point is that only an AG chelate but no GA chelate is found, although the latter adduct has been reported in a dinucleotide study with d(GpA).[35] After the first reaction step of *cis*-Pt with GAG, the intermediate complex in which the platinum is bound to the 3'-guanine (see Scheme I) can react further with the 5'-guanine (about 70%; with a 45/65 ratio, 100%) or with the adenine (about 30%; with a 20/65 ratio, 100%). However, when *cis*-Pt is coordinated to the 5'-guanine after the first platination step, only *GAG* is ultimately formed. One has, however, to note[36] that—assuming a B-DNA like conformation for GAG—the proximity of the platinum atom, when monofunctionally bound to the 3'-guanine, to the adenine N7 is about 2 Å, roughly the usual Pt–N7 distance found in most Pt–nucleobase crystal structures. The platinum–adenine N7 distance is much larger when platinum is coordinated to the 5'-guanine. These geometrical considerations can nicely explain why only AG and no GA chelate is observed. Since the tetranucleotide d(GpAgGpA) adopts a B-DNA type structure in solution,[39] the assumption of a similar structure for GAG seems valid.

These findings agree well with results obtained from the earlier study in which *cis*-Pt adducts formed in DNA were identified,[6] as well as from a crystallographic study concerning *cis*-Pt-soaked $tRNA^{Phe}$ crystals.[36] In both cases, only AG and no GA chelation was observed. Apart from N7, N1 platination of adenine in modified nucleobases and dinucleotides has also been observed.[23,37] This binding mode is probably less interesting, since N1 sites of purines in double-stranded DNA are involved in Watson–Crick base pairing. In our study with a single-stranded trinucleotide offering the possibility of N1 binding, no indications for this chelation type were obtained.

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(36) Dewan, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 7239.
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(39) Rinkel, L. J., personal communication.

Concluding Remarks. Summarizing the results of this study, it can be concluded that after the reaction of *cis*-Pt with the trinucleotide d(GpApG), two main products can be identified in a ratio that appears to be unaffected by the reaction temperature. Also no temperature effect can be observed for the first binding step with one of both terminal guanines, simulated by the binding of [PtCl(dien)]Cl. Partial or complete hydrolysis of *cis*-Pt, leading to different aquated *cis*-Pt species also has no effect on the product ratio.

We can conclude that the GAG sequence used in this trinucleotide offers a good model system to study kinetic aspects of *cis*-Pt interactions with oligonucleotides in a search for a better insight into the formation of the adducts of *cis*-Pt with DNA. However, we cannot translate the results described above immediately to larger DNA fragments. For that reason, studies have been started with larger oligonucleotides (both single and double stranded) that contain this sequence.

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Registry No. *cis*-$PtCl_2(NH_3)_2$, 15663-27-1; *cis*-$Pt(NH_3)_2$[d(GpApG)-*N7*(*1*),*N7*(*3*)], 105121-41-3; *cis*-$Pt(NH_3)_2$[d(GpApG)-*N7*(*2*),*N7*(*3*)], 105121-42-4; [PtCl(dien)]Cl, 14215-58-8; *cis*-Pt(OH)$(H_2O)(NH_3)_2^+$, 54933-51-6; Pt(dien)[d(GpApG)-*N7*(*3*)], 105121-43-5; Pt(dien)[d(GpApG)-*N7*(*1*)], 105121-44-6.

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Synthesis and Characterization of Tetra-N-alkylated Cyclam Ligands That Contain a Functionalized Nitrogen Substituent[1]

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Eight monofunctionalized, tetra-N-alkylated cyclam ligands have been prepared by derivatization of the secondary amine in trimethylcyclam (1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane). Syntheses and properties of nickel(II) and/or copper(II) complexes of these ligands are given along with evidence for interconversion of diastereoisomers of the nickel and copper complexes of trimethylcyclam.

Introduction

There is an ever increasing number of applications for metal complexing agents that contain additional reactive functional groups. The presence of suitable functional groups can allow the binding of the complexing agent, or perhaps a complexed form, to biomolecules or to polymers and other solid supports. In the former case the ultimate application might be to bind a radioactive nuclide for either diagnostic or therapeutic purposes. In the latter case it might be to make a metal ion concentration device or to prepare a redox-active electrode coating. It may also be possible to prepare multinuclear metal complexes by coupling reactions involving these functional groups.

Our interest in this general area has been directed toward the synthesis of macrocyclic tetraamine ligands that have appended side chains containing functional groups. In principle, side chains can be attached at either carbon or nitrogen positions and they may be introduced before or after the cyclization reaction has been performed. The work described here deals with the synthesis of ligands **2**–**9** and their nickel and/or copper complexes.

Ligand **3**, its *N*,*N*-dimethyl analogue, and their Co(II), Ni(II), and Cu(II) complexes have been reported previously by Basak and Kaden.[2] Nickel, copper, and zinc complexes of **2** have been reported,[3] but preparative details and physical properties of the ligand have not. The syntheses of **2**–**9** utilize 1,4,8-trimethyl-

(1) Abstracted in part from: (a) Hodges, K. D. Ph.D. Thesis, University of Illinois, Urbana, 1978. (b) Freeman, G. M. Ph.D. Thesis, Georgia Institute of Technology, 1983. (c) Foster, K. A. Ph.D. Thesis, Georgia Institute of Technology, 1986.

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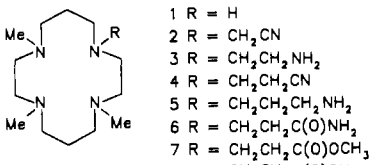

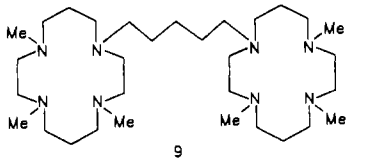

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1,4,8,11-tetraazacyclotetradecane[4] (trimethylcyclam, **1**) as starting material. Secondary, but significant, aspects of this work are the development of two moderate-scale syntheses of **1** and the observation of interconversion of diastereomeric complexes of **1** with Ni(II) and Cu(II).

Experimental Section

Analytical data for new complexes are contained in Table I (supplementary material). Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Electronic absorption spectral data are contained in Table II. Spectra were obtained by using Varian DMS-90 (350-900 nm) or Cary 14 (350-700 nm) spectrophotometers. Solution spectra were obtained by using 1-cm quartz cells; solid-state spectra were obtained by the diffuse transmittance method with mineral oil mulls on filter paper. ^{1}H NMR spectra were obtained on $CDCl_3$ solutions at 300 MHz (Bruker 300W FT spectrometer) with chemical shifts (δ) given relative to internal Me_4Si unless otherwise indicated. Mass spectra were obtained with a Varian 112S spectrometer by EI and/or CI (isobutane) methods as appropriate.

1-(2-Aminoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (**3**), $[Ni(\mathbf{3})](ClO_4)_2$, and $[Cu(\mathbf{3})](ClO_4)_2$ were prepared by procedures similar to those used by Basak and Kaden.[1a,2] *Caution!* These perchlorate salts and those prepared in this study represent a potential explosive hazard and should be treated accordingly.

1,4,8-Trimethyl-1,4,8,11-tetraazacyclotetradecane (1). Method 1. An oven-dried, 1-L, three-neck, round-bottom flask fitted with a nitrogen inlet, rubber septum, addition funnel, and magnetic stirring bar was charged with 75.0 g (0.154 mol) of $[Ni(1,4\text{-}Me_2cyclam)](ClO_4)_2$ (C_2 isomer)[5] and 750 mL of dry Me_2SO. The addition funnel was charged with 64.5 mL of 2.4 M *n*-BuLi in hexane (0.154 mol), which was added dropwise over 2 h to the vigorously stirred solution. The resulting intensely blue solution was stirred for 0.5 h and then treated with 15 mL (33 g, 0.23 mol) of methyl iodide over 0.5 h. After being stirred for 0.5 h, the solution was evacuated to remove excess methyl iodide, hexane, and butane. The brown solution was then poured into 1.2 L of well-stirred 2-propanol to precipitate the complex. The orange-brown solid was collected, washed with ethanol and ether, and dried in vacuo; 75 g of a mixture of perchlorate and iodide salts was obtained.

A 60-g portion of the complex was decomposed by heating it with 30 g of NaCN (0.61 mol) in 300 mL of H_2O at 80 °C for 14 h. After the reaction mixture was cooled in an ice bath, any solids that formed were removed by filtration and the filtrate was extracted with five 75-mL portions of $CHCl_3$. After being dried with Na_2SO_4, the extract was rotary evaporated to a yellow oil, which was fractionally distilled in vacuo. The portion boiling at 85–87 °C (0.06 mm Hg) (15.5 g) was collected. Yield: 52% based on starting dimethyl complex. The purity of the product was determined by GLC to be greater than 99% when the distillation was carefully done.

Pure $[Ni(\mathbf{1})](ClO_4)_2$ could be obtained from the crude reaction product by fractional crystallization from hot H_2O with addition of $HClO_4$. Usually two or three recrystallizations were necessary to eliminate starting material and tetraalkylated complex as well as all iodide from the product.

Method 2. 1-Benzyl-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane[6] (6.00 g, 18.0 mmol) and 0.4 g of palladium catalyst (10% Pd on carbon) were added to 200 mL of glacial acetic acid. This mixture was shaken under hydrogen (50 psi) on a Parr apparatus at ca. 65 °C until H_2 uptake ceased. The catalyst was removed by gravity filtration and the filtrate evaporated on a rotary evaporator. The oil was dissolved in 25 mL of water and the pH adjusted to 9–10 by adding portions of 25% w/w aqueous NaOH. This solution was extracted with three 25-mL portions of chloroform. The chloroform extracts were combined, dried over Na_2SO_4, and evaporated to a light yellow oil. Yield: 4.2 g or 89%. ^{1}H NMR: 2.69 (t, J = 5.5 Hz, 2 H), 2.63 (t, J = 5.5 Hz, 2 H), 2.50–2.35 (m, 10 H), 2.30 (t, J = 6 Hz, 2 H), 2.21, 2.19, and 2.16 (three s, 9 H), 1.7 (q, J = 6 Hz, 2 H), 1.59 (q, J = 6 Hz, 2 H). Mass spectrum: m/e for parent ion 242, calcd 242. IR: $\nu_{N\text{-}H}$ 3290 cm^{-1} (neat). The elemental analysis and the presence of an O–H absorption in the infrared spectrum of the material after exposure to air are consistent with its formulation as a monohydrate.

Table II. Electronic Absorption Spectral Data

compd	color	λ/nm (ϵ/M^{-1} cm^{-1})
$[Ni(\mathbf{3})](ClO_4)_2$[a]	blue	765 (8), 594 (54), 453 (20, sh), 378 (136)[b] 740 (4), 592 (14), 450 (14, sh), 377 (120)[c]
$[Ni(\mathbf{3+H})](ClO_4)_3$	pink	525[d]
$[Ni(\mathbf{4})](ClO_4)_2$	red	532 (168)[c]
$[Ni(\mathbf{5})](ClO_4)_2$	green	780 (8), 640 (62), 470 (sh), 395 (156)[b] 780 (6), 635 (63), 465 (sh), 393 (168)[c]
$[Ni(\mathbf{5+H})](ClO_4)_3$	pink	524 (200)[c]
$[Ni(\mathbf{6})](ClO_4)_2$	green	629 (52), 460 (sh), 388 (141)[b]
$[Ni(tmc)](ClO_4)_2$[e]	red	519 (184);[c] 520[d]
$[Cu(\mathbf{3})](ClO_4)_2$[a]	blue	684 (205)[b]
$[Cu(\mathbf{3+H})](ClO_4)_3$	red-violet	570[d]
$[Cu(\mathbf{4})](ClO_4)_2$	violet	590 (200)[c]
$[Cu(\mathbf{5})](ClO_4)_2$	aqua	671 (246)[b]
$[Cu(\mathbf{5+H})](ClO_4)_3$	red-violet	566 (255)[b]
$[Cu(\mathbf{6})](ClO_4)_2$	blue	667 (256)[b]
$[Cu(\mathbf{6\text{-}H})]^+$		699 (238)[f]
$[Cu(\mathbf{7})](ClO_4)_2$	blue	625 (264);[b] 625 (271)[c]
$[Cu(\mathbf{8})](ClO_4)_2$	blue	600[d]
$[Cu(\mathbf{8\text{-}H})]^+$		691 (228)[f]
$[Cu(tmc)](ClO_4)_2$[g]	blue	640 (257);[b] 583 (214);[c] 580[d]

[a] Kaden[2] reports similar aqueous solution data. [b] H_2O. [c] CH_3NO_2. [d] Solid state. [e] Data from ref 8. [f] H_2O, pH ≥11; complex not isolated. [g] Data for water from ref 19; data for CH_3NO_2 and solid state from ref 8.

Separation of Diastereoisomers of $[Cu(\mathbf{1})](ClO_4)_2$. An aqueous solution of **1**·H_2O (0.20 g, 0.77 mmol in 10 mL) was treated with an aqueous solution of $CuCl_2 \cdot 6H_2O$ (0.18 g, 0.77 mmol in 5 mL) over 10 min. The solution was stirred at room temperature for 3 h and then gravity filtered. The filtrate was chromatographed on a Sephadex C-25 column (2 cm × 40 cm) using 0.25 M sodium perchlorate as eluent. Only a single band developed on the column, but it was collected as two approximately equal-volume fractions; fraction 1 was bluish purple whereas fraction 2 was more reddish purple. Fraction 1 was extracted with portions of nitromethane, and the combined extracts were evaporated to dryness. The solid residue was dissolved in 15–20 mL of water and the solution chromatographed on the Sephadex C-25 column using 0.25 M sodium perchlorate as eluent. The single band that developed was collected as three equal-volume fractions. The first two fractions were recombined and chromatographed a second time. The initial two-thirds of the eluant was collected and chromatographed a third time, with two-thirds being reserved for isolation of the complex. Fraction 2 was treated in a completely analogous manner as fraction 1 except that the last two fractions of each run (of the three collected) were combined for further chromatography. Evaporation of the sodium perchlorate solutions obtained after the final runs led to the crystallization of the diastereoisomers. These were collected, washed with 2-propanol, and dried in vacuo at room temperature. A deep purple complex designated as α-$[Cu(\mathbf{1})](ClO_4)_2$ (0.08 g or 21%) was obtained from fraction 1, and a maroon complex designated as β-$[Cu(\mathbf{1})](ClO_4)_2$ (0.06 g or 15%) was obtained from fraction 2.

1-(Cyanomethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (2).[7] Sodium bisulfite (1.03 g, 10 mmol) was dissolved in 2.5 mL of H_2O, and 0.75 mL of 37% formaldehyde was added. The solution,

(4) Wagner, F.; Barefield, E. K. *Inorg. Chem.* **1976**, *15*, 408.
(5) (a) Barefield, E. K.; Wagner, F.; Hodges, K. D. *Inorg. Chem.* **1976**, *15*, 1370. (b) The ca. 6:1 mixture of the C_2 and C_s diastereoisomers that is produced in the 24-h cyclization reaction can be used without a decrease in the yield of **1**.
(6) Barefield, E. K.; Freeman, G. M.; Van Derveer, D. G. *Inorg. Chem.* **1986**, *25*, 552.
(7) The procedure used here is essentially the same as that used by Moore and co-workers for protonation of other functionalized macrocyclic ligand complexes: Alcock, N. W.; Kingston, R. G.; Moore, P.; Pierpoint, C. *J. Chem. Soc., Dalton Trans.* **1984**, 1937.

heated briefly to boiling, was then cooled to room temperature, and 2.60 g (10 mmol) of $1 \cdot H_2O$ was added with good stirring. After 2 h a solution of 0.50 g (10 mmol) of NaCN in 1.3 mL of H_2O was added. The mixture was stirred well and left to stand for 15 h. A white solid formed, which was extracted with four 40-mL portions of $CHCl_3$. The extracts were dried with Na_2SO_4 and stripped to yield a white solid (mp 80.5–82 °C; EI mass spectrum m/e 281, calcd 281). Yield: 2.65 g; 88%, assuming that the material is a monohydrate. The presence of water was indicated by the infrared spectrum and by the ^1H NMR spectrum. ^1H NMR: 1.62 (m, 4 H), 1.69 (b s, 2 H), 2.18 (s, 6 H), 2.19 (s, 3 H), 2.37–2.46 (m, 12 H), 2.59–2.65 (m, 4 H), 3.63 (s, 2 H). IR: ν_{OH} 3300 cm^{-1}, ν_{CN} 2220 cm^{-1}.

[Ni(3+H)](ClO4)3. To a well-stirred suspension of 0.5 g (0.89 mmol) of $[Ni(3)](ClO_4)_2$ in 10 mL of ethanol was added 0.45 g (4.5 mmol, 5 equiv) of 70% perchloric acid. The blue color of the complex changed immediately to pink. After 20 min of stirring, the solid was collected, washed with five 5-mL portions of anhydrous ethanol, and dried in vacuo at room temperature. Yield: 0.49 g or 83%.

[Cu(3+H)](ClO4)3. This complex was prepared in 85% yield by the same procedure used for the analogous Ni complex.

1-(2-Cyanoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (4). A solution consisting of $1 \cdot H_2O$ (0.70 g, 2.7 mmol) and acrylonitrile (1.0 mL, 15 mmol) in 10 mL of chloroform was heated at reflux for 6 h. The chloroform and excess acrylonitrile were removed by evaporation on a rotary evaporator. The resulting oily product exhibited no N—H stretching absorption in the infrared spectrum but did have a strong C≡N stretch at 2245 cm^{-1}. Yield: 0.80 g or 100%. ^1H NMR: 1.6 (q, J = 6.8, 4 H), 2.16 (s, 3 H), 2.17 (s, 6 H), 2.37–2.45 (m, 14 H), 2.53–2.59 (m, 4 H), 2.75–2.81 (m, 2 H).

[Ni(4)(NCS)2]. Ligand **4** (0.50 g, 1.7 mmol) in 25 mL of methanol was treated with a methanol solution of $NiCl_2 \cdot 6H_2O$ (0.40 g, 1.7 mmol in 5 mL) over 1–2 min. The green solution was stirred at room temperature for 1 h, after which anhydrous ether was slowly added to precipitate a yellow-green solid. The supernatant was decanted off, the solid dissolved in 20 mL of water, and the solution gravity-filtered. The filtrate was treated with an aqueous solution of NaSCN (1.0 g, 12 mmol in 5 mL) over 1–2 min, which resulted in the precipitation of a finely divided, light blue solid, which was collected, washed with portions of 2-propanol, and dried in vacuo (0.01 Torr, 100 °C). Yield: 0.51 g or 64%.

[Ni(4)](ClO4)2. A solution of 0.5 g (1.69 mmol) of **4** in 5 mL of methanol was treated with a 5-mL methanolic solution of 0.62 g (1.69 mmol) of hydrated nickel perchlorate. The pale green solid that precipitated was collected, washed with ether, and air-dried prior to dissolution in hot acetonitrile. The resulting aqua-colored solution was gravity-filtered and then concentrated to ca. 2 mL by heating at 50 °C, at which point blue-green crystals began to form. One milliliter of 2-propanol was added to the solution, after which it was cooled to 5 °C for 30 min to complete the crystallization. The blue-green crystals were collected, washed with ether, and dried in vacuo (0.01 Torr) at 100 °C for 24 h. During this time the color of the complex changed from blue-green to red-violet. Yield: 0.83 g (89%).

[Cu(4)](ClO4)2. This complex was prepared in 85% yield by the same procedure used to prepare the nickel complex. A blue solid was obtained from acetonitrile, which turned violet upon heating in vacuo.

1-(3-Aminopropyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (5). The pentaamine was prepared by catalytic hydrogenation of **4** according to the procedure used for the preparation of **3**.[1a,2] ^1H NMR: 1.5–1.64 (m, 6 H), 2.14 (s, 3 H), 2.16 (s, 3 H), 2.17 (s, 3 H), 2.36–2.50 (m, 18 H), 2.68 (t, J = 6.6, 2 H). IR: ν_{NH} 3350 (br), 1675 cm^{-1}.

[Ni(5)](ClO4)2. This complex was prepared by combining ethanolic solutions containing equimolar amounts of **5** and $Ni(ClO_4)_2 \cdot 6H_2O$. The blue-green precipitate that formed was collected and recrystallized from hot water to give green platelets (70%). The complex was recovered unchanged from an aqueous solution after heating at reflux for 48 h.

[Cu(5)](ClO4)2. This complex was prepared in the same fashion as the corresponding Ni complex. It was obtained in 92% yield as aqua-colored needles after recrystallization from hot 1 M $NaClO_4$ solution.

[Ni(5+H)](ClO4)3 and [Cu(5+H)](ClO4)3. These complexes were prepared in 91% and 94% yields, respectively, from $[Ni(5)](ClO_4)_2$ and $[Cu(5)](ClO_4)_2$ by the same procedure used for $[Ni(3+H)](ClO_4)_3$.

1-(2-Carbamoylethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (6). To 0.5 g (1.92 mmol) of $1 \cdot H_2O$ were added 0.136 g (1.92 mmol) of acrylamide and 1 mL of methanol. This mixture was heated at ca. 75 °C for 36 h, after which volatiles were removed by rotary evaporation to leave a very viscous oil. Yield: 0.63 g or 100%. ^1H NMR spectrum contained no resonances for **1** or for acrylamide: 1.52 (m, 2 H), 1.66 (m, 2 H), 2.13 (s, 3 H), 2.16 (s, 3 H), 2.18 (s, 3 H), 2.36–2.51 (m, 18 H), 5.21 (b s, 2 H).

[Ni(6)](ClO4)2. This complex could be prepared by combination of nickel perchlorate with **6** in methanol or by hydrolysis of $[Ni(4)](ClO_4)_2$ as follows. A solution consisting of 0.2 g (0.36 mmol) of $[Ni(4)](ClO_4)_2$ and 10 mL of water was heated at reflux for 40 h. After filtration, 0.6 g (5 mmol) of sodium perchlorate was added and the volume was reduced to 5 mL by rotary evaporation. The solution was maintained at 5 °C for 12 h, and the green crystals that formed were collected, washed with ethanol, and dried in vacuo (0.1 Torr, room temperature). Yield: 0.17 g or 84%. This complex could be recovered unchanged from an aqueous solution after heating at reflux for 48 h. The filtrate that remained after collection of the product, which was yellow, was extracted with three 5-mL portions of nitromethane. The extract was dried with sodium sulfate and evaporated to give a yellow solid that was identified as *R*,*R*,*S*,*S*-$[Ni(1)](ClO_4)_2$ by ^1H NMR spectroscopy. Yield: 0.022 g or 12%.

[Cu(6)](ClO4)2. This complex could also be prepared directly from the free ligand or by hydrolysis of $[Cu(4)](ClO_4)_2$ by the same procedures described for the nickel complex. From hydrolysis of 0.2 g of $[Cu(4)](ClO_4)_2$ were isolated 0.136 g (66%) of $[Cu(6)](ClO_4)_2$ and 0.045 g (25%) of $[Cu(1)](ClO_4)_2$. The latter complex was assigned the *R*,*R*,*S*,*S* stereochemistry on the basis of a comparison of its infrared spectrum with the spectrum of *R*,*R*,*S*,*S*-$[Ni(1)](ClO_4)_2$.

1-(2-Carbomethoxyethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (7). A solution consisting of $1 \cdot H_2O$ (0.50 g, 1.9 mmol) and methyl acrylate (1.0 mL, 11 mmol) in 10 mL of chloroform was heated at reflux for 6 h. The chloroform and excess methyl acrylate were removed by evaporation on a rotary evaporator. The resulting oily product exhibited a strong C=O stretching absorption at 1742 cm^{-1} in the infrared spectrum, but no N—H stretching absorptions were present. Yield: 0.63 g or 100%. ^1H NMR: 1.57 (overlapping q, 4 H), 2.14 (s, 3 H), 2.15 (s, 3 H), 2.16 (s, 3 H), 2.33–2.44 (m, 14 H), 2.46–2.52 (m, 4 H), 2.67–2.76 (m, 2 H), 3.61 (s, 3 H).

[Cu(7)](ClO4)2. Ligand **7** (0.63 g, 1.92 mmol) in 15 mL of absolute ethanol was treated with an ethanol solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.71 g, 1.92 mmol in 4 mL) over 1–2 min. A deep blue precipitate was obtained upon addition of the copper perchlorate. After the mixture was allowed to stand for ca. 1 h at room temperature, the complex was collected, washed with portions of isopropyl alcohol, and dried in vacuo (0.01 Torr, 65 °C) overnight. Yield: 1.1 g or 97%. The complex could be recrystallized from hot acetonitrile with 75% recovery.

Kinetics of Ester Hydrolysis in [Cu(7)](ClO4)2. Solutions of $[Cu(7)](ClO_4)_2$ at pH 8.7 and 9.5 (Borax buffer) were maintained at 25 °C and monitored spectrophotometrically over the range 850–500 nm. Absorbance data were utilized to construct log $(A_t - A_\infty)$ vs. time plots, which were linear over 3 half-lives. A_∞ was determined from a solution of complex, which had been made strongly basic with sodium hydroxide (pH >11), after there was no further change in the absorption spectrum.

Dealkylation of [Cu(6)](ClO4)2 and [Cu(7)](ClO4)2. An attempt was made to couple $[Cu(6)](ClO_4)_2$ and $[Cu(7)](ClO_4)_2$ by heating a 1:1 mixture (0.26 mmol each) with $NaOCH_3$ (20 mg, 0.37 mmol) in 20 mL of dry acetonitrile (freshly distilled from CaH_2) at reflux for 24 h. The reaction mixture was cooled, gravity-filtered, and evaporated to dryness on a rotary evaporator. The solid residue was dissolved in water and chromatographed on a Sephadex C-25 column (40 cm × 2 cm) using 0.25 M $NaClO_4$ as eluent. Two bands developed on the column and were collected as separate fractions; band 1 (minor) was light blue and band 2 (major) was reddish purple. Band 1 was not characterized. The volume of band 2 was reduced to ca. 30 mL and the solution extracted with two 30-mL portions of nitromethane. The nitromethane extracts were combined and evaporated to dryness. The solid residue was dissolved in 20 mL of dry acetonitrile and the complex precipitated by the slow addition of anhydrous ether. The finely divided, maroon solid was collected, washed with fresh ether, and dried in vacuo (0.01 Torr) at room temperature. The complex was identified as β-$[Cu(1)](ClO_4)_2$ on the basis of its infrared and electronic spectra. Yield: 0.2 g or 76% based on total copper.

[Cu(8)](ClO4)2. A mixture of $[Cu(7)](ClO_4)_2$ (0.40 g, 0.68 mmol) and NaOH (1.0 g, 25 mmol) in 50 mL of water was stirred at room temperature for ca. 3 h. The reaction mixture was slowly brought to pH 5 (pH paper) by the addition of concentrated $HClO_4$ and extracted with three 50-mL portions of nitromethane. The nitromethane extracts were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the filtrate volume reduced to 10–15 mL on a rotary evaporator. Anhydrous ether was slowly added with continuous stirring to precipitate the crude complex. The supernatant was decanted off and the solid residue triturated with several fresh portions of ether. The finely divided, deep blue solid was collected, washed with additional fresh ether, and dried in vacuo (0.01 Torr) at room temperature. Yield: 0.2 g or 51%.

Dealkylation of [Cu(8)](ClO4)2. Aqueous solutions of $[Cu(8)](ClO_4)_2$ were found to undergo an almost instantaneous color change from blue to reddish purple upon acidification with $HClO_4$ to pH 1. The resulting Cu(II) species was identified as β-$[Cu(1)]^{2+}$ by comparison of its visible absorption spectrum to that of an authentic sample.

$[Ni_2(9)](ClO_4)_4$. Ligand $1 \cdot H_2O$ was dried with 4A molecular sieves for 24 h prior to use. A solution of 3.00 g (12.3 mmol) of **1** in 20 mL of $CHCl_3$ prepared under an inert atmosphere and cooled in an ice bath was treated with 1.0 mL of dry pyridine, followed by 0.81 mL (1.08 g, 6.14 mmol) of 97% glutaryl dichloride. A yellow coloration developed immediately. The solution was stirred at room temperature overnight and then washed with three 15-mL portions of 4 M aqueous NH_3. The ammonia washings were back-extracted with two 20-mL portions $CHCl_3$; the combined $CHCl_3$ solutions were dried with Na_2SO_4. Removal of the solvent under reduced pressure afforded 3.4 g (94%) of dark oil. The ^1H NMR spectrum ($CDCl_3$) indicated this to be predominantly the expected diamide, and it was used without further purification.

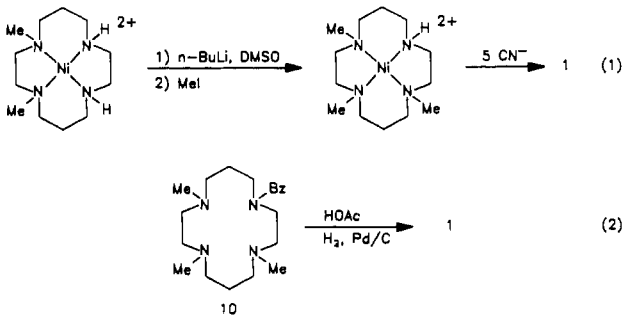
Approximately 90 mL of 1 M BH_3·THF was added under N_2 to an oven-dried 250-mL three-neck flask, which was fitted with a condenser, addition funnel, nitrogen inlet, and magnetic stirring bar, and the flask was placed in an ice bath. The diamide from above was dissolved in 50 mL of freshly distilled THF, and the mixture was added dropwise to the cold borane solution by way of the addition funnel over ca. 0.5 h. A white precipitate and yellow solution developed during the addition. After the diamide had been added, the ice bath was removed and the solution was heated at reflux for 7 h. The reaction mixture was cooled to room temperature, and 50 mL of 6 M HCl was added very carefully through the additional funnel (severe frothing occurred). After complete addition of the acid, the solution was heated overnight at reflux. The volume of the solution was decreased to about 75 mL by distillation and the solution made strongly basic (pH >12) by adding solid NaOH in small portions. Enough H_2O was added (ca. 50 mL) to afford a homogeneous solution, which was then extracted with five 25-mL portions of $CHCl_3$. The extracts were dried with Na_2SO_4 and evaporated to all oil at 80 °C in vacuo. The yield of dark, viscous oil was 3.7 g (108% based on 12.3 mmol of **1**).

The oil from above was dissolved in 50 mL of ethanol, and the solution was added to 4.50 g (12.2 mmol) of $Ni(ClO_4)_2 \cdot 6H_2O$ in 50 mL of H_2O. Precipitate formed immediately, subsequently dissolving to give a deep red solution when the mixture was heated to boiling. The solution was taken to dryness on a rotary evaporator, and the resultant red oil was triturated with ethanol to give a red solid. The product was collected and washed well with ethanol and then with ether. After the product was dried in vacuo, the yield of red powder was 5.82 g (89% based on 12.3 mmol of **1**). A solution of 1.00 g of this product, dissolved in ca. 50 mL of H_2O, was carefully placed on a 3.5 × 30 cm column packed with 25 g of Sephadex C-25 resin that had been swelled in distilled water. Elution with 0.1 M $NaClO_4$ moved a small red band (band I) and a yellow band (band II, identified as $[Ni(1)]^{2+}$ rapidly. Increasing the eluant concentration to 0.2 M $NaClO_4$ developed two red bands, band III and band IV (major band). Elution with 0.5 M $NaClO_4$ moved two more, poorly separated, red bands (bands V and VI).

The desired complex was determined to be in band IV and was isolated by extraction with nitromethane. Evaporation of the nitromethane in vacuo afforded a semisolid material, which was stirred with ethanol for several hours, collected, and dried to yield 0.18 g of red solid. Metathesis of this material to the PF_6^- salt by precipitation from hot water with ammonium hexafluorophosphate followed by recrystallization from 1:1 acetone/water gave material that analyzed satisfactorily. A sample of the complex was decomposed in water with sodium cyanide and the solution extracted with $CHCl_3$. After the extracts were dried, the solvent was removed on a rotary evaporator to give a colorless, viscous oil. Mass spectrum: found EI *m/e* 552, CI (NH_3) *m/e* 553; calcd 552. ^1H NMR: 1.18 (q, $J \approx 7.5$ Hz, 2 H), 1.36 (q, $J \approx 7.5$ Hz, 4 H), 1.55 (overlapping quintets, 8 H), 2.12 (s, 3 H), 2.14 (s, 3 H), 2.15 (s, 3 H), 2.35 (m, 18 H), 2.46 (t, J = 6–7 Hz, 2 H), 2.48 (t, J = 6–7 Hz, 2 H).

Results

Ligand Syntheses. Eight tetra-N-alkylated cyclam ligands, **2–9**, in which one of the *N*-alkyl groups is functionalized have been prepared. The precursor to these ligands was trimethylcyclam (**1**). This ligand was first reported by Wagner[4] and was used by Kaden for the preparation of **2**.[2] However, the original synthesis was conducted on only a small scale and no improvements have been reported. In the course of this work, two moderate-scale routes were developed. The first of these utilizes the original monodeprotonation–methylation scheme of Wagner[4] but employs *n*-butyllithium as the base (eq 1). The second route involves the hydrogenolysis of the recently reported benzyltrimethylcyclam (**10**) (eq 2).[6]



Ligand **2** was prepared by a standard cyanomethylation of **1** (Strecker synthesis).[1a,2] Catalytic hydrogenation of the nitrile gave **3**. Although neither we nor Kaden has done so, presumably **2** could be hydrolyzed to the carboxylic acid. Ligand **4** was obtained by alkylation of **1** with acrylonitrile and was catalytically hydrogenated to **5**. Ligand **6** was obtained by alkylation of **1** with acrylamide or, in complexed form, by hydrolysis of both nickel and copper complexes of **4**. Ligand **7** was obtained by alkylation of **1** with methyl acrylate. We were unable to alkylate **1** with acrylic acid; ligand **8** was obtained only as its copper complex by basic hydrolysis of $[Cu(7)]^{2+}$ followed by acidification; vide infra.

The binucleating ligand **9** was prepared by coupling of **1** with glutaryl dichloride followed by reduction of the diamide with BH_3·THF. Appreciable cleavage of the amide occurred, however, and the complicated product mixture was separated by generation of nickel complexes followed by ion-exchange chromatography.

Preparation and Characterization of Metal Complexes. Nickel(II) perchlorate complexes of ligands **3–6** were prepared by combination of the ligands with aquated Ni^{2+}, but we were unable to find a satisfactory preparation for a complex of **7**. The perchlorate salt of $[Ni_2(9)]^{2+}$ could not be adequately purified, but satisfactory analyses were obtained on the PF_6^- salt. Copper(II) perchlorate complexes of ligands **3–7** were also prepared from the free ligands. Nickel and copper complexes of **6** were also prepared by hydrolysis of the complexes of **4** in 84% and 66% yields, respectively.

Protonated forms of $[M(3)]^{2+}$ and $[M(5)]^{2+}$ (M = Ni, Cu) were obtained by treating suspensions of the complexes in ethanol with perchloric acid.[7] Attempts to selectively protonate the primary amino group in $[Ni(3)]^{2+}$ and $[Ni(5)]^{2+}$ by addition of acid to their aqueous solutions were not successful. The former complex began to decompose when 2 equiv of trifluoroacetic acid had been added but without appearance of absorptions attributable to the four-coordinate species $[Ni(3+H)]^{3+}$. Kaden has previously noted that $[Cu(3)]^{2+}$ was not protonated at pH 3.[2] Addition of acid to aqueous $[Ni(5)]^{2+}$ produced an immediate color change from green to red and produced absorptions characteristic of the four-coordinate species. Spectrophotometric titration indicated that significant decomposition began after addition of 1.5 equiv of acid. Qualitatively, the relative stabilities in 0.1 M acid were $[Ni(tmc)]^{2+} \approx [Ni(3)]^{2+} > [Ni(5)]^{2+}$ (tmc is 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane).

$[Cu(7)](ClO_4)_2$ was stable in water, but when the pH was raised to >11, a rapid reaction took place to produce a new species with an absorption maximum at 691 nm (ϵ = 228 M^{-1} cm^{-1}, assuming complete conversion). This complex is assumed to contain the conjugate base of **8** (**8-H**) although it could not be successfully crystallized. Acidification of such solutions to a pH of about 5 followed by extraction with nitromethane gave blue $[Cu(8)](ClO_4)_2$. The rates of base hydrolysis of $[Cu(7)]^{2+}$ were measured at pH 8.7 and 9.5, and the pseudo-first-order rate constants were determined to be 3.1×10^{-4} s^{-1} and 1.6×10^{-3} s^{-1}, respectively. These data suggest a second-order rate constant in the range of 50–60 M^{-1} s^{-1}.

When a solution of $[Cu(6)]^{2+}$ was made strongly basic (pH ≥11), the absorption maximum increased from 667 to 699 nm after a short time. Presumably this spectral change results from deprotonation of the amide nitrogen and isomerization of the O-bound species to an N-bound form as described by Kaden for the carbamoylmethyl analogue.[3] No attempt was made to measure the rate of this transformation.

Systematic attempts were not made to prepare acido complexes of most of the new complexes. $[Ni(4)]^{2+}$ gave what appeared to be [Ni(4)Cl]Cl by reaction of **4** with nickel chloride in methanol,

although it was not characterized. $[Ni(4)(NCS)_2]$ precipitated upon addition of aqueous sodium thiocyanate to a methanol solution of the chloro complex. Additions of salts of coordinating anions to most of the other nickel complexes did not result in a visible change. More extensive efforts were made to prepare derivatives of $[Ni_2(9)]^{4+}$. Although samples did not analyze satisfactorily for sulfur, $[Ni_2(9)(NCS)_4]$ appeared to form upon treatment of $[Ni_2(9)]^{2+}$ with thiocyanate. The absorption spectrum of this complex was identical with that of $[Ni(tmc)(NCS)_2]$ with respect to number and wavelength of absorptions.[8] Reaction with azide gave what appeared to be $[Ni_2(9)(N_3)_2]^{2+}$, which was isolated as the PF_6^- salt, but again satisfactory analytical results were not obtained. Attempts to generate a monoazide-bridged species were not successful.

Electronic absorption spectral data for the new complexes are given in Table II. The appearance of spectra of the nickel complexes of all ligands except **4** and protonated forms of **3** and **5** (**3+H** and **5+H**) suggest that they are most likely high-spin, five-coordinate species. The energy of the single absorption band observed for each copper complex suggests that all of the copper complexes except those of **4**, **3+H**, and **5+H** are five-coordinate.[9] The variation in the position of the absorption maxima for these five-coordinate species suggests that the ligand field strength of the axial donor varies in the order $CH_2CH_2CO_2H < CH_2CH_2C(O)OCH_3 < CH_2CH_2C(O)NH_2 < CH_2CH_2CH_2NH_2 < CH_2CH_2NH_2 < CH_2CH_2CO_2^- < CH_2CH_2C(O)NH^-$.[9]

The stereochemistry of the tertiary nitrogen donor set is assumed to be such that all of the nitrogen substituents are on the same side of the nominal metal–nitrogen plane in both the nickel and copper complexes. Although structural data are not available, strong evidence for this stereochemistry is available for several of the nickel complexes based on comparison of their electronic absorption spectra with that of *R,S,R,S*-$[Ni(tmc)]^{2+}$ (i.e., 1-(*R*),4(*S*),8(*R*),11(*S*)-(1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II)),[8,10] whose structure is known.[11] Nitromethane solutions of *R,S,R,S*-$[Ni(tmc)]^{2+}$ exhibit a single absorption at ca. 519 nm (ϵ = 184 M^{-1} cm^{-1}), and the solid absorbs at 520 nm. Very similar spectra are observed for $[Ni(4)]^{2+}$ (532 nm, ϵ = 168 M^{-1} cm^{-1}) and $[Ni(5+H)]^{2+}$ (524 nm, ϵ = 200 M^{-1} cm^{-1}) in nitromethane. $[Ni(3+H)](ClO_4)_3$, which is insoluble in nitromethane, absorbs at 525 nm in solid form. The absorption spectrum of $[Ni_2(9)]^{4+}$ also suggests that it has the same stereochemistry as *R,S,R,S*-$[Ni(tmc)]^{2+}$. This complex can exist in two diastereomeric forms but no evidence is available concerning its isomeric composition.

The spectra of $[Cu(3+H)](ClO_4)_3$, $[Cu(4)](ClO_4)_2$, and $[Cu(5+H)](ClO_4)_3$ closely match those observed for $[Cu(tmc)]^{2+}$ (solid state, λ_{max} = 580 nm; nitromethane, λ_{max} = 583 nm, ϵ = 214 M^{-1} cm^{-1}).[8] Structural data are not available for any derivative of $[Cu(tmc)]^{2+}$, but on the basis of the proven tendency for other divalent first-row metals to form complexes by reaction with free tetramethylcyclam that have *R,S,R,S* donor stereochemistry,[11-14] it can reasonably be assumed that copper does as well.

During the hydrolysis of $[M(4)]^{2+}$ (to $[M(6)]^{2+}$) a competitive dealkylation reaction resulted in the formation of $[M(1)]^{2+}$, which was isolated in 12% and 25% yields for M = Ni and Cu, respectively. The ^1H NMR and infrared spectra of the nickel product indicated that it was *R,R,S,S*-$[Ni(1)]^{2+}$ (i.e., 1(*R*),4(*R*),8(*S*),11(*S*)-(1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II)), which raised the possibility that $[Ni(4)]^{2+}$ might have this set of nitrogen configurations. Although this possibility is not totally excluded, we found that authentic *R,S,R,S*-$[Ni(1)]^{2+}$ had isomerized completely to the *R,R,S,S* form upon heating aqueous solutions at reflux for 20 h.

Aqueous solutions of the nickel complexes of ligands **3**, **5**, and **6** were heated at reflux for 48 h. After evaporation of the water and drying of the recovered materials, their infrared spectra were identical with those of the starting materials. This strongly suggests that no appreciable decomposition or isomerization had occurred.

$[Cu(1)]^{2+}$, which was not previously known, was synthesized by direct combination of **1** with Cu^{2+} in water. Repeated ion-exchange chromatography of this material yielded two isomers with different absorption spectra. The isomer with the largest R_f (α) was purple with $\lambda_{max}(H_2O)$ = 567 nm, ϵ = 235 M^{-1} cm^{-1}; the second isomer (β) was maroon with $\lambda_{max}(H_2O)$ = 532 nm, ϵ = 185 M^{-1} cm^{-1}. Comparison of the infrared spectra of these isomers with those of $[Ni(1)]^{2+}$ suggested that the α isomer had the *R,S,R,S* set of nitrogen configurations and that the β isomer was then *R,R,S,S* isomer. The absorption spectrum of the initial reaction product mixture could be accounted for by a 5.5:4.5 mixture of the *R,S,R,S* and *R,R,S,S* isomers.

$[Cu(1)]^{2+}$, identical with the above β isomer, was obtained in 76% yield (based on total copper) when a mixture of $[Cu(6)]^{2+}$ and $[Cu(7)]^{2+}$ was heated in acetonitrile with sodium methoxide. Mixtures that contained substantial amounts of β-$[Cu(1)]^{2+}$ were also obtained when solutions of $[Cu(8)]^{2+}$ were made strongly acidic (pH <1) with perchloric acid.

Discussion

Trimethylcyclam can be easily converted, in high yield, to a variety of tetraalkylated cyclam ligands with an appended functional group by reaction with Michaels acceptors. Retro-Michaels reactions must be considered as possibilities for complexes that contain *N*-cyanoethyl, *N*-carboxyethyl or *N*-carbamoylethyl substituents. Elevated temperatures and/or acidic or basic conditions should be avoided to minimize the likelihood of dealkylation. Dealkylation reactions can thwart attempts to perform coupling reactions between functionalized complexes if acidic or basic catalysts are required. Although coupling of two trimethylcyclam molecules with glutryl chloride proceeded smoothly and in high yield, reduction of the resulting amide did not. The low yield of this reaction and the lengthy purification required make this a poor route to dinuclear complexes. Other potential coupling methods, such as reaction with α,ω-dihaloalkanes and various modifications of the Leuckart–Wallach[1a,15] reaction, failed in our hands.

The complexes formed from these functionalized tetraalkylated cyclam ligands with both nickel and copper probably all have *R,S,R,S* nitrogen stereochemistry. However, this has been unambiguously proven only for the nickel complexes of **3**, **4**, **5**, and **9** by comparison of the absorption of the four-coordinate complexes with $[Ni(tmc)]^{2+}$, whose stereochemistry is known.[11] The observation of *R,R,S,S*-$[M(1)]^{2+}$ as a product of dealkylation of some of the complexes might raise doubts about the stereochemistry (or stereochemical integrity) of the precursors. Isomerizations of $[Ni(tmc)]^{2+}$ and nickel complexes of tetraalkylated cyclam ligands with two, or more, functionalized *N*-alkyl substituents have been observed,[16-18] but there is no evidence that such isomerization occur for complexes of the monofunctionalized derivatives. The available evidence strongly suggests that the isomerization occurs after (or perhaps simultaneous with) loss of the functionalized alkyl group.

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Prior to this work only the nickel complex of **1** had been prepared.[4] Generation of this complex from the free ligand gave a 3:1 ratio of *R,S,R,S* to *R,R,S,S* stereoisomers. The stability of these diastereomers had not been investigated. Formation of the copper complex apparently occurs with lower selectivity, ca. 5.5:4.5. Because of the difficulty of completely separating the two diastereomeric copper complexes, studies to determine the stability of the individual isomers toward isomerization have not yet been made. However, preliminary studies on the mixture suggest that both an acid-catalyzed and a thermally promoted isomerization can occur to shift the ratio toward the *R,R,S,S* stereoisomer. Curiously, prolonged exposure to aqueous acid appears to give exclusively the *R,R,S,S* stereoisomer but with substantial decomposition of the sample. Further studies of the trimethylcyclam complexes of copper, nickel, and zinc are under way.

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Supplementary Material Available: Table I, giving analytical data for metal complexes (1 page). Ordering information is given on any current masthead page.

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Isolation and Characterization of a Five-Coordinate Manganese(III) Porphyrin Cation. Crystal and Molecular Structure of Aquo(tetraphenylporphinato)manganese(III) Triflate

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Five-coordinate cationic manganese(III) porphyrin complexes exist in nonpolar organic media in the presence of a limiting amount of water. Slow diffusion of heptane into a benzene solution of (tetraphenylporphinato)manganese(III) triflate containing 1 equiv of water produces crystals of aquo(tetraphenylporphinato)manganese(III) triflate, $[(H_2O)Mn^{III}TPP]^+OTf^-$ (**1**), the first unequivocal and isolated example of a five-coordinate cationic manganese(III) porphyrin complex. Solvate-free crystals of **1** crystallize in space group $P\bar{1}$. The unit cell has a = 11.1735 (47) Å, b = 13.0503 (80) Å, c = 13.8998 (121) Å, α = 81.102 (60)°, β = 79.476 (53)°, γ = 75.312 (41)°, V = 1915.07 (2.17) Å^3, and Z = 2. The structure was solved by conventional heavy-atom methods and converged to a final R = 0.0746. Complex **1** has a d_{Mn-O} of 2.105 (4) Å, and the Mn atom resides 0.17 and 0.19 Å above the mean 24-atom plane and the mean N_4 plane, respectively. The molecular stereochemistry and the electronic spectra for **1** clearly establish the Mn to be in the high spin, S = 2, state. Complex **1** reacts only with a large excess of iodosylbenzene to form one or more high-valent Mn porphyrin species. The five-coordinate cationic form of Mn^{III} porphyrins is accessible under the literature conditions for both the homogeneous catalytic oxygenation of hydrocarbons and the homogeneous oxidation of water by Mn porphyrins.

The ability of manganese porphyrin complexes to oxidize alkanes and other organic compounds of low reactivity,[1,2] as well as water,[3,4] one of the most oxidatively resistant inorganic substances, has generated substantial efforts recently to characterize these complexes. Much progress has been made with respect to the isolation, purification, and rigorous characterization of Mn(III),[5-8] Mn(IV),[9-11] and Mn(V)[12,13] porphyrins of relevance to catalytic organic oxygenation processes. In contrast, little progress has been made with respect to the isolation and rigorous characterization of Mn porphyrins of relevance to water oxidation and oxygen evolution.[14] In our attempts to isolate tractable and

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