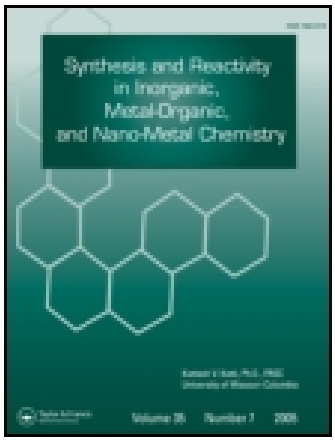

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Monofunctionalized Tetraazacrowns for Use in Bioconjugation and Catalysis

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Alkylation of 1,4,7,11-tetraazacyclododecane (cyclen) with 4-nitrobenzyl bromide, *p*-chloromethylbenzyl alcohol, 4-iodobenzyl bromide, or 4-vinylbenzyl bromide in acetonitrile gave *N*-monoalkylated cyclen ligands 1–4 in 38–60% yield. Compounds 3 and 4 reacted with cobalt chloride hexahydrate in methanol, followed by air oxidation and addition of HCl, gave cobalt complexes dichloro{*N*-(4-iodobenzyl)-1,4,7,10-tetraazacyclotetradecane}cobalt(III) chloride (5) and dichloro{*N*-(4-vinylbenzyl)-1,4,7,10-tetraazacyclotetradecane}cobalt(III) chloride (6) in 34–55% yield. Compounds 1–6 were characterized by ^{1}H NMR, ESI-MS, UV-visible, and IR spectroscopies.

Keywords cyclen, alkylation, cobalt

INTRODUCTION

Macrocyclic polyamines or azacrowns form thermodynamically stable and kinetically inert complexes with transition metals, main group, and lanthanide metals and can coordinate to a wide variety of ions in different oxidations states and metal complex geometries. As such, these types of ligand and associated metal complexes have found application in areas as diverse as metal-based artificial nucleases and peptidases (Hegg and Burstyn, 1998), NMR contrast agents (Bianchi et al., 2000), molecular recognition (Reichenbach-Klinke and König, 2002), catalysis, and synthetic ionophores (Burger and Still, 1995). To further the development of these applications, the ability to synthesize a diverse library of functionalized ligands becomes of paramount concern, and most important the ability to selectively introduce reactive groups which may be modified using modern synthetic methods.

Monofunctionalized azamacrocycles may be prepared by introduction of a functional group onto either (1) the methylenic component of the macrocycle or (2) via *N*-substitution. By far the simplest method involves *N*-alkylation (or *N*-arylation) and has been widely reported in the literature. Methods for introducing a functional-group side chain onto a single nitrogen atom of a tetraazamacrocyle include: temporary blocking of three amine nitrogens of the macrocyclic ring using a sterically demanding group, e.g., transition metal carbonyls (Patinec et al., 1995); selective protection/deprotection using classical organic protecting groups such as *t*-Boc (Kimura et al., 1997), tosyl (Dischino et al., 1991), or guanidinium groups (Li and Undheim, 1998); use of an excess of macrocycle to prevent polyalkylation (Li and Wong, 2002); and palladium catalyzed monoarylation (Beletskaya et al., 2002).

We recently reported the synthesis of a new monofunctionalized cyclen ligand containing a pendant methylbenzoic acid

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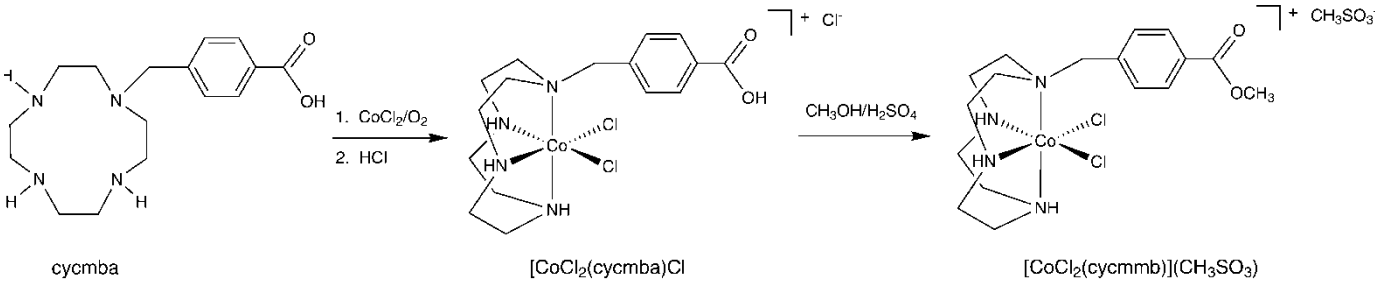


SCH. 1. Previously reported cycmba ligand and cobalt complexes.

group, cycmba (Scheme 1), and demonstrated that the ligand coordinates cobalt(III) in the expected manner without competing coordination of the −COOH moiety to the cobalt ion (Knight et al., 2004). The carboxylic acid could be further elaborated to a methyl ester $[CoCl_2(cycmmb)]CH_3SO_3$ by reaction with methanol/sulfuric acid (Deschamps et al., 2003). Furthermore, we showed that $[CoCl_2(cycmba)]Cl$ is active in phosphodiester hydrolysis, and could be conjugated to an amine-functionalized polystyrene bead using conventional EDC coupling. The methyl ester complex is very potent in inhibiting the translation of RNA into protein (Delehanty et al., 2005). For example, a contact time as short as 10 min is sufficient to achieve complete inhibition of the translation of a concentrated luciferase RNA solution into the enzyme in a cell-free translation system. The inhibition appears to proceed through two pathways, via the kinetic inertness of the Co(III) for the phosphate groups of the nucleotides at short contact times and also by the hydrolysis of phosphodiester bonds at longer contact times.

Herein we describe a simple synthetic procedure for the mono-*N*-alkylation of cyclen using controlled addition of benzyl halide alkylation agents in acetonitrile without the need for the presence of excess cyclen ligand. Four different alkation agents which were chosen, based on their potentional utility in further derivitazation. In addition, we report the complexation of two representative examples of ligands to cobalt ion giving *cis* complexes of the type $[CoCl_2L]Cl$ (L = ligand).

EXPERIMENTAL

General Data

IR spectra were recorded on a Bruker Tensor 27 spectrometer. All ^1H and ^{13}C spectra were recorded on a Varian Inova 400 or Bruker DRX 400 spectrometer and referenced to internal tetramethylsilane. UV-visible absorption spectra were recorded at room temperature on an HP8453 diode array spectrometer in 1.0-cm quartz cuvettes. ESI mass spectra were obtained using an Applied Biosystems Qstar Pulsar i instrument using the ESI technique, with nitrogen as the nebulizing gas. Mass spectra were recorded on freshly prepared methanolic or aqueous methanolic solutions of ligand and cobalt complexes.

Solvents were as follows: 2-propanol, $CHCl_3$, CH_2Cl_2, ether (Sigma-Aldrich), methanol, acetonitrile (Fisher), CD_3CN, CD_3OD, $CDCl_3$ (Cambridge Isotope Laboratories), used as received. Silica gel (200–400 mesh, 60 Å, Sigma-Aldrich) was used as received.

Reagents were obtained as follows: cyclen (Strem), $CoCl_2 \cdot 6H_2O$, ammonium hydroxide, hydrochloric acid, *p*-chloromethylbenzyl alcohol, 4-iodobenzyl bromide, 4-vinylbenzyl bromide, 4-nitrobenzyl bromide, triethylamine (Sigma-Aldrich) used as received.

Synthesis

*N-(4-nitrobenzyl)-1,4,7,10-tetraazacyclotetradecane (**1**)*

The following procedure was adapted from ref. 1 (Chappel, 1998). A 250-mL flask was charged with cyclen (2.31 g, 13.4 mmol), acetonitrile (ca. 65 mL), and triethylamine (2.4 mL). Then, a solution of 4-nitrobenzyl bromide (2.89 g, 13.4 mmol) in acetonitrile (ca. 25 mL) was added dropwise with stirring over a period of 45 min. The solution was stirred for 48 h, and reduced under rotary evaporation to give an orange oil. CH_2Cl_2 (40 mL) was added and the resulting precipitate of $[Et_3NH]^+Br^-$ was removed via filtration through a pad of Celite and the solvent removed by rotary evaporation. The residue was dissolved in $CHCl_3$/MeOH/conc. NH_4OH (12:4:1) and the solution chromatographed on a 30-mm silica gel column [25 g, $CHCl_3$/MeOH/conc. NH_4OH (12:4:1)]. The solvent was removed from the eluate to give **1** as a spectroscopically pure orange gum. Yield 2.389 g, 60%. ^1H NMR (CD_3CN): δ 8.20 (d, 2H, C_6H_4), 7.63 (d, 2H, C_6H_4), 3.86 s, 2H, $C_6H_4\underline{CH_2}$), 2.88–2.59 (m, 8CH_2), 3.20 (br, 3H, NH) ESI-MS (m/z) = 308 ($1 + H^+$).

*N-(4-(hydroxymethyl)benzyl)-1,4,7,10-tetraazacyclotetradecane (**2**)*

A 300-mL flask was charged with cyclen (1.5 g, 17 mmol), acetonitrile (125 mL), and triethylamine (3 mL). Then, a solution of *p*-chloromethylbenzyl alcohol (1.33 g, 8.50 mmol) in acetonitrile (25 mL) was added dropwise with stirring over a period of 75 min. The solution was refluxed for 3 h, and reduced under rotary evaporation to give a yellow oil. 2-Propanol (40 mL) was added and the resulting white

precipitate of $[Et_3NH]^+Br^-$ was removed via filtration through a pad of Celite. The solvent was removed under rotary evaporation to give crude **2** as a sticky yellow solid (1.23 g, 49%). IR (KBr pellet): ν(OH) br, 3394 cm^{-1}. ^1H NMR (CD_3OD): δ 7.8–7.4 (m, 4H, C_6H_4), 4.6 (s, 2H, $C_6H_4C\underline{H_2}O$), 3.8 (s, 2H, $C_6H_4C\underline{H_2}N$), 3.6–2.4 (m, 19H of $8CH_2$, 3NH).

*N-(4-iodobenzyl)-1,4,7,10-tetraazacyclotetradecane (**3**)*

A 100-mL three-neck flask was charged with cyclen (0.58 g, 3.4 mmol), acetonitrile (45 mL), and triethylamine (2.00 mL). Then, a solution of 4-iodobenzyl bromide (1.00 g, 3.36 mmol) in acetonitrile (20 mL) was added dropwise with stirring over a period of 45 min. The solution was refluxed for 4 h, and reduced under rotary evaporation to give a yellow oil. CH_2Cl_2 (20 mL) was added and the resulting precipitate of $[Et_3NH]^+Br^-$ was removed via filtration through a pad of Celite and the solvent removed by rotary evaporation. This process was repeated ($\times$4) to give **3** (0.569 g, 43%). ^1H NMR ($CDCl_3$): δ 7.77 (d, 2H, C_6H_4), 7.51 (d, 2H, C_6H_4), 3.51 (s, 2H, $C_6H_4C\underline{H_2}$), 3.6–2.4 (m, 19H of $8CH_2$, 3NH).

*N-(4-vinylbenzyl)-1,4,7,10-tetraazacyclotetradecane (**4**)*

A 100-mL three-neck flask was charged with cyclen (0.50 g, 2.9 mmol), acetonitrile (35 mL), and triethylamine (2.0 mL). Then, a solution of 4-vinylbenzyl bromide (0.44 g, 2.9 mmol) in acetonitrile (15 mL) was added dropwise with stirring over a period of 45 min. The solution was stirred at room temperature for 48 h, and reduced under rotary evaporation to give a yellow oil. CH_2Cl_2 (50 mL) was added and the resulting precipitate of $[Et_3NH]^+Br^-$ was removed via filtration through a pad of Celite and the solvent removed by rotary evaporation. The residue was dissolved in $CHCl_3$/MeOH (75:25) and the solution chromatographed on a 110-mm silica gel column [90 g, $CHCl_3$/MeOH (75:25) then adjusted to 100:0 MeOH] to give **4** as a yellow glassy solid (0.32 g, 38%). ^1H NMR (CD_3CN): δ 7.47–7.20 (m, 4H, C_6H_4), 6.70 (m, 1H, $C\underline{H}{=}CH_2$), 5.80 (t, 2H, $CH{=}C\underline{H_2}$), 3.74 (s, 2H, $C_6H_4C\underline{H_2}$), 3.56–2.67 (m, 19H of $8CH_2$, 3NH) ESI-MS (m/z): 289 (cycmst + H^+).

*Dichloro{N-(4-iodobenzyl)-1,4,7,10-tetraazacyclotetradecane}cobalt(III) chloride, [Co(cycmbi)Cl_2]Cl (**5**)*

A 100-mL flask was charged with **3** (0.570 g, 1.48 mmol), cobalt chloride hexahydrate (0.35 g, 1.5 mmol), and methanol (35 mL) and the solution was gently warmed for 30 min. Then, hydrochloric acid (1 mL) was added dropwise and the solution was stirred in air for 3 h. The resulting blue solid was collected via filtration and dried *in vacuo* to give **5** (0.454 g, 55%). Electron absorption spectra, λ_{max}, nm (ε, dm^3 mol^{-1} cm^{-1}): MeOH, 569 (137), 398 (122). ESI-MS (m/z): 467 ($[Co(cycmbi)(OH_2)]^{2+}$ + 2H).

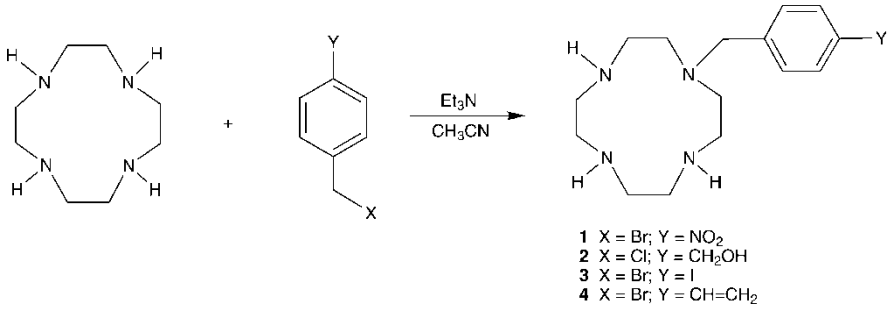
*Dichloro{N-[(4-vinylphenyl)methyl]-1,4,7,10-tetraazacyclotetradecane}cobalt(III) chloride, [Co(cycmst)Cl_2]Cl (**6**)*

A 100-mL flask was charged with **4** (1.976 g, 6.85 mmol), cobalt chloride hexahydrate (1.630 g, 6.850 mmol), and methanol (30 mL) and the solution was gently warmed for 30 min. Then, hydrochloric acid (ca. 1 mL) was added dropwise and the solution was stirred in air for 4 h. The solution was concentrated to 15 mL via rotary evaporation and the resulting blue solid collected, washed with methanol (20 mL) and ether (20 mL), and dried *in vacuo* to give **6** (1.067 g, 2.350 mmol, 34% yield). Electron absorption spectra, λ_{max}, nm (ε, dm^3 mol^{-1} cm^{-1}): MeOH, 576 (310), 396 (347). ESI-MS (m/z): 345 ($[Co(cycmst)]^{3+}$ − 2H), 381 ($[Co(cycmst)Cl]^{2+}$ − H), 417 ($[Co(cycmst)Cl_2]^+$ − H).

RESULTS AND DISCUSSION

Synthesis of *N*-Monoalkylated Cyclen Ligands

To expand the availability of *N*-monoalkylated cyclen ligands with pendant reactive groups, we chose hydroxymethyl-, nitro-, iodo-, and vinyl- groups attached in the *para* position of the benzene ring. The hydroxymethyl group was chosen for potential entry into phosphoramidite chemistry (DNA synthesis), the nitro group may be further reduced to a synthetically useful primary amine, aryl iodides are useful for palladium-catalyzed arylations (C–C, C–O, C–N, and C–P bond-forming reactions, and the vinyl groups is useful for epoxide formation and can be readily converted to aminated, hydrated, or reduced, to give amines, alcohols, or alkanes, respectively. Benzylic halide, either bromide or chloride, was chosen as the electrophile to achieve sufficient reactivity. Following the synthetic protocol described in a previous publication (Knight, 2004), alkylation of the tetraazamacrocycle, cyclen, using either chloro- or bromomethyl-disubstituted aryl compounds proceeded in a straightforward manner as shown in Scheme 2. Very slow addition of an acetonitrile solution of the alkylation agent to the macrocycle in acetonitrile, in the presence of triethylamine, is necessary to prevent extensive polyalkylation of the ring, and triethylamine hydrochloride salt is formed during the reaction, which is removed by filtration. After work-up, the crude monoalkylated cyclen ligands **1**–**4** were obtained as either viscous oils or glassy solids, and analyzed by ESI-MS and then purified by chromatography on silica gel, or used without further purification for the preparation of cobalt complexes (see Experimental section). ESI-MS analysis prior to purification showed either no, or surprisingly small, amounts of di- and trialkylated cyclen compounds. Thus, tetrazamacrocycle ligands with pendant hydroxymethyl-, iodo-, nitro-, and vinyl-functional groups were obtained with overall yields of **1**–**4** of 38–60%. All of the ligands are hygroscopic in the free base form and were stored under dry N_2 or in a dessicator before use.



SCH. 2. Synthesis of monoalkyated cyclen ligands.

^{1}H NMR spectra for ligands **1**–**4** were obtained in $CDCl_3$ or CD_3OD (see Experimental section). All new *N*-functionalized macrocycles show either a pair of doublets, or a multiplet at 8.20–7.20 ppm corresponding to the aromatic protons of a 1,4-disubstituted benzene ring. The benzylic protons resonate as singlets at 3.86–3.51 ppm. Compound **2** has an additional resonance at 4.6 ppm, assigned to the methylenic protons on the carbon atom adjacent to –OH. The CH_2 protons of the macrocycle resonate as a broad set of multiplets at 3.6–2.4 ppm and the NH protons experience quadripolar broadening due to the nitrogen atoms.

Synthesis of Cobalt Complexes

We previously reported that methylbenzoic acid and methylbenzonitrile-functionalized cyclen ligands react with either $Na_3[Co(CO_3)_3]$ or $CoCl_2/O_2$ to give the new cobalt complexes $[CoCl_2$(cycmba)]Cl [cycmba = 4-(1,4,7,10-tetraazacyclotetradec-1-yl)methylbenzoic acid] and $[CoCl_2$(cycmbn)]Cl [cycmbn = 4-(1,4,7,10-tetraazacyclotetradec-1-yl)methylbenzonitrile (Knight et al., 2004). IR spectroscopy of the complexes showed that the carboxylic acid and nitrile functionalities do not coordinate to the cobalt ion in either an intra- or intermolecular fashion. It was also shown that $[CoCl_2$(cycmba)]Cl can undergo esterification of the benzoic acid group using methanol and sulfuric acid to give the methyl ester complex as the methylsulfate salt (Scheme 1). While neither of the chloride complexes could be crystallized to give X-ray-quality crystals, exchange of the chloride countertion for methylsulfate allowed for single-crystal formation and the crystal structure of dichloro (methyl-4-[(1,4,7,10-tetraazacyclododec-1-yl)methylbenzoate) cobalt(III) methyl sulfate has been solved (Deschamps et al., 2003).

Reaction of either an equimolar or a slight excess of cyclen ligands **3** and **4** with $CoCl_2 \cdot 6H_2O$ in MeOH for 30 min with gentle warming, followed by the addition of concentrated HCl and air oxidation for 3–4 h, results in the formation of an intense violet-purple colored solution. After work-up (see Experimental section), the new cycmbi and cycmst cobalt(III) complexes $[CoCl_2$(cycmbi)]Cl (**5**) and $[CoCl_2$(cycmst)]Cl (**6**) were obtained as blue solids in 34–55% yield (Figure 1). Complex **5** is stable in air for days, but the styrene complex **6** undergoes polymerization after approximately 24 h in either aqueous or methanolic solution at room temperature and under ambient light conditions. Interestingly, thin films of the polymerized material may be drawn from the surface of methanolic solutions of **6**, suggesting a future possible application of catalytic thin films or polymer-supported hydrolytic cobalt complexes. The solubility propeties of **5** and **6** are typical of complexes of this type, i.e., they are soluble in water, HCl, and methanol and are insoluble in other common organic solvents. Our attempts to crystallize **5** and **6** from water, HCl, and methanol have been unsuccessful, however. ESI-MS provides evidence that the complexes are obtained in high purity. The ESI mass spectrum for **5** recorded in

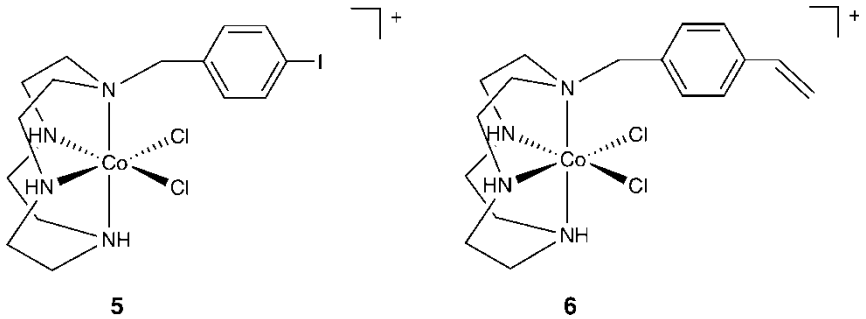


FIG. 1. Cobalt(III) cyclen complexes (counterions not shown).

aqueous methanol shows a molecular ion peak at $m/z = 467$, corresponding to loss of two chloride ligands and addition of a water molecule. Compound **6**, recorded in neat methanol, shows an intense molecular ion peak at $m/z = 417$ and two smaller peaks at 381 and 345, corresponding to loss of one and two chloride ligands, respectively.

The UV-visible spectra of **5** and **6** were recorded in MeOH and show two absorbances at 569 and 398, and 576 and 396 nm, respectively, which remain unchanged over time. These absorbances are consistent with previously reported dichloro(tetramine)cobalt(III) complexes, with chloride ligands in the *cis* configuration (Collman and Schneider, 1966). When the UV-visible spectrum of **5** was immediately recorded in water, the absorbances underwent a shift to 371 and 539 nm, and this is entirely consistent with the initial aquation of **5** to give an aquo-chloro complex which in turn slowly undergoes aquation to give the pink bis aquo complex.

In summary, we have developed a simple synthetic protocol for the monoalkylation of the tetraazamacrocyle cyclen using the carefully controlled addition of a suitable alkylating agent. The procedure is tolerant of a variety of functional groups and is amenable to scale-up. The monofunctionalized cyclen ligand coordinates to Co(III) in the expected manner to give octahedral complexes. Further studies on the postalkylation derivitization of monofunctionalized tetraazamacrocycles are curently in progress.

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