Tetrahedron Vol. 47, No. 42, pp. 8863-8868, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

SYNTHESIS OF NEW MULTIDENTATE LIGANDS FOR THE COORDINATION OF INDIUM(III), GADOLINIUM(III) AND THORIUM(IV)

Yizhen Sun, Arthur E. Martell and Michael J. Welch†*

Department of Chemistry
Texas A&M University
College Station, TX 77843-3255, U. S. A.

†The Edward Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri 63110

(*Received in USA* 5 *September* 1991)

Abstract. Efficient syntheses are described for five new multidentate ligands containing 3-hydroxy-6-methyl-2-pyridyl donor groups: 4,7,10-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1-oxa-4,7,10-triazacyclododecane, **2**; 4,10,13-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,7-dioxa-4,10,13-triazacyclopentadecane, **3**; 4,10,16-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,7,13-trioxa-4,10,16-triazacyclooctadecane, **4**; 1,4,7,10-tetrakis(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane, **5**; 1,4,8,11-tetrakis(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane. **2**, **3**, and **4** are designed for the coordination of In(III) and Gd(III); **5** and **6** are for Th(IV).

Introduction

A new multidentate ligand consisting of 3-hydroxypyridyl substituents into triazacyclononane macrocycle, 1,4,7-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane, **1**, was prepared and investigated in this laboratory.[1,2] This ligand was found to have unusually high affinity for Fe(III), that its stability constant is greater than that recently reported for enterobactin.[3] This ligand also has the advantage of lower pK's of the phenolate donors.

New chelating agents for other trivalent metal ions with larger ionic radius are of medicinal interest. A series of triaza macrocyclic ligands have been synthesized in which the three ring nitrogens are separated by one, two and three oxa groups, and the macrocyclic aza groups are substituted with the same pendant substituents the 3-hydroxy-6-methylpyridyl-methyl group (see Figure 1, compounds **2**, **3**, **4**). In addition to the triaza macrocyclic ligands, the tetraaza complexes **5** and **6** (Fig. 2) were also prepared. These ligands are designed for complexing metal ions having coordination numbers of eight such as Th(IV) and other actinides.

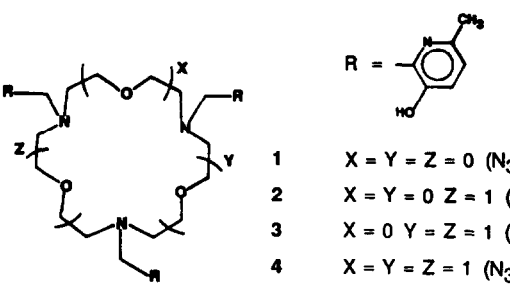


Figure 1

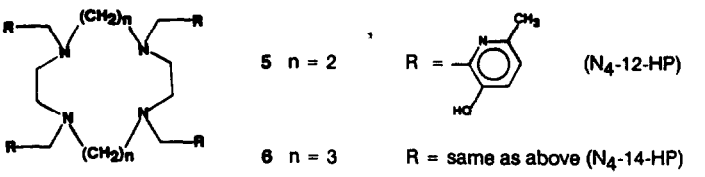


Figure 2

The triazacyclononane derivative with hydroxylpyridyl pendant groups, **1**, has a high affinity for Fe(III) and Ga(III). Also, the triacetate of the triazatrioxa macrocycle, analogous to **4**, forms a stable gadolinium complex with all nine-coordination sites

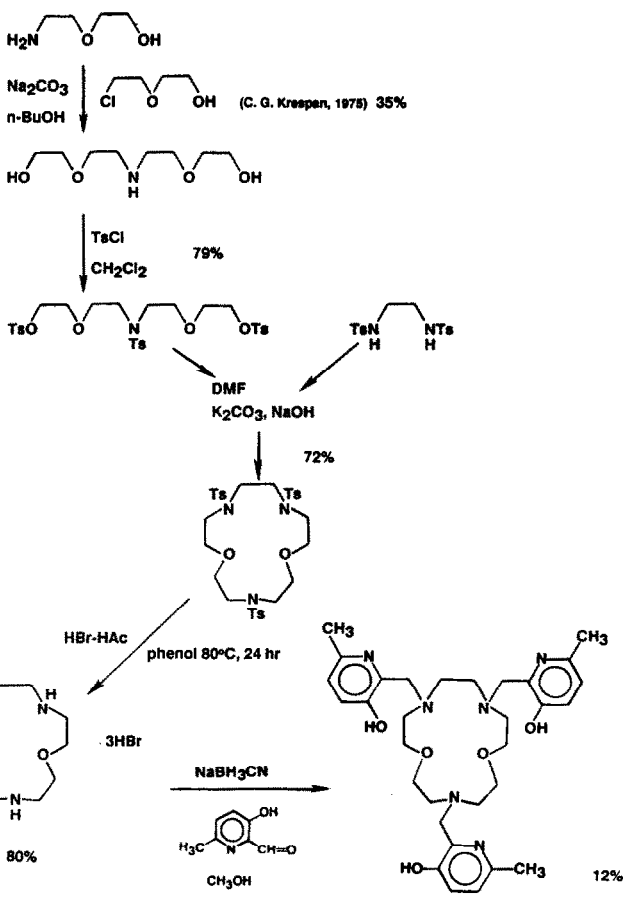
of the ligand bound to the metal ion.[6] One can see a progression of macrocyclic derivatives containing 3-hydroxy pyridyl groups which differ in the size of the macrocyclic and the corresponding size of the cavity provided to the metal ion. Thus while the lower members of the series are selective for Fe(III) and Ga(III), the higher members of the series would be suitable for the larger lanthanide ions. The intermediate member of the series, **2**, would be suitable for trivalent metal ions of intermediate size such as as In(III).

The 12- and 14-membered tetraaza macrocyclics, derivatized with four hydroxypyridyl groups to give compounds **5** and **6** provide eight donor groups to the metal ions and are suitable for the actinides, Th(IV) and similar metal ions. While a number of actinides have stable tetravalent forms and would tend to form stable complexes with ligands that provide a -4 charge, the ligands involved should also have high affinities for the lathanides.

Results and Discussion

Although there are published procedures for the syntheses of 1,7-dioxo-4,10,13-triazacyIcopentadecane (N_3O_2)[4] and 1,7,13-trioxa-4,10,16-triazacyclooctadecane (N_3O_3),[5,6] we found that it is simpler to prepare these compounds through an intermediate: 3,9-dioxa-6-azaundecane-1,11-diol (Scheme 1), which can be prepared in large quantity with the modified procedure of Krespan.[7]

SCHEME 1

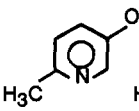
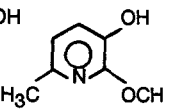


Ligand **1** was prepared by the procedure routinely used for the Mannich reaction. However, when similar conditions were used for the preparation of ligand **2**, a large amount of undesirable by-product formed, and the yield was very low. For ligands **2**, **4**, **5** and **6** benzene was used as the solvent instead of ethanol or methanol and the water in the reaction mixture was gradually removed by azeotropic distillation. Yields of the purified products obtained were 75%, 48%, 25% and 51%, respectively.

However, when the above Benzene-Mannich procedure was used to prepare ligand **3**, the yield was lower than 8%, the main by-product was a partially substituted compound with one of the nitrogens blocked by some unknown substituent (from TLC and ^{1}H NMR). Reductive amination was used for the preparation of this ligand, A 12% yield was obtained, the di-substituted by-product, which was collected from silica gel chromatography, can be realkylated. The total yield was ~30%.

Table 1 shows the relative R_f values of the six ligands and the two starting materials which were used to prepare them. We can see that as one, two and three oxo groups added to the macrocycles, the R_f values increase (the polarities

Table 1. Relative R_f Values of Ligands **1**, **2**, **3**, **4**, **5**, **6**. Developed by $CHCl_3$:MeOH (v:v) = 9:1.

	N_3-HP	N_3O-HP	N_3O_2-HP	N_3O_3-HP	N_4-12-HP	N_4-14-HP		
Ligand	**1**	**2**	**3**	**4**	**5**	**6**		
R_f	0	0.29	0.47	0.52	0	0	0.49	0.41

decreased). Thus ligand N_3O_2-HP and N_3O_3-HP have very close R_f values to the corresponding starting pyridine derivatives. This means that these two ligands cannot be purified by the silica gel flash chromatography method alone. Since the two pyridine derivatives are much smaller molecules than the ligand they can be easily removed by vacuum distillation. So HMDS was used to silylate the reaction mixture. The excess starting material and other low boiling point impurities were removed after vacuum distillation at 0.1 mm Hg, 110-120°C for several hours. After this process, the product was very easy to purify by silica gel, and the trimethyl groups on the ligand were lost automatically, no other desilylation step was necessary.

The free ligand of **5** and **6** are insoluble in boiling toluene, benzene, ethanol and methanol. They can be dissolved in water with a small amount of acid.

Experimental

Materials and Methods. The compounds obtained from commercial sources were as follows: 2-(2-aminoethoxy)-ethanol, 2-(2-chloroethoxy)ethanol, triethyl amine, toluenesulfonyl chloride, ethylenediamine, 5-hydroxy-2-methylpyridine, sodium cyanoborohydride, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), hydrogen bromide, 30 wt % solution in acetic acid, phenol from Aldrich Chemical Company; 1,4,8,11-tetraazacyclotetradecane (Cyclam) from Strem Chemical; formaldehyde, 37% solution from J. T. Baker Chemical Company. All these material were used as supplied without further purification. The *thin layer chromatography plastic sheets, silica gel 60 F_{254} were from EM Science.* 3-Hydroxy-6-methyl-2-pyridinecarboxaldehyde was prepared by the method of Weis,[8] 1-oxa-4,7,10-triazacyclododecane and 1,4,7,10-tetraazacyclododecane were synthesized by the method of Richman and Atkins.[9] 1,7,13-Trioxa-4,10,16-triazacyclooctadecane trihydrobromide salt (N_3O_3.3HBr) was supplied as a generous gift from Professor Dian Chen.

The proton and carbon-13 NMR spectra were recorded with a Varian XL-200 spectrometer operating at 200 MHz, and the chemical shifts are reported in ppm relative to tetramethylsilane. The C, H, N analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

4,7,10-Tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1-oxa-4,7,10-triazacyclododecane (N_3O-HP), 2. Ground potassium hydroxide pellets, 0.39 g (87%, 0.006 m) were added to a suspension of 0.983 g N_3O-3HBr (0.002 m) and 10 ml absolute ethanol. This mixture was stirred at room temperature for 1 hr. The KBr was removed by filtration and the solvents were removed by vacuum distillation. Benzene, 10 ml, was added to the residue, then 0.55 g (0.0066 m) of 37% formaldehyde aqueous solution. This reaction mixture was stirred in a 40-50 °C bath for 10 min. 3-Hydroxy-6-methylpyridine, 0.72 g (0.0066 m) and 10 ml benzene were added, and the mixture was heated to reflux for 24 hr. The water in the reaction mixture was removed by azeotropic distillation. After cooling the reaction mixture was concentrated to about 3-4 ml and was loaded on 7 g of silica gel 60 (Aldrich Co. 28.854-9) (column size: 25x50 mm) which was pre-equilibrated with acetonitrile. The impurities were eluted by acetonitrile:methanol (v:v) = 98:2, and the product was eluted by $CHCl_3$:methanol (v/v) = 95:5. Totally 0.8 g pure product was obtained, yield = 75%. The product was recrystallized from toluene-heptane (v/v = 1:3). ^1H NMR ($CDCl_3$): 7.02-6.93 (m, 6H, 4 and 5-H of pyridyl); 3.93 and 3.91 (2 singlets, 6H, -CH2- of pyridylmethyl); 3.59 (t, 4H, $-CH_2-O-CH_2-$); 3.00, 2.95 and 2.82 (3 triplets, 12H, $-CH_2-N-$); 2.42 and 2.40(2 singlets, 9H, methyl). ^{13}C NMR ($CDCl_3$); 152.4, 152.3, 148.8, 148.5, 142.4 (2,3,6-C of pyridyl); 124.9, 124.6, 124.1, 124.0 (4,5-C of pyridyl); 70.3 ($-CH_2-$ of pyridylmethyl); 62.4 ($-CH_2-O-CH_2-$); 54,2,

52.0, 50.4 (-CH_2-N-CH_2-CH_2-N-; 23.9 and 23.8 (methyl). Anal. Calcd. for $C_{29}H_{40}N_6O_4.1/4H_2O$: C, 64.38; H, 7.49; N, 15.54. Found: C, 64.22; H, 7.76; N, 15.49.

1,7-Dioxo-4,10,13-triazacyclopentadecane trihydrobromide salt ($N_3O_2.3HBr$). A solution of 2-(2-aminoethoxy)ethanol, 42 g (0.40 m), 2-(-chloroethoxy)ethanol, 50 g(0.40 m) in 200 ml 1-butanol and 42 g (0.40 m) anhydrous sodium carbonate were mixed and heated to reflux for 1.5 hr. After cooling, the inorganic salt was removed by filtration. The solvent was removed by distillation under 5 mm Hg pressure. About 80 g brown oil was obtained. This mixture was vacuum distilled at 1 mm-0.1 mm Hg pressure. The distillate which was collected at 150-158 °C, 0.1 mm Hg was the pure product, 3,9-dioxa-6-azaundecane-1,11-diol, 27.3 g was obtained, yield = 35%. ^{1}H NMR ($CDCl_3$): 2.85 (t, 4H, HN-CH_2-); 3.59 and 3.64 (t, 8H, -CH_2-O-CH_2-); 3.72 (t, 4H, -CH_2-OH).

3,9-dioxa-6-azaundecane-1,11-diol, 9.65 g (0.05 m), triethylamine, 15.2 g (0.15 m) were dissolved in 15 ml of methylene chloride. Toluenesulfonyl chloride, 28.5 g (0.15 m) was dissolved in 38 ml methylene chloride. The diol solution was added dropwise to the toluenesulfonyl chloride solution in an ice-water bath within 40 min. The reaction mixture was allowed to stand in the refrigerator for 16 hr. To the reaction mixture 100 ml distilled water was added and the organic phase was separated. This CH_2Cl_2 solution was washed with cold 2 M HCl, Na_2CO_3 2% solution and saturated NaCl solution, and was filtered and dried with anhydrous Na_2SO_4 for 16 hr. CH_2Cl_2 was removed, 40 ml methanol was added to the oily product and the mixture was stirred in a salt-ice water bath (~-10-15 °C) for 1 hr then it was cooled in dry-ice, the supernatant solution was decanted and discarded. The white viscous material was vacuum dried under 5 mm Hg pressure for 30 min, 26 g product, which was 1,11-di(*p*-toluenesulfonyloxy)-6-(*p*-toluenesulfonyl)-3,9-dioxa-6-azaundecane and characterized by ^{1}H NMR was obtained, yield 79%. This product was pure enough for the next step, ring closure reaction. ^{1}H NMR ($CDCl_3$): 7.8 (m, 6H, 2-H of tosyl), 7.3-7.4 (m, 6H, 3-H of tosyl), 4.1 (m, 4H, -CH_2-OTs), 3.6 (m, 8H, -CH_2-O-CH_2-), 3.3 (t, 4H, -CH_2-NTs-CH_2-), 2.4 (s, 9H, methyl).

In a one liter three necked flask, N,N'-ditoluenesulfonylethylenediamine,[10] 21.3 g (0.059 m) was suspended in 300 ml DMF (dried by 4A molecular sieves). To this, 4.63 g sodium hydride (60% dispersion) was added, and this mixture was stirred at room temperature for 1 hr. With mechanical stirring, a solution of 38 g of the di-tosyl ester and 250 ml DMF was added to the di-Na^+ salt dropwise, while the temperature was maintained at 100-120 °C with an oil bath. After the addition was completed the reaction mixture was kept at this temperature with vigorous stirring for 6 hr, then allowed to stand at room temperature for 16 hr. The insoluble material was removed by filtration, and the DMF was removed by vacuum distillation. To the residue 280 ml water and 140 ml CH_2CL_2 was added. The CH_2Cl_2 phase was washed with 5% NaOH, 2M HCl and saturated NaCl solution, and was dried with anhydrous $MgSO_4$ for 24 hr. After removing the inorganic salt and solvent, 40 g pale yellow oil was obtained. This yellow oil was loaded on silica gel 60 and was eluted with benzene and benzene-ether mixture. The product was eluted out by benzene:ethylether (v/v) = 95:5 and 90:10. Totally 28 g colorless oil was obtained, yield = 72%. This colorless oil was 4,10,13-tritoluenesulfonyl-1,7-dioxy-4,10,13-triazacyclopentadecane which was characterized by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR ($CDCl_3$): 7.7 and 7.65 (d, 6H, 2-H of tosyl); 7.3 (m, 6H, 3-H of tosyl); 3.5 (m, 12H, 15,2,3,5,6,8-CH_2- of the cyclopentadecane); 3.4 (s, 4H, 11,12-CH_2- of the cyclopentadecane); 3.25 (t, 4H, 9,14, -CH_2- of the cyclopentadecane); 2.42 (s, 9H, methyl). ^{13}C NMR ($CDCl_3$): 143.7, 137.2, 136.0, 130.1, 127.7, 127.2 (aromatic carbons); 72.1 and 71.9 (-CH_2-O-CH_2-); 51.5, 50.8, 48.7 (-CH_2-NTs-); 21.8 (methyl).

To 9 g of the above tritosyl macrocyclic compound, 13.2 g phenol and 220 ml of hydrogen bromide, 30 wt % solution in acetic acid were added and this mixture was heated in an oil bath at 40-50 °C 2 hr, 50-60 °C 1 hr and 80-85 °C for 20 hr. A large amount of white precipitate was separated. After cooling at room temperature the white precipitate was collected by filtration and was washed with 3/80 ml ethyl ether. This product was redissolved in water and extracted with ethyl ether. The aqueous solution was filtered with Whatman No.42 filter paper. To the concentrated aqueous solution, ethyl alcohol was added portionwise, and the mixture was allowed to stand in the refrigerator for 6 hr. The product was collected by filtration and washed with absolute ethanol and ethyl ether. After vacuum drying over P_2O_5 at room temperature for 20 hr, 4.96 g product was obtained, yield = 83%. ^{1}H NMR (D_2O, acetone as internal standard, 2.05 ppm): 3.68-3.8 (m, 8H, -CH_2-O-CH_2-); 3.45 (s, 4H, -NH-CH -CH -NH-); 3.2-3.36 (m, 8H, NH-CH -CH -O-). ^{13}C NMR (D_2O acetone as internal standard, 29.2 ppm): 64.8

and 63.8 ($-CH_2-O-CH_2-$); 45.5, 44.4, 41.1 ($-CH_2-NH^+{}_2-$). Anal. Calcd. for $C_{10}H_{26}N_3O_2Br_3 \cdot 1/2H_2O$: C, 25.59; H, 5.76; N, 8.96. Found. C, 25.45; H, 5.53, N, 9.34

4,10,13-Tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,7-dioxa-4,10,13-triazacyclopentadecane (N_3O_2-HP), 3. Ground KOH pellets (87%), 0.13 g (0.002 m) were added to a mixture of 0.92 g (0.002 m) $N_3O_2 \cdot 3HBr$ and 3 ml of methanol. After stirring for 15 min, 0.82 g (0.006 m) 3-hydroxy-6-methyl-2-pyridinecarboxaldehyde and 0.26 g of sodium cyanoborohydride were added. After the reaction mixture was stirred at room temperature for 40 hr the solvent was removed by vacuum distillation. To the residue, 10 ml H_2O was added and 2.5 M NaOH was added to this mixture until pH of the aqueous solution became 9. Chloroform (3/10 ml) was used to extract the product and the aqueous phase was discarded. The chloroform solution was filtered and dried with anhydrous $MgSO_4$ for 16 hr. After removing the magnesium salt and $CHCl_3$ a brown oil was obtained. To this 5 ml of HMDS was added and the reaction mixture was heated in a 110-120 °C oil bath for 6 hr. The reaction mixture was vacuum distilled at 30 °C/20mm Hg to remove the excess HMDS, then at 110-120 °C/0.1 mm Hg for 6 hr. Several ml of chloroform were added to the dark brown residue in the distillation flask. The $CHCl_3$ solution was loaded on 7 g silica gel 60 in a 25 x 50 mm column. The silica gel was pre-equilibrated with chloroform. Pure $CHCl_3$ was used to elute the impurities, the product was eluted out by $CHCl_3$:MeOH (v:v) = 98:2, its R_f value is 0.47 when developed by $CHCl_3$:MeOH (v:v) = 9:1; 0.14 product was obtained, yield = 12%. After nearly all the product had been collected, the column was washed with $CHCl_3$:methanol (v:v) = 9:1, to collect the incompletely substituted product (mostly, the disubstituted compound). After retreatment of this disubstituted product with 3-hydroxy-6-methyl-2-pyridinecarboxaldehyde and $NaBH_3CN$ and working up with the above procedure another 0.21 g pure product was obtained, total yield =30%. ^1H NMR ($CDCl_3$): 7.1-6.9 (m, 6H, 4,5-H of pyridyl); 3.94 (s, 6H, $-CH_2-$ of pyridylmethyl); 3.58 (t, 8H, $-CH_2-O-CH_2-$); 3.03 (s, 4H, $-N-CH_2-CH_2-N-$); 2.88 and 2.85 (2 triplets;, 8H, $-N-\underline{CH_2}-CH_2-O-$); 2.44 and 2.42 (2 singlets, 9H, methyl). ^{13}C NMR ($CDCl_3$); 152.5, 152.3, 148.4, 148.1, 143.0, 141.9 (3, 2.6-C of pyridyl); 124.5, 124.3, 123.6 (4,5-C of pyridyl); 69.0 and 68.4 ($-CH_2-$ of pyridylmethyl); 61.4 and 60.9 ($-CH_2-O-CH_2-$); 55.1, 54.3, 52.8 ($-N-CH_2-$); 23.7 (methyl). Anal. Calcd. for $C_{31}H_{44}N_6O_5 \cdot 2.5H_2O$: C, 59.52; H, 7.84; N, 13.44. Found: C, 59.35; H, 7.08; N, 13.29.

4,10,16-Tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,7,13-trioxa-4,10,16-triazacyclooctadecane (N_3O_3-HP), 4. Ground KOH pellets, 0.19 g (87%, 0.003 m) was added to a suspension of 0.504 g (0.001 m) of $N_3O_3 \cdot 3HBr$ and 10 ml absolute ethanol, and this mixture was stirred at room temperature for 1 hr. The KBr was removed by filtration, the solvents by vacuum distillation. To the white residue (N_3O_3) obtained 10 ml of benzene was added, then 0.28 g (0.0033 m) 37% formaldehyde solution, and the mixture was stirred at 40-50 °C bath for 10 min. 3-hydroxy-6-methyl-2-pyridine, 0.36 g (0.0033 m) and another 10 ml of benzene were added and the reaction mixture was heated to reflux for 20 hr, the water in the system was removed by azeotropic distillation. After cooling and removing the solvent, 15 ml HMDS was added and the mixture was heated in a 110 °C bath for 6 hr. Vacuum distilled to remove excess HDMS and other volatile material. The residue was vacuum dried at 100 °C 0.1 mm Hg for 6 hr. The brown oil obtained was dissolved in 3 ml of $CHCl_3$ and was loaded on 7 g of silica gel 60 which was pre-equilibrated with $CHCl_3$. $CHCl_3$ (3 x 30 ml) was used to remove impurities; $CHCl_3$:CH_3OH (v:v) = 99:1 was used to elute the product. After vacuum drying at 1 mm Hg. 40 °C for 2 hr, 0.3 g pure product was obtained , yield = 48%. ^1H NMR ($CDCl_3$): 6.96 (m, 6H, 4,5-H of pyridyl); 3.94 (s, 6H, $-CH_2-$ of pyridylmethyl); 3.60 (t, 12H, $-CH_2-O-CH_2-$); 2.86 (t, 12H, $-CH_2-N-CH_2-$); 2.43 (s, 9H, methyl). ^{13}C NMR ($CDCl_3$): 152.3, 148.0, 142.6, 124.1, 123.3 (carbon in pyridyl ring); 68.46 ($-CH_2-$ in pyridyl ring); 60.79 ($-CH_2-O-CH_2-$); 54.48 ($-CH_2-N-CH_2-$); 23.59 (methyl). Anal. Calcd. for: $C_{33}H_{48}N_6O_6 \cdot 2H_2O$: C, 60.00; H, 7.89; N, 12.73. Found: C, 59.89; N, 7.51; N, 12.48.

1,4,7,10-Tetrakis(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4-7,10-tetraazacyclododecane (N_4-12-HP), 5. Ground KOH pellets (87%), 0.52 g (0.008 m) was added to a suspension of 0.99 g (0.002 m), 1,4,7,10-tetraazacyclododecane tetrahydrobromide salt and 10 ml of ethanol. This mixture was stirred at room temperature for 1 hr then the KBr and solvent were removed to obtain the free base (N_4-12, cyclen). To the N_4-12, l0 ml benzene and 0.67 (0.008 m) 37% formaldehyde was added, and heated in 40-50 °C for 10 min. To this reaction mixture, 0.87 g (0.008 M) of 3-hydroxy-6-methylpyridine and 10 ml benzene were added. The reaction mixture was heated to reflux for 16 hr, while the water in the system was removed azeotropically. Benzene was removed by vacuum distillation, and 15 ml ethanol was added to the brown residue and heated to

boiling. A pale yellow precipitate was separated from the brown solution, and it was collected by filtration. This crude product was suspended in 15 ml methanol and heated to reflux for 1 hr. After cooling to room temperature the white precipitate was separated by filtration and washed with CH_3OH and ethyl ether, then air dried, 0.33 g pure product was obtained, yield = 25%. ^1H NMR (D_2O-DCl, acetone as internal standard, 2.05 ppm): 7.71 (d, 4H, 4-H of pyridyl); 7.50 (d, 4H, 5-H of pyridyl); 4.20 (s, 8H, -CH_2- of pyridylmethyl); 3.31 (s, 16H, -CH_2-N-CH_2-); 2.51 (s, 12H, methyl). ^{13}C NMR (D_2O-DCl, acetone as internal standard, 29.2 ppm): 153.7, 146.5, 132.7, 132.4, 128.7 (carbons of pyridyl); 49.73 (-CH_2- of pyridylmethyl); 48.38 (-CH_2-N-CH_2-); 18.54 (methyl). Anal. Calcd. for $C_{36}H_{48}N_8O_4.2H_2O$: C, 62.43; H, 7.51; N, 16.18. Found: C, 62.75; H, 6.94; N, 16.04.

1,4,8,11-Tetrakis(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane (N_4-14-HP), 6. Cyclam 0.4 g (0.002 m) was used as starting material. The procedure is the same as the preparation of N_4-12-HP, 0.70 g pure product was obtained, yield = 51%. ^1H NMR (D_2O-DCl, acetone as standard): 7.87 (d, 4H, 4-H of pyridyl); 7.62 (d, 4H, 5-H of pyridyl); 4.38 (s, 8H, -CH_2- of pyridylmethyl); 3.48 (s, 8H, -N-CH_2-CH_2-N-); 3.17 (7, 8H, -$\underline{CH_2}$-CH_2-$\underline{CH_2}$-N-); 2.55 (s, 12H, methyl); 2.15 (b, 4H, -N-CH_2-$\underline{CH_2}$-CH_2-N-). ^{13}C NMR (D_2O-DCl, acetone as standard): 153.4, 146.6, 133.7, 129.8, 129.4 (carbons of pyridyl); 50.14 (-CH_2- of pyridylmethyl); 49.18 (-N-CH_2-CH_2-N-); 45.73 (-N-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-N-); 19.0 (-N-CH_2-$\underline{CH_2}$-CH_2-N-); 17.8 (methyl). Anal. Calcd. for $C_{38}H_{52}N_8O_4$: C, 66.67; H, 7.60; N, 16.37. Found: 66.61; H, 7.70; N, 16.02.

Acknowledgement. This work was supported by the National Cancer Institute, U. S. Public Health Service, under contract No. CA-42925 and by U.S. Public Health Service, National Heart, Lung and Blood Institute, Grant No. HL-42780.

References

1. Sun, Y.; Martell, A. E.; Reibenspies, J. H.; Welch, M. J. *Tetrahedron*, **1991**, *47(3)*, 357.
2. Martell, A. E.; Motekaitis, R. J.; Welch, M. J. *J. Chem. Soc. Chem. Commun.* **1990**, 1748.
3. Loomis, L. D.; Raymond, K. N. *Inorg. Chem.* **1991**, *30*, 906.
4. Broan, C. J.; Cox, J. P. L.; Craig, A. S.; Kataky, R.; Parker, D.; Harrison, A.; Randall, A. M.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 2*, **1991**, 97.
5. Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 5022.
6. Chen, D.; Squattrito, P. J.; Martell, A. E.; Clearfield, A. *Inorg. Chem.* **1990**, *29*, 4366.
7. Krespan, C. G. *J. Org. Chem.* **1975**, *40*, 1205.
8. Weis, C. D. *J. Heterocyclic Chem.* **1978**, *15*, 29.
9. Richman, J. K.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268.
10. Dietrich, B.; Hosseini, M. W.; Lehn, J. M.; Sessions, R. B. *Helv. Chim. Acta* **1983**, *66*, 1261.