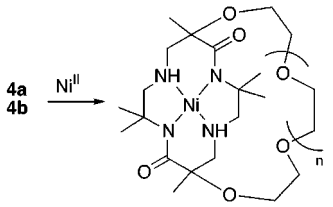
The requisite polyether-linked carbene complexes were synthesized by O-acylation of the tetramethylammonium salt **1** followed by acyl group replacement with tri- and tetra(ethylene glycol) to give bis-carbene complexes **2a** and **2b** in good yield (Scheme 1). It was essential that the diols be scrupulously dried to ensure good yields in this step and that the resulting carbene complexes be completely freed from pivalic acid and excess pivaloyl chloride to ensure good yields in the photochemical step. Photolysis of complexes **2a** and **2b** in the presence of an achiral imidazoline followed by hydrogenolysis of the Cbz group produced bis-azapenams **3a** and **3b** in good yield, as mixtures of diastereoisomers. These were not separated, but rather the mixture was subjected to the standard acid-catalyzed cleavage/dimerization/imine reduction conditions (Scheme 1).

Instead of the expected mixture of diastereoisomers of "homo" dimers obtained with the diol-linked systems in eq 1, this process produced "basket" homo monocyclams (**4a**,**b**) from the (*R*,*R*)/(*S*,*S*) bis-azapenam cyclizing on itself, as well as the expected "homo" dimers **5a**,**b** from the (*R*,*S*) bis-azapenam. This result shows the strong propensity for centers of like configuration to undergo reaction. The (*R*,*R*)/(*S*,*S*) pair could bring two centers of like configuration together to give the "basket" homo monocyclam while the only way the (*R*,*S*) bis-azapenam could bring centers of like configuration together was to dimerize. Compounds **4** and **5** were highly soluble in solvents such as water, alcohols, ethers, and chlorinated hydrocarbons, but much less soluble in hydrocarbon solvents. (Their water-solubility resulted in some losses during isolation, reducing the yields.)

Compounds **4b** and **5a** were recrystallized from methanol/water, and their structures were determined by X-ray diffraction (Figure 1).[11] Each has a well-defined polyether chain. The bridged "basket" monocyclam **4b** has one water of crystallization within the cavity (disordered with respect to the amine nitrogens (N-2 and N-4) and two waters outside the cavity. The linked bis-cyclam **5a** has two waters within the cavity, and four outside. Each structure has well-defined tetraaza coordination sites for the complexation of transition metals, as well as Crown ether-type sites for alkali or alkaline earth metals.

As can be seen from the stereoview of basket monocyclam **4b**, the 14-membered ring adopts a regular, zigzag conformation, with the amines projecting into the cavity formed by the polyether bridge, toward the included water molecule, while amide carbonyl groups project outward from the cavity. In the solid state, **4b** adopts a very symmetrical conformation. Bridged bis-cyclam **5a** has similar structural features.

Treatment of monocyclams **4a** and **4b** with nickel(II)-bromide·3DMF (**4a**) or nickel(II) tetrafluoroborate [from nickel(II) bromide and silver tetrafluoroborate (**4b**)] in THF produced neutral nickel(II) monocyclam complexes **6a** and **6b** (eq 2). These complexes maintained the

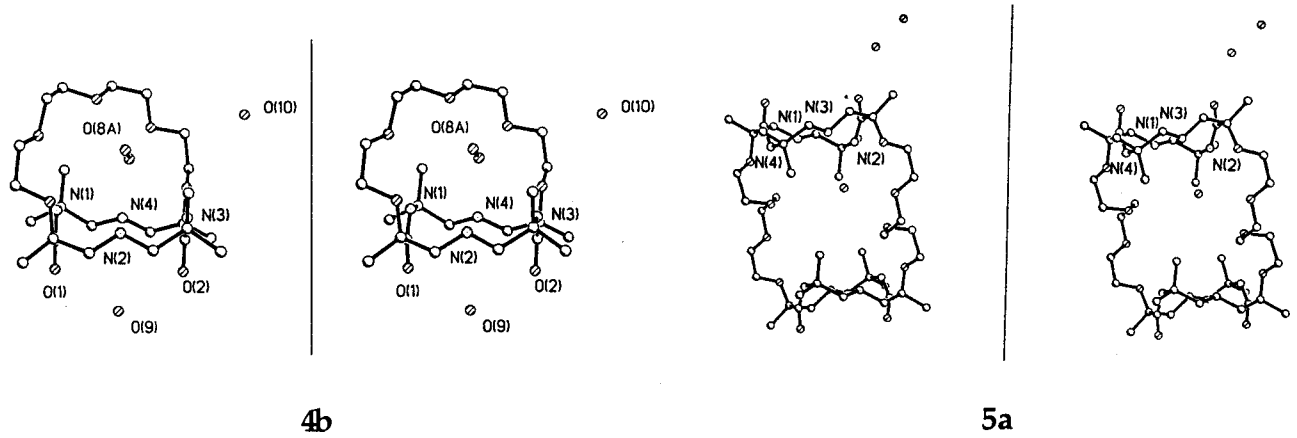


(Eq. 2)

solubility properties of the free ligands, having appreciable solubility in most polar solvents including water, and nonpolar solvents, with the exception of hydrocarbon solvents. Stereoviews of these complexes are shown in Figure 2. As expected, complexation to nickel(II) flattened and rigidified the 14-membered ring. The two complexes differed primarily by the extension and disposition of the polyether bridge, and, as a consequence, by the size of the polyether cavity.

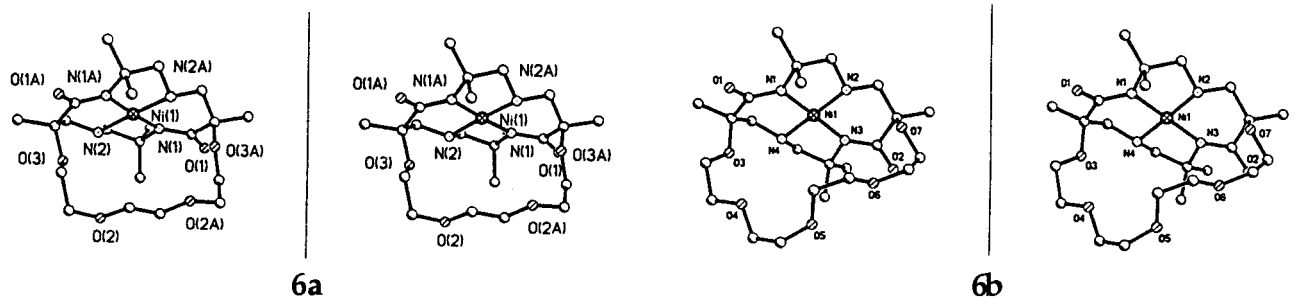
Bis-cyclams **5a** and **5b** similarly formed bis-nickel complexes **7a** (60%) and **7b** (80%) when treated with $Ni(BF_4)_2$. Again, these complexes had appreciable solubility in a wide range of solvents, with the exception of hydrocarbons. A stereoview of complex **7a** is shown in Figure 3. In contrast to the shorter propylene glycol linked bis-cyclam bis-nickel complexes previously reported[10a] (in which the two macrocyclic rings were strictly face-to-face and eclipsed, with a nickel−nickel distance of ≈7 Å), in complex **7a**, the two rings are canted at an angle of 27.3° and are rotated almost 90° with respect to one another, with the amide nitrogens of one ring aligning with the amines of the other, and the nickel−nickel distance is 9.466 Å. The stereoview of complex **7a** shows that the two 14-membered rings are not stacked on top of one another, but rather are cantilevered, with the bottom ring projecting out from under the top ring. This is probably a consequence of crystal packing, since in solution the two rings are indistinguishable by ^1H and ^{13}C NMR spectroscopy.

(11) Full crystallographic details are available as Supporting Information.



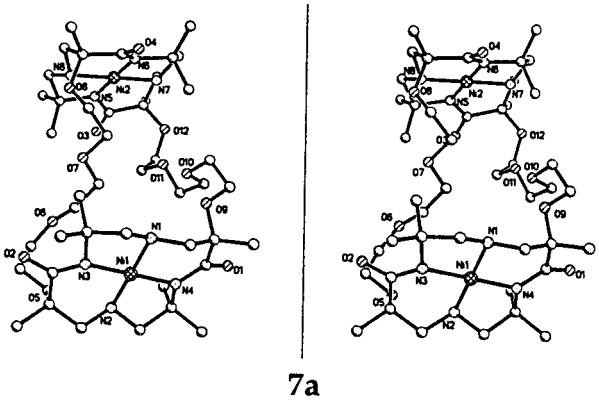
4b **5a**

Figure 1. Stereo Views of Compounds **4b** and **5a**.



6a **6b**

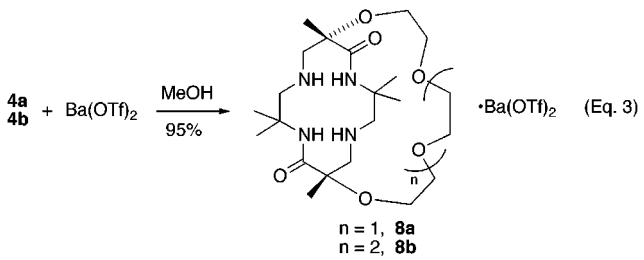
Figure 2. Stereo Views of Compounds **6a** and **6b**.



7a

Figure 3. Stereo View of Complex **7a**.

Both free ligands **4a**,**b** and **5a**,**b**, as well as nickel complexes **6a**,**b** and **7a**,**b**, contain polyether sites with the potential to complex "hard" metal ions. Treatment of triethylene glycol "basket" compound **4a** with a slight excess of barium triflate in methanol at reflux, followed by solvent removal, produced a white solid (eq 3). The



FAB mass spectrum had a strong peak at *m*/*z* 745, corresponding to [**4a**·Ba(OTf$_2$]-OTf (as is typical for barium complexes of this type[2]) with the calculated isotope distribution for the monobarium complex **8a**. The base peak in the mass spectrum was that of the free ligand **4a**. However, the infrared spectrum and both the ^{1}H and ^{13}C NMR spectra in d_4-methanol showed no changes from that of **4a**. Attempted dissolution in chloroform gave an insoluble white residue and a clear supernatant; the ^{1}H NMR spectra of both the supernatant (in $CDCl_3$) and the residue (in d_4-methanol) were identical to that of **4a**. These data imply that barium is only loosely coordinated to **4a** and dissociates readily in solvents in which the complex is soluble.

In contrast, treatment of the larger tetra(ethylene glycol) "basket" **4b** under the same conditions gave a complex with a strong (base) peak at *m*/*z* 789 in the FAB mass spectrum [**4b**·Ba(OTf)$_2$]-OTf, again with the calculated isotope distribution for the monobarium complex, along with a very small peak for free **4b**. Both the ^{1}H and ^{13}C NMR spectra showed small but discernible shifts from those of the free ligand,[2] and the amide carbonyl group stretching frequency shifted from 1668 to 1654 cm^{-1}, suggesting that the amides are also involved in coordination to barium.

Similarly, treatment of poly(ethylene glycol) linked biscyclams **5a** and **5b** with barium triflate produced bisbarium complexes **9a** and **9b**, respectively. For **9a**, the FAB mass spectrum had a moderately strong peak at *m*/*z* 1639 [**5a**·2Ba(OTf)$_2$]-OTf, a medium peak at *m*/*z* 1353 [**5a**·Ba(OTf)$_2$], and a base peak at *m*/*z* 1203 [**5a**·Ba(OTf)$_2$]-OTf in a ratio of 2:1:4 with *no* peak for free **5a**. Similarly the FAB mass spectrum of **9b** had a small peak at *m*/*z* 1721, [**5b**·2Ba(OTf)$_2$]-OTf, a base peak at *m*/*z* 1291, [**5b**·Ba(OTf)$_2$]-OTf, and no peak corresponding to free **5b**. The isotope distribution pattern for all of these barium-containing species corresponded to the calculated patterns. All resonances in both the ^{1}H and ^{13}C NMR spectra

of **9a** and **9b** were substantially broadened in comparison to the free ligands, and the amide carbonyl absorption in the infrared spectra shifted from 1670 cm^{-1} in the free ligands **5a** and **5b**, to 1650 cm^{-1} in **9a**, and 1634 cm^{-1} in **9b**. No absorption corresponding to free ligand was seen.

The ability of the polyether bridge or link *alone* to complex barium was probed by attempting to introduce barium into nickel complexes **6b** and **7b**. Treatment of these complexes with barium triflate produced mono-nickel−mono-barium complex **10b** and bis-nickel−bis-barium complex **11b**. The only visual change noted upon complexation was a slight color change. No change in CO stretching frequencies of amide carbonyl groups was noted for either complex, and only very minor changes in the ^1H and ^{13}C NMR spectra were noted. The main evidence for the complexation of barium came from FAB mass spectra. Mono-nickel−mono-barium complex **10b** had a very strong peak at *m*/*z* 845 [**6b**·$Ba(OTf)_2$]-OTf, while the bis-nickel−bis-barium complex **11b** had peaks at *m*/*z* 1838 [**7b**·2$Ba(OTf)_2$]-OTf and *m*/*z* 1403 [**7b**·$Ba(OTf)_2$]-OTf. Again, the isotope distribution patterns were consistent for complexes having one Ni and one Ba, and two Ni's and two Ba's, respectively.

Although there is strong spectroscopic evidence for the incorporation of barium into both the free mono- and bis-cyclams, as well as their nickel complexes, the exact site and mode of coordination of barium remains uncertain. Attempts to grow X-ray quality crystals of **8b**, **5a**, **10b**, and **11b** were unsuccessful due to problems with disorder and to twinning.

In the past decade, polyamine macrocycles having additional oxygen-based coordinating groups have become increasingly useful as ligands for Gd^{3+} to produce magnetic resonance imaging (MRI) contrast agents.[12] Since both the "basket" monocyclams **4a** and **4b**, and the linked bis-cyclams **5a** and **5b**, have features similar to some known MRI agents, their ability to complex Gd^{3+} was briefly examined. Treatment of both **4a** and **4b** with a slight excess of $Gd(NO_3)_3$ produced complexes **12a**,**b** which had infrared spectra lacking free amide carbonyl bands at ≈1670 cm^{-1}, these being replaced by bands at ≈1635 cm^{-1} (for **4a** and **4b**) indicative of coordinated amides. For both complexes, the base peaks in the FAB mass spectrum corresponded to that of the free ligand; the peak for [**4a**,**b**·$Gd(NO_3)_3$]-NO_3 was substantially smaller. Treatment of bis cyclam **5a** with 2 equiv of $Gd(NO_3)_3$ produced complex **13a** with an infrared spectrum with an amide carbonyl band at 1654 cm^{-1}. In contrast to **12a,b** whose base peak was that of the free ligand, **13a** had a small peak in the FAB mass spectrum at *m*/*z* 1541 corresponding to [**5a**·2$Gd(NO_3)_3$]-NO_3, a base peak at *m*/*z* 1198, corresponding to [**5a**·$Gd(NO_3)_3$]-NO_3, and a very small peak due to uncomplexed **5a**. Attempts to grow X-ray quality crystals of **13a** instead produced crystals of the free ligand, suggesting that gadolinium is only weakly coordinated. Future efforts will focus on the synthesis of more highly functionalized versions of the ligands reported above, with the goal of producing more stable Gd^{3+} complexes.

Experimental Section

General Procedures. All ^1H NMR spectra (300 MHz for ^1H NMR and 75 MHz, for ^{13}C NMR) were recorded in $CDCl_3$ unless otherwise stated. Pentacarbonyl[(methyl)-{(tetramethylammonio)oxy}carbene]chromium(0)[13] was prepared by literature methods. The tri- and tetra(ethylene glycol)s were dried over P_2O_5 and distilled under reduced pressure. THF was distilled from sodium−benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; MeOH was stored over 3 Å sieves prior to use. Column chromatography was performed with ICN 32−63 nm, 60 Å silica gel. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ.

4,4-Dimethyl-4,5-dihydro-1*H*-imidazole. Into a flame-dried, 100 mL round-bottom flask were placed 11.25 g (127.6 mmol) of 1,2-diamino-2-methylpropane and 14.7 g (127.6 mmol) of *N*,*N*-dimethylformamide dimethylacetal. This mixture was placed under Ar and heated to 60 °C overnight. The solution was cooled to room temperature and distilled under vacuum (0.1 mmHg). The fraction boiling at 40 °C was collected to yield 10.1 g (102.9 mmol, 81%) of 4,4-dimethyl-4,5-dihydro-1*H*-imidazole as a clear oil. ^1H NMR δ 6.79 (s, 1H); 4.48 (bs, 1H); 3.32 (s, 2H); 1.29 (s, 6H).

4,4-Dimethyl-4,5-dihydroimidazole-1-carboxylic Acid Benzyl Ester. Into a flame-dried, 500 mL round-bottom flask was placed 10.1 g (102.9 mmol) of 4,4-dimethyl-4,5-dihydro-1*H*-imidazole, along with 52 g (574.9 mmol) triethylamine and 250 mL CH_2Cl_2. This was placed under Ar and cooled to 0 °C. Benzyl chloroformate, (20.3 g, 119.1 mmol) was slowly added over 15 min. The solution was stirred at 0 °C for 30 min and warmed to room-temperature overnight. The solution was washed with sat. $NaHCO_{3\ (aq)}$ and water. The organic layer was separated and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting yellowish oil was distilled under vacuum (0.01 mmHg) at 105 °C to give 16.8 g (72.4 mmol, 70%) of 4,4-dimethyl-4,5-dihydroimidazole-1-carboxylic acid benzyl ester as a clear oil. The pressure at which the product is distilled is critical. The temperature cannot exceed 120 °C or the yield will be decreased significantly. ^1H NMR δ 7.42 (m, 5H); 5.26 (s, 2H); 3.47 (s, 2H); 1.34 (s, 6H).

Bis-carbene Complex 2a. Into a flame-dried, 250 mL round-bottom flask were placed 3.8 g (12.6 mmol) of **1** and 63 mL of dry CH_2Cl_2. This solution was cooled to −40 °C, and 1.42 mL (11.5 mmol) of pivaloyl chloride was added. The mixture was stirred at −40 °C for 20 min. Then, 0.67 mL (5.0 mmol) of dry tri(ethylene glycol) was added. The mixture was allowed to slowly warm to room-temperature overnight. The reaction mixture was filtered and washed once with 5% $NaHCO_{3\ (aq)}$ and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum, adsorbing the product onto silica gel. The mixture was purified by column chromatography (silica gel) using 8:1 hexane:ethyl acetate until the excess pivalic acid had eluted and then with 2:1 hexane:ethyl acetate to collect 1.995 g (3.4 mmol, 68%) of product as a yellow oil. ^1H NMR δ 5.01 (bs, 4H); 4.04 (bs, 4H); 3.76 (bs, 4H); 2.97 (bs, 6H); ^{13}C NMR δ 360.0, 223.1, 216.6, 71.0, 70.7, 69.1, 27.0; IR (thin film) ν 2064, 1899 cm^{-1}; HRMS FAB (M^+) $C_{20}H_{18}O_{14}Cr_2$ Calcd 585.9507. Found 585.9510.

Bis-carbene Complex 2b. Into a flame-dried, 250 mL round-bottom flask were placed 4.0 g (12.9 mmol) of **1** and 120 mL of dry CH_2Cl_2. This solution was cooled to −40 °C and 1.6 mL (12.9 mmol) of pivaloyl chloride was added. This solution was left to stir at −40 °C for 1 h. Then, 0.89 mL (5.16 mmol) of dry tetra(ethylene)glycol was added. This mixture was allowed to slowly warm to room temperature over 24 h. The solution was filtered and the solvent removed under vacuum, adsorbing the product onto silica gel. Purification was accomplished using column chromatography (silica gel) and eluting with 4:1 hexane:ether until the excess pivalic acid had eluted and then with ether to collect 2.84 g (4.5 mmol, 87%) product as a yellow oil. ^1H NMR δ 5.04 (bs, 4H); 4.05 (m, 4H); 3.74 (m, 8H); 2.99 (s, 6H); ^{13}C NMR δ 359.4, 223.2, 216.3, 71.2, 70.9, 69.4, 27; IR (thin film) ν 2063, 1916 cm^{-1}; HRMS FAB (M^+) $C_{22}H_{22}O_{15}Cr_2$ Calcd 629.9769. Found 629.9767.

Bis-azapenam 3a. Into an oven dried 125 mL Ace pressure tube were placed 1.0 g (1.7 mmol) of bis-carbene complex **2a**, 57 mL of CH_2Cl_2, and 0.76 g (3.3 mmol) of 4,4′-dimethyl-4,5-dihydroimidazole-1-carboxylic acid benzyl ester. This mixture

(12) For a recent review, see: Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293.

(13) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445.

was freeze−pump−thaw degassed three times and flushed with CO (the pressure tube was filled with 80 psi of CO and slowly released) three times. The pressure tube was filled with 80 psi CO and irradiated (4 × 500 W halogen lamps) at 55 °C. After 7 h, the reaction was removed from the 55 °C bath and irradiated at room temperature (450 W Conrad-Hanovia 7825, Pyrex well) for 2 days. The solvent was removed under vacuum, and methanol was added to precipitate the $Cr(CO)_6$. This was removed by filtration, and the methanol was removed under vacuum. The residue was dissolved in 1:1 hexane:ethyl acetate and placed into sunlight to oxidize any residual chromium complexes (usually 1 day), the mixture was filtered, and the solvent was removed under vacuum. Purification was accomplished using column chromatography (silica gel) eluting with 3:1 hexane:ethyl acetate until the unreacted imidazoline was off and then with ethyl acetate to obtain 0.916 g (1.3 mmol, 74%) as a clear oil.

Cbz-protected **3a** (0.866 g, 1.2 mmol), 500 mg of 10% Pd/C, 60 mL of dry methanol, and 60 drops of triethylamine were added to an oven dried 125 mL Ace pressure tube. This was pressured with 80 psi H_2 and stirred at room temperature for 2 h. The mixture was filtered and the solvent removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed one time with 5% $NaHCO_3$ (aq). The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum to yield 0.545 g (1.2 mmol, 100%) of free azapenam **3a** as a clear oil. ^{1}H NMR δ 4.75 (s, 2H); 3.79−3.84 (m, 4H); 3.62−3.75 (m, 8H); 3.05 (d, J = 11.1 Hz, 2H); 2.65 (d, J = 11.4 Hz, 2H); 2.35 (bs, 2H); 1.54 (s, 6H); 1.30 (s, 6H); 1.08 (s, 6H); ^{13}C NMR δ 175.5, 89.5, 77.9, 70.4, 65.3, 61.9, 60.8, 24.8, 21.6, 14.7; IR (thin film) ν 1747 cm^{-1}; HRMS FAB (M + 1) $C_{22}H_{39}N_4O_6$ Calcd 455.2870. Found 455.2864.

Bis-azapenam 3b. Using a procedure similar to that of **3a**, 1.3 g (2.1 mmol) of bis-carbene complex **2b**, 0.94 g (4.1 mmol) of 4,4′-dimethyl-4,5-dihydroimidazole-1-carboxylic acid benzyl ester, and 70 mL of CH_2Cl_2 were irradiated (4 × 500 W halogen lamps) at 55 °C for 5 h and then at room temperature (450 W Conrad-Hanovia 7825, Pyrex well) for 2 days, followed by isolation as with **3a** to give 1.4 g (1.8 mmol, 83%) of Cbz-protected azapenam **3b**. The Cbz group was removed under standard conditions using 1.1 g (1.4 mmol) of azapenam, 560 mg of 10% Pd/C, 70 mL of methanol, and 2 mL of triethylamine to yield 1.4 g (1.3 mmol, 91%) of free azapenam **3b** as a clear oil. ^{1}H NMR δ 4.82 (s, 2H); 3.88 (m, 2H); 3.70−3.81 (m, 14H); 3.10 (d, J = 11.4 Hz, 2H); 2.66 (d, J = 11.1 Hz, 2H); 2.38 (bs, 2H); 1.60 (s, 6H); 1.36 (s, 6H); 1.14 (s, 6H); ^{13}C NMR δ 175.5, 170.8, 89.5, 77.8, 70.5, 70.4, 70.3, 69.0, 65.2, 63.5, 61.9, 60.8, 24.9, 21.7, 20.9, 14.8. IR (thin film) ν 1745 cm^{-1}; HRMS FAB (M + 1) $C_{24}H_{43}N_4O_7$ Calcd 499.3132. Found 499.3121.

Dioxocyclam 4a, 5a. Into a 250 mL round-bottom flask were placed 0.496 g (1.09 mmol) of azapenam **3a**, 32 mg (0.14 mmol) of racemic camphor sulfonic acid, and 110 mL of dry CH_2Cl_2. This was allowed to stir at room temperature for 3 days. The solution was then washed with 5% $NaHCO_{3\,(aq)}$, and the aqueous layer was extracted three times with CH_2Cl_2. The solution was dried over Na_2SO_4 and the solvent removed under vacuum. The residue was dissolved in 55 mL of CH_2Cl_2 and 55 mL of methanol. To this were added a small crystal of bromocresol green and 151 mg (2.4 mmol) of $NaCNBH_3$. The mixture was cooled to 0 °C, and sat. HCl/MeOH was added until a yellow-green color persisted (pH ∼ 6). The reaction was warmed to room temperature and stirred at this temperature overnight, adding additional HCl/MeOH as needed to keep the pH ∼ 6. Saturated HCl/MeOH was added to give a pH = 1. Then, 10% $NaOH_{(aq)}$ was added to give a pH = 10. The aqueous layer was extracted three times with CH_2Cl_2 and dried over Na_2SO_4, and the solvent was removed under vacuum. Purification was accomplished using column chromatography (silica gel) eluting with 95:5 CH_2Cl_2:MeOH to yield 0.149 g (0.33 mmol, 30%) of basket cyclam **4a** as a white solid, and then 10:1 CH_2Cl_2:MeOH to yield 0.123 g (0.13 mmol, 25%) of bis-cyclam **5a** as a white solid.

Dioxocyclam 4a. ^{1}H NMR (d_6-acetone) δ 7.57 (s, 2H); 3.45−3.72 (m, 12H); 3.03 (d, J = 11.3 Hz, 2H); 2.80, (d, J = 11.7 Hz, 2H); 2.65, (d, J = 11.8 Hz, 2H); 2.11, (d, J = 11.3 Hz, 2H); 1.97−2.02 (m, 2H); 1.32, (s, 6H); 1.20, (s, 6H); 1.14 (s, 6H); ^{13}C NMR (d_6-acetone) δ 172.7, 80.3, 71.6, 71.3, 63.6, 58.2, 57.1, 53.5, 26.7, 25.0, 20.1; IR (thin film) ν 1667 cm^{-1}. Anal. Calcd C: 57.62, H: 9.23, N: 12.22. Found: C: 57.44, H: 9.10, N: 12.27.

Dioxocyclam 5a. ^{1}H NMR δ 7.07 (s, 4H); 3.45−3.72 (m, 24H); 2.88 (d, J = 12.0 Hz, 4H); 2.62 (d, J = 12.3 Hz, 4H); 2.12 (d, J = 11.1 Hz, 4H); 1.42 (s, 12H); 1.32 (s, 12H); 1.25 (s, 12H); ^{13}C NMR δ 171.9, 80.1, 70.8, 70.7, 62.7, 56.9, 56.4, 52.9, 26.8, 25.2, 19.3; IR (thin film) ν 1670 cm^{-1}. This solid was recrystallized from MeOH:H_2O to give X-ray quality crystals. mp 134 °C.

Dioxocyclam 4b, 5b. The dimerization and reduction of **3b** were accomplished using the general conditions for **4a**, **5a**. Using 0.64 g (1.3 mmol) of free azapenam **3b**, after the reduction and purification, 0.23 g (0.45 mmol, 35%) of **4b** as a white solid and 0.097 g (0.10 mmol, 15%) of **5b** as a white solid were obtained.

Dioxocyclam 4b. ^{1}H NMR δ 7.05 (s, 2H); 3.72−3.85 (m, 2H); 3.67−3.70 (m, 12H); 3.57−3.66 (m, 4H); 2.92 (d, J = 11.7 Hz, 2H); 2.57 (d, J = 11.7 Hz, 2H); 2.04 (d, J = 10.8 Hz, 2H); 1.43 (s, 6H); 1.33 (s, 6H); 1.29 (s, 6H); ^{13}C NMR δ 172.1, 80.2, 71.0, 70.6, 70.3, 63.0, 57.3, 56.5, 53.1, 27.2, 25.4, 19.4; IR (thin film) ν 1668 cm^{-1}; HRMS FAB (M + 1) $C_{24}H_{47}N_4O_7$ Calcd 503.3445. Found: 503.3434. This solid was recrystallized from MeOH:H_2O to give X-ray quality crystals.

Dioxocyclam 5b. ^{1}H NMR δ 6.96 (s, 4H); 3.59−3.71 (m, 28H); 3.45−3.54 (m, 8H); 2.84 (d, J = 12.0 Hz, 4H); 2.53 (d, J = 12.3 Hz, 4H); 2.07 (d, J = 10.8 Hz, 4H); 1.38 (s, 12H); 1.29 (s, 12H); 1.22 (s, 12H); ^{13}C NMR δ 172.0, 80.4, 71.0, 70.8, 70.7, 63.0, 57.3, 56.4, 53.1, 27.0, 25.4, 19.3; IR (thin film) ν 1668 cm^{-1}; HRMS FAB (M + 1) $C_{48}H_{93}N_8O_{14}$ Calcd 1005.6811. Found: 1005.6781.

Nickel Complex 6a. Into a flame-dried, 100 mL round-bottom flask under Ar were placed 114 mg (0.249 mmol) of basket cyclam **4a**, 544 mg (1.2 mmol) of $NiBr_2$·3DMF, one drop of triethylamine, and 30 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled to room temperature and filtered through Celite, and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed once with water. The aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification was accomplished using column chromatography (silica gel) eluting with 8:1 ethyl acetate: methanol to yield 71 mg (0.138 mmol, 55%) of **6a** as a pink solid: ^{1}H NMR δ 4.18−4.11 (m, 2H); 3.99−3.75 (m, 8H); 3.54 (d, J = 10.4 Hz, 2H); 3.22 (t, J = 12.6 Hz, 2H); 2.78 (dd, J = 10.8 Hz, 13.8 Hz, 2H); 2.52 (t, J = 11.6 Hz, 2H); 2.13 (dd J = 11.1, 1.6 Hz, 2H); 1.84, (dd, J = 10.5, 2.7 Hz, 2H); 1.40 (s, 6H); 1.29, (s, 6H); 1.20, (s, 6H); ^{13}C NMR δ 172.7, 70.3, 69.5, 65.6, 62.1, 58.5, 57.1, 25.1, 22.7, 20.1; IR (thin film) ν 1550 cm^{-1}. This solid was recrystallized from CH_2Cl_2:MeOH to give X-ray quality crystals.

Nickel Complex 7a. Into a flame-dried, 50 mL round-bottom flask under Ar were placed 571 mg (2.9 mmol) of $AgBF_4$, 634 mg (2.9 mmol) of $NiBr_2$, and 29 mL of THF. This solution was heated to reflux for 1 h. The resulting pale green solution was filtered hot through Celite into an oven-dried, 125 mL Ace pressure tube containing 265 mg (0.29 mmol) of bis-cyclam **5a**, 0.15 mL of triethylamine, and 10 mL of THF. The tube was sealed and heated to 80 °C for 2 days. The resulting pink solution was cooled to room temperature, and 20 mL of 5% $NaHCO_{3\,(aq)}$ was added. This solution was extracted with 3 × 20 mL of CH_2Cl_2 and dried over Na_2SO_4, and the solvent was removed under vacuum to yield 180 mg (0.175 mmol, 60%) of **7a** as a pink solid. mp > 200 °C; ^{1}H NMR δ 3.65−3.87 (m, 28H); 3.06 (t, J = 12.6 Hz,6H); 2.75 (dd, J = 10.8, 13.5 Hz. 4H); 2.50 (t, J = 11.7 Hz, 4H); 2.13, (d, J = 9.9 Hz, 4H); 1.84 (d, J = 10.5 Hz, 4H); 1.35 (s, 12H); 1.26 (s, 12H); 1.17 (s, 12H); ^{13}C NMR δ 172.5, 76.8, 70.9, 70.5, 65.3, 62.8, 58.4, 56.5, 24.8, 22.6, 20.3; IR (thin film) ν 1574 cm^{-1}. This solid was recrystallized from $CHCl_3$:pentane to give X-ray quality crystals.

Nickel Complex 6b. Nickel complex **6b** was synthesized under the conditions for **7a** using 0.209 g (1.06 mmol) of $AgBF_4$,

0.232 g (1.06 mmol) of $NiBr_2$, and 10 mL of THF. This was filtered hot through Celite into an oven-dried, 40 mL Ace pressure tube containing 0.133 g (0.26 mmol) of cyclam **4b**, 0.15 mL of triethylamine, and 5 mL of THF. This mixture was heated to 80 °C for 2 days and isolated as for **7a**, to yield 0.145 g (0.26 mmol, 100%) of **6b** as a pink solid. mp > 200 °C; ^{1}H NMR δ 3.55−4.06 (m, 16H); 3.11 (t, J = 12.9 Hz, 2H); 2.69 (t, J = 11.7 Hz, 4H); 2.21 (dd, J = 2.4, 12.0 Hz, 2H); 1.85 (dd, J = 3.3, 10.5 Hz, 2H); 1.40 (s, 6H); 1.35 (s, 6H); 1.24 (s, 6H); ^{13}C NMR δ 172.8, 71.1, 70.9, 70.5, 66.0, 63.2, 58.7, 57.1, 24.9, 22.6, 20.3; IR (thin film) ν 1574 cm^{-1}. This solid was recrystallized from $CHCl_3$:hexane to give X-ray quality crystals.

Nickel Complex 7b. Nickel complex **7b** was synthesized under the conditions for **7a** using 0.209 g (1.1 mmol) of $AgBF_4$, 0.127 g (0.58 mmol) of $NiBr_2$, and 10 mL of THF. This was filtered through Celite into an oven-dried, 40 mL Ace pressure tube containing 53 mg (0.05 mmol) of bis-cyclam **5b** and 5 mL of THF and heated to 80 °C overnight. The product was isolated as for **7a** to yield 45 mg (0.04 mmol, 80%) of bis-nickel complex **7b** as a pink solid. mp > 200 °C; ^{1}H NMR δ 3.75−4.01 (m, 28H); 3.17 (t, J = 12.9 Hz, 4H); 2.82 (dd, J = 10.5, 13.2 Hz, 4H); 2.61 (t, J = 11.7 Hz, 4H); 2.23 (dd, J = 1.8, 11.1 Hz, 4H); 1.91 (dd, J = 3.3, 10.5 Hz, 4H); 1.43 (s, 12H); 1.35 (s, 12H); 1.26 (s, 12H); ^{13}C NMR δ 172.9, 76.9, 71.3, 70.9, 70.5, 65.5, 63.2, 58.6, 56.8, 24.8, 22.7, 20.6; IR (thin film) ν 1579 cm^{-1}; HRMS FAB (M + 1) $C_{48}H_{89}N_8O_{14}Ni_2$ Calcd 1117.5205. Found: 1117. 5205.

Barium Complex 8a. Into a 100 mL round-bottom flask were placed 0.17 g (0.36 mmol) of basket cyclam **4a**, 0.18 g (0.41 mmol) of $Ba(OTf)_2$ and 37 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.84−5.56 (m, 12H); 3.08 (d, J = 11.7 Hz, 2H); 2.92 (d, J = 12.3 Hz, 2H); 2.86 (d, J = 12 Hz, 2H); 2.37 (d, J = 12.0 Hz, 2H); 1.44 (s, 6H); 1.34, (s, 6H); 1.31, (s, 6H); ^{13}C NMR (CD_3OD) δ 174.8, 81.1, 71.6, 71.4, 63.9, 58.3, 57.3, 54.7, 26.8, 24.7, 19.8; IR (thin film) ν 1668 cm^{-1}; MS FAB ((**4a**·$Ba(OTf)_2$)-OTf) $C_{23}H_{42}BaF_3N_4O_9S$ Calcd 745.17, Found 745.32.

Barium Complex 8b. Into a 50 mL round-bottom flask were placed 60 mg (0.12 mmol) of basket cyclam **4b**, 72 mg (0.17 mmol) of $Ba(OTf)_2$, and 17 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.55−3.76 (m, 16H); 3.35 (bd, 2H); 2.79 (d, J = 11.7 Hz, 1H); 2.67 (d, J = 12.0 Hz, 1H); 2.19 (bs, 2H); 1.36 (s, 6H); 1.31 (s, 6H); 1.29 (s, 6H); ^{13}C NMR (DMSO-d^6) δ 171.5, 120.7 (q, J = 319 Hz); 79.0, 72.4, 69.9, 69.4, 62.9, 56.2, 56.1, 55.5, 52.1, 26.4, 24.9, 18.8; IR (thin film) ν 1654 cm^{-1}; MS FAB (**4b**·($Ba(OTf)_2$)-OTf)) $C_{25}H_{46}BaF_3N_4O_{10}S$ Calcd 789.19, Found 789.37.

Barium Complex 9a. Into a 50 mL round-bottom flask were placed 0.100 g (0.11 mmol) of bis-cyclam **5a**, 0.500 g (1.14 mmol) of $Ba(OTf)_2$, and 15 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.73−3.77 (m, 32H); 2.9 (bs, 10H); 1.33−1.50 (bm, 36H); ^{13}C NMR (DMSO-d_6, CD_3OD) δ 173.5, 121.5 (q, J = 317 Hz); 80.7, 71.0, 70.8, 63.4, 57.0, 56.8. 53.5, 27.1, 25.4, 19.4. IR (thin film) ν 1650 cm^{-1}, MS FAB (**5a**·(2($Ba(OTf)_2$)-(OTf)) $C_{47}H_{84}Ba_2F_9N_8O_{21}S_3$ calcd 1639.29, found 1639.30 and (**5a**·($Ba(OTf)_2$)) $C_{46}H_{84}BaF_6N_8O_{18}S_2$ calcd 1352.43, found 1353.28, and (**5a**·($Ba(OTf)_2$)-(OTf)) $C_{45}H_{84}BaF_3N_8O_{15}S$ Calcd 1203.48, Found 1203.37.

Barium Complex 9b. Into a 100 mL round-bottom flask were placed 0.308 g (0.31 mmol) of bis-cyclam **5b**, 1.1 g (2.5 mmol) of $Ba(OTf)_2$, and 31 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.68−3.82 (m, 36H); 2.91−2.94 (bm, 10H); 2.53 (bs, 4H); 1.37−1.42 (m, 36H); ^{13}C NMR (DMSO-d_6); 171.6, 120.8, 79.4, 69.9, 69.5, 62.8, 56.4, 55.7, 52.3, 48.8, 26.5, 25.0, 19.1; IR (thin film) ν 1634 cm^{-1}; MS FAB (**5b**·(2($Ba(OTf)_2$)-(OTf))) $C_{51}H_{92}Ba_2F_9N_8O_{23}S_3$ Calcd 1727.3, Found 1727.1 (**5b**·($Ba(OTf)_2$-(OTf) $C_{49}H_{92}BaF_3N_8O_{17}S$ Calcd 1291.5, Found 1291.5

Barium Complex 10b. Into a 50 mL round-bottom flask were placed 0.120 g (0.21 mmol) of nickel cyclam **6b**, 0.187 g (0.43 mmol) of $Ba(OTf)_2$, and 21 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.94−4.06 (m, 4H); 3.67−3.87 (m, 12H); 3.54−3.61 (m, 2H); 3.14 (t, J = 12.9 Hz, 2H); 2.78 (dd, J = 10.5, 13.8 Hz, 2H); 2.64 (t, J = 11.7 Hz, 2H); 2.26 (dd J = 2.4, 12.3 Hz, 2H); 1.98 (dd, J = 3.9, 11.1 Hz, 2H); 1.39 (s, 6H); 1.37 (s, 6H); 1.20 (s, 6H); ^{13}C NMR (CD_3OD) δ 175.4, 120.3, 78.4, 72.4, 72.0, 71.6, 66.9, 64.3, 60.3, 57.5, 25.3, 23.2, 20.5; IR (thin film) ν 1573 cm^{-1}; MS FAB (**6b**·($Ba(OTf)_2$)-(OTf) $C_{25}H_{44}BaF_3N_4NiO_{10}S$ Calcd 845.11, Found 845.31.

Barium Complex 11b. Into a 40 mL Ace pressure tube were placed 45 mg (0.04 mmol) of bis-nickel cyclam **7b**, 60 mg (0.14 mmol) of $Ba(OTf)_2$, and 10 mL of MeOH. The tube was sealed and heated to 70 °C overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield a white solid. ^{1}H NMR (CD_3OD) δ 3.71−4.02 (m, 32H); 3.15 (t, J = 12.0 Hz, 4H); 2.89 (d, J = 11.1 Hz, 2H); 2.84 (d, J = 10.2 Hz, 2H); 2.66 (t, J = 11.7 Hz, 4H); 2.33 (dd, J = 2.1, 12.3 Hz, 4H); 2.06, (dd, J = 3.0, 11.1 Hz, 4H); 1.40, (s, 12H); 1.38 (s, 12H); 1.22 (s, 12H); ^{13}C NMR δ (CD_3OD) 175.7, 121.9 9 (q, J_{C-F} = 316 Hz); 79.1, 72.3, 71.9, 71.8, 66.6, 64.1, 60.5, 57.0, 25.2, 23.3, 20.8; IR (thin film) ν 1556 cm^{-1}; MS FAB (**7b**·(2($Ba(OTf)_2$)-(OTf) $C_{51}H_{88}Ba_2N_8F_9Ni_2O_{23}S_3$ Calcd 1839.18, Found 1838.61 and (**7b**·($Ba(OTf)_2$)-(OTf)) $C_{49}H_{88}BaF_3Ni_2O_{17}S$ Calcd 1403.37, Found 1403.36.

Gadolinium Complex 12a. Into a 100 mL round-bottom flask were placed 0.149 g (0.33 mmol) of the basket-cyclam **4a**, 0.314 g (0.70 mmol) of $Gd(NO_3)_3$·$6H_2O$, and 30 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under vacuum to give **12a** as a white solid. IR (thin film) ν 1635 cm^{-1}. MS FAB (**4a**·($Gd(NO_3)_3$)-(NO_3)) $C_{22}H_{42}GdN_6O_{12}$ Calcd 740.21, Found 740.36.

Gadolinium Complex 12b. Into a 100 mL round-bottom flask were placed 0.060 g (0.12 mmol) of the basket-cyclam **4b**, 0.100 g (0.22 mmol) of $Gd(NO_3)_3$·$6H_2O$, and 30 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled, and the solvent was removed under vacuum to give **12b** as a white solid. IR (thin film) ν 1635 cm^{-1}. MS FAB (**4b**·($Gd(NO_3)_3$)-(NO_3)) $C_{24}H_{46}GdN_6O_{13}$ Calcd 784.24, Found 784.37.

Gadolinium Complex 13a. Into a 10 mL round-bottom flask were placed 0.036 g (0.04 mmol) of the bis-cyclam **5a**, 0.037 g (0.08 mmol) of $Gd(NO_3)_3$·$6H_2O$ and 5 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled to room temperature, and the solvent was removed under vacuum to yield **13a** as a white solid. IR (thin film) ν 1654 cm^{-1}. MS FAB (**5a**·(2($Gd(NO_3)_3$))-(NO_3)) $C_{44}H_{84}Gd_2N_{13}O_{27}$ calcd 1542.41, found 1541.46 and (**5a**·($Gd(NO_3)_3$)-(NO_3)) $C_{44}H_{84}GdN_{10}O_{18}$ Calcd 1198.52, Found 1198.42.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2a**,**b**, **3a**,**b**, **4a**,**b**, **5a**,**b**, **6a**,**b**, **7a**,**b**, **8a**,**b**, **9a**,**b**, **10b**, and **11b**. For compounds **4b**, **5a**, **6a**,**b**, and **7a**, ORTEP diagrams, crystal data and structure refinement parameters, atomic coordinates, bond lengths and bond angles, anisotropic displacement coefficients, and H-atom coordinates. Also, for compounds **8a**,**b**, **9a**,**b**, **10b**, **11b**, **12b**, and **13a**, theoretical isotope distribution and actual isotope distribution patterns from mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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