*Tetrahedron* Vol. 47, No. 3, pp. 357-364, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

# SYNTHESES OF MULTIDENTATE LIGANDS CONTAINING HYDROXYPRYIDYL DONOR GROUPS

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

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

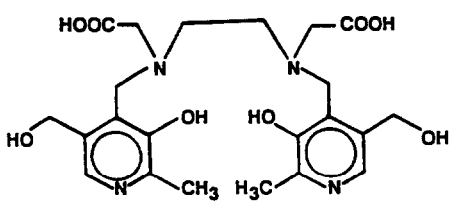
†The Edward Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri 63110

(*Received in USA* 4 *October* 1990)

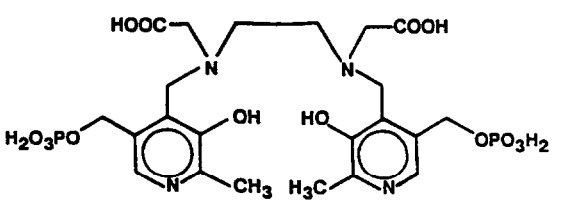
**Abstract**. Efficient syntheses are described for three new multidentate ligands containing 3-hydroxy-6-methyl-2-pyridyl donor groups; N,N′-bis(3-hydroxy-6-methyl-2-pyridylmethyl)ethylenediamine-N,N′-diacetic acid, N,N″-bis(3-hydroxy-6-methyl-2-pyridylmethyl)diethylenetriamine-N,N′,N″-triacetic acid, and N,N′,N″-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane.

## Introduction

The first multidentate ligand containing hydroxypyridyl donor groups, N,N′-bispyridoxylethylenediamine-N,N′-diacetic acid (PLED), **1**, was prepared and investigated in this laboratory.[1,2] This hexadentate ligand was found to have high affinities for trivalent metal ions (Ga(III) and Fe(III)), low ligand protonation constants, and high water solubility. Recently, Rocklage et al.[3] prepared the 5,5′-bisphosphate analog of PLED, N,N′-dipyridoxylethylenediamine-N,N′-diacetic acid 5,5′-bisphosphate (DPDP), **2**. and studied its divalent metal ion complexes for NMR imaging contrast enhancement. The disadvantage of these 3-hydroxy-4-pyridyl type ligands is that they contain sterically demanding methyl groups derived from the use of commercially available pyridoxal and pyridoxal-5-phosphate as starting materials. The pyridine nitrogens *meta* to the phenolic groups have the important functions of lowering the pK′s of the ligands; however, they are also attacked by the bromoacetate employed in the final alkylation step of the ligand synthesis, thus producing a poor yield of the desired product.




**PLED, 1**

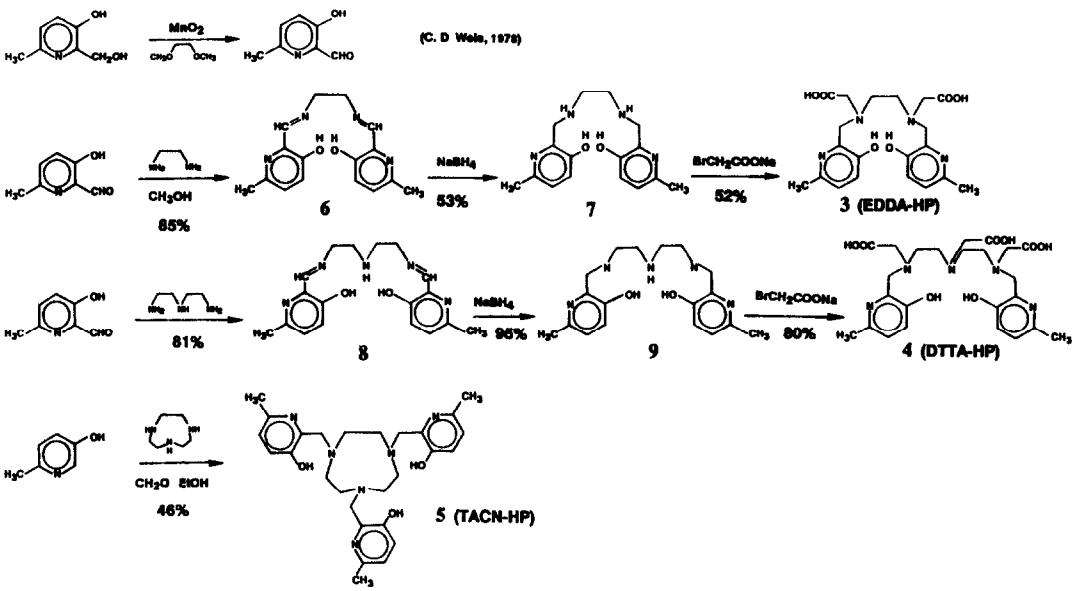



**DPDP, 2**

In order to solve these problems a series of new 3-hydroxy-2-pyridyl containing ligands were designed and synthesized. The new sexadentate ligands, **3** and **5**, designed for Ga(III), Fe(III) and In(III) and one octadentate ligand, **4**, designed for In(III) and Gd(III) ions are reported. By changing the positions of the pyridine nitrogen and the substituted methyl group, from that which exists in pyridoxal derivatives, ligands **3** and **4** can be

prepared from a simple aldehyde, 3-hydroxy-6-methyl-2-pyridinecarboxaldehyde. Because the 2- and 6- positions of the pyridine rings are blocked in compounds **7** and **9**, the undesirable quaternization side-reaction in the final alkylation of the synthesis is avoided. Ligand **5**, which is designed to form a neutral complex with small trivalent metal ions such as those of Ga(III) and Fe(III), can be prepared readily from triazacyclononane, formaldehyde, and 3-hydroxy-6-methyl-pyridine by the standard Mannich reaction.

**Scheme**




## Results and Discussion

**Synthesis**. As suggested above, the synthetic routes described in the experimental for the preparation of **3**, **4**, and **5** by the use of the modified Mannich reaction, or Schiff base formation followed by reduction and alkylation with bromoacetate, proved to be efficient, and the products were found to be relatively free of impurities, leading to greater ease of purification than was possible in the preparation of the analogous ligands **1** and **2**. The overall yields based on the staring materials (aldehyde or triazacyclononane) were 23% for **3**, 62% for **4**, and 46% for the one-step synthesis of **5**.

In the ligands derived from pyridoxal, **1** and **2**, the hydrophilic $HOCH_2$-groups and their phosphate esters do not assist in metal ion coordination, and impart high water solubility to these ligands, thus complicating the purification process. Their Ga(III) and In(III) chelates are also too hydrophilic to be effective imaging agents.[4] The new ligands, **3**, **4**, and **5**, do not have the hydrophilic groups, but are soluble both in water and in a wide range of organic solvents. They can be purified chromatographically with a silica gel column; ligand **5** can also be recrystallized from toluene.

**Metal Ion Affinities.** A detailed potentiometric study of metal ion affinities of **3**, **4**, and **5** is in progress.[8] Preliminary results indicate, as suggested in the introduction, that the metal ion complexes of **3** are somewhat more stable than those of **1**. Qualitative information obtained with **5** suggests that its complexes with small trivalent ions are exceptionally stable, and may be the most stable complexes obtained thus far with synthetic ligands. It was found,[8] for example, that its 1:1 complexes with Ga(III) and Fe(III) are not dissociated appreciably in acid solution, at pH values as low as 1.0. Moreover, the ligands EDTA, DTPA, and CDTA, which are frequently used as competing ligands for removal of metal ions from other chelating agents at low pH, do not compete at all with the Fe(III) chelate of **5**, even at pH values as low as 1.0. A rough estimate of the stability constant of the iron(III) chelate of **5** was obtained by measuring the Fe(II)/Fe(III) reduction potential at low pH, and was found to be ~$10^{50}$, a little lower than $10^{52}$, estimated for enterobactin by Raymond.[9] On the other hand, because of the lower ΣpK of **5** relative to that of enterobactin, Fe(III) is bound more strongly at physiological pH than it is by enterobactin.

Because of the basicities of the three uncoordinated pyridine nitrogens in **5**, the Fe(III) chelate is triprotonated in acid solution, to give a complex having the formula $FeLH_3^{3+}$. As the pH is increased hydrogen ions are dissociated so that above pH 6 the formula of the complex is FeL, with zero charge. The electron-withdrawing effect of the pyridine nitrogens would be greatly amplified by protonation , so that the protonated forms in acid solution would be much less stable than the completely deprotonated high-pH form of the chelate.

**Structure of the Fe(III) Chelate.** Crystals of the Fe(III) chelate **5** were obtained at pH 4, and preliminary results of the X-ray crystal structure study[10] indicate the arrangement of donor atoms illustrated in Figure 1*. Only one protonated pyridine nitrogen is found, probably because of the fact that the complex is only partially protonated at this pH. Therefore it was decided to study the structure of the completely deprotonated iron(III) complex crystallized from more strongly acid solution, at about pH 2. That has been accomplished, and the structure determination is now underway.[10]

---

* Crystal data for Figure 1: $C_{27}H_{58}N_6O_{15}ClFe$, $M$ = 798.1 g $mol^{-1}$, rhombohedral, space groups R $\bar{3}$ (No.148), $a$ = 15.368(9)Å, $c$ = 30.32(4)Å, $V$ = 6202(11)Å$^3$, $Z$ = 6.00, $D_x$ = 1.282 g $cm^{-3}$, F(000) = 2550 $e^-$, MoK$\alpha$ $\lambda$ = 0.71073Å radiation, $\mu$ = 4.91 $cm^{-1}$, $R$ = 0.094, wR = 0.106. 3906 reflections collected at 193°K employing $\theta/2\theta$ scan between 4.0° ≤ 2$\theta$ ≤ 40.0° on a Nicolet R3m X-ray difffractometer. Structure solved by Direct Methods (SHELXTL-PLUS). 773 unique observed reflections [$I \geq 4.0\ \sigma(I)$] used to refine 155 parameters by full-matrix least-squares to convergence [SHELXTL-PLUS, quantity minimized $\sum w(F_c-F_o)^2$, w = $(\sigma^2F + 0.00001F^2)^{-1}$]. Hydrogen atoms placed in idealized positions. Full details are given in Supplementary Material. Atomic co-ordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center. See Notice to Authors, Issue No.1.

The closest analogs of the Fe(III) chelate of **5** in the literature are the Fe(III) chelate tris(2-hydroxybenzyl)triazacyclononane and its 2-hydroxy-3-tert-butylbenzyl analog recently described by Auerbach et al.[11] Also, the structure of the Ga(III) chelate of N,N′,N″-tris(2-hydroxy-3,5-dimethylbenzyl)-1,4,7-triazacyclononane has been described by Moore et al.[12] In both cases the triazacyclononane macrocyclic ring forms the face of a distorted octahedron. Other Fe(III) and Ga(III) complexes of tri-N-substituted hexadentate ligands derived from 1,4,7-triazacyclononane, such as the triacetate, NOTA show considerable distortion of the structure toward that of a triangular prismatic configuration.[13] The distortion is apparently due to the restrictions of the bridge (i.e., the connecting linkages are too short) between the nitrogens of the macrocycle and the oxygen donors of the opposite face of the distorted octahedron. It is seen that the preliminary structure assigned to the Fe(III) chelate of **5** in Figure 1 is quite analogous to the pseudo octahedral structure of the corresponding phenolic analog illustrated in Figure 2, described by Auerbach et al.[11]

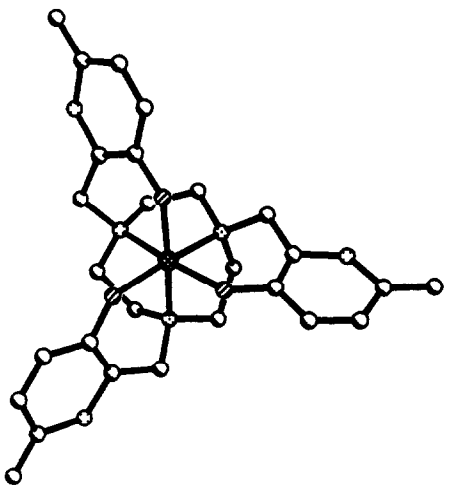


**Figure 1** Structure of the monoprotonated Fe(III) complex of N,N′,N″-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-N,N′,N″-triazacyclononane at pH = 4.

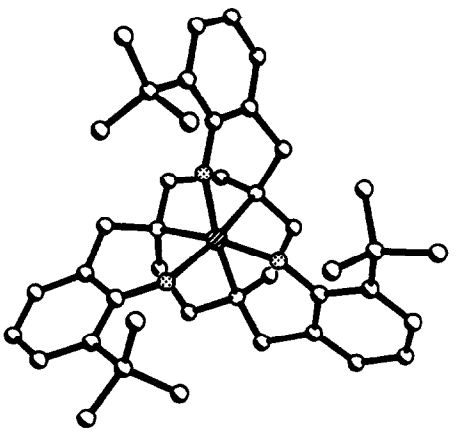


**Figure 2** Structure of the neutral Fe(III) complex of N,N′,N″-tris(3-tert-butyl-2-hydroxybenzyl)-N,N′,N″-triazacyclononane.[11]

## Experimental

**Materials and Methods**. 2,6-Lutidine-$\alpha^2$,3-diol, activated manganese dioxide, 5-hydroxy-2-methylpyridine, sodium borohydride, bromoacetic acid, silica gel, Merck, grade 60, were purchased from Aldrich Chemical Company and were used without further purification. Ethylene glycol dimethyl ether, ethylenediamine, and diethylenetriamine were purified with conventional methods.[5] 3-Hydroxy-6-methyl-2-pyridinecarboxaldehyde was prepared by the method of Weis,[6] and 1,4,7-triazacyclononane was synthesized by the method of Richman and

Atkins.[7] Other solvents were purchased from Fisher Scientific or Aldrich and were used without further purification.

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 mass spectra were obtained with a VG analytical 70S high resolution double focusing magnetic sector spectrometer, with attached VG analytical 11/250J data system. The C, H, N analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

**N,N′-bis(3-hydroxy-6-methyl-2-pyridoxylidene)ethylenediamine, 6.** 3-Hydroxy-6-methyl-2-pyridinecarboxaldehyde, 2.74 g (0.02 mole), was dissolved in 35 ml of methanol, to which 0.57 g of freshly distilled ethylenediamine was added. The reaction mixture was stirred in a 50-60°C bath for 30 min, and it was then allowed to stand at 5°C for 20 hr. The yellow crystalline Schiff base was filtered and washed with cold methanol and ethyl ether, and was air dried at room temperature for 20 hr. 2.4 g of pure product was obtained, yield = 85%, m.p. = 163-164°C.

$^1$H NMR (in $CDCl_3$): 8.57 (s, 2H, -CH=N-); 7.22 (d, 2H, 4-proton of pyridoxylidene); 7.09 (d, 2H, 5-proton of pyridoxylidene); 4.02 (s, 4H, ethylene); 2.50 (s, 6H, methyl). $^{13}$C NMR (in $CDCl_3$): 168.5 (-CH=N-); 156.3, 135.7, 126.6, 125.5 (pyridoxyl carbons); 60.0 (ethylene); 23.7 (methyl). Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.43; H, 6.04; N, 18.79. Found: C, 64.59; H, 6.09; N, 18.79. FAB. M.S. $(M+H)^+$ = 299.

**N,N′-bis(3-hydroxy-6-methyl-2-pyridylmethyl)ethylenediamine, 7.** 3.92 g (0.013 mole) of the Schiff base was suspended in 85 ml of absolute ethanol, to which 0.48 g (0.013 mole) of $NaBH_4$ was added portionwise. The solution became colorless. It was stirred at room temperature for 1 hr. The solvent was removed by distillation. To the residue, 10 ml of water was added and 2.5 M HCl was used to adjust the pH of the solution to 9.0. After removal of the water by evaporation, 160 ml of benzene was added and the mixture was distilled azeotropically, from the clear dry hot benzene solution, 2.9 g of pale yellow oil was obtained. It was dissolved in 30 ml of boiling toluene, filtered hot, and cooled in a freezer for 2 days. The crystalline product was collected by filtration, and was washed by cold toluene and ethyl ether. After it was vacuum dried at 55°C and 0.1 mm Hg for 6 hr, 2.05 g of pure product was obtained, yield = 53%. $^1$H NMR (in $CDCl_3$): 7.0 and 6.9 (d, 4H, 4 and 5 protons of pyridyl);4.16 (s, 4H, $-CH_2-$ of pyridylmethyl); 2.89 (2, 4H, ethylene); 2.43 (s, 6H, methyl). $^{13}$C NMR (in $CDCl_3$): 152.4, 148.6, 142.2, 124.5, 123.6 (carbons of pyridyl); 55.3 ($-CH_2-$ of pyridylmethyl); 48.6 (ethylene); 23.8 (methyl). Anal. Calcd. for $C_{16}H_{22}N_4O_2$: C, 63.58; H, 7.28; N, 18.54. Found: C, 63.68; H, 7.33; N, 18.16. FAB M.S. $(M+H)^+$ = 303.

**N,N′-bis(3-hydroxy-6-methyl-2-pydridylmethyl)ethylenediamine-N,N′-diacetic acid (EDDA-HP), 3.** 1.35 g (0.0045 mole) of N,N′-bis(3-hydroxy-6-methyl-2-pyridylmethyl)ethylenediamine was dissolved in 24 ml of water containing 0.715 g of 50% NaOH solution (0.0089 mole). Bromoacetic acid, 1.24 g (0.089 mole), was dissolved in 24 ml of water in an ice water bath. To this solution, 0.75 g (0.0089 mole) of $NaHCO_3$ was added portionwise. The two solutions were mixed and the reaction mixture was heated to 40°C with a water bath. NaOH (50% solution) was used to maintain the pH of the solution in the range 11.8-12.3 for 6 hr. The reaction mixture was then allowed to

stand at room temperature. for 16 hr. 6N HCl was added to the reaction solution until pH was reduced to 4.5. This solution was evaporated to dryness. To the pale yellow residue thus obtained 15 ml of methanol was added. The insoluble inorganic salts were removed by filtration. The filtrate was concentrated to 3-4 ml and was loaded on a column of silica gel 60. The loaded column was eluted with methanol, and the first 3 to 4 collections which contained $Br^-$ and $Cl^-$ salts, were discarded. The eluants which showed one spot on a TLC plate (Rf = 0.55 developed by methanol) were combined and were concentrated to 10 ml. Upon the addition of 30-40 ml of *i*-PrOH to the methanol solution, a large amount of white precipitate separated out. The crude material was reprecipitated from MeOH-*i*-PrOH solution, and 0.97 g product was obtained, yield = 52% (after vacuum drying at 50°C, 0.1 mm Hg for 5 hr).

$^1$H NMR (in $D_2O$-DCl): 8.0, 7.9 (d, 4H, 4 and 5 protons of pyridyl); 4.7 (s, 4H, -$CH_2$- of pyridylmethyl); 4.1 (s, 4H, -$CH_2COO$); 3.7 (ethylene); 2.8 (s, 6H, methyl). $^{13}$C NMR (in $D_2O$-DCl): 173.1 (-COOH); 155.0 (3-C of pyridyl); 148.0 (2-C of pyridyl); 135.1 (4-C of pyridyl); 134.3 (6-C of pyridyl); 130.9 (5-C of pyridyl); 55.7 (-$CH_2$- of pyridylmethyl); 53.1 (-$CH_2$- of acetate); 52.2 (ethylene); 19.6 (methyl). Anal. Calcd. for $C_{20}H_{26}N_4O_6.H_2O$; C, 55.04; H, 6.42; N, 12.84. Found: C, 54.84; H, 6.29; N, 12.50. FAB M.S. $(M+H)^+$ = 419.

**N,N″-bis(3-hydroxy-6-methyl-2-pyridylmethylidene)diethylenetriamine, 8.** 3-Hydroxy-6-methyl-2-pyridinecarboxaldehyde, 2.74 (0.020 mole), was suspended in 12 ml of absolute ethanol, to which 1.0 g (0.010 mole) of freshly distilled diethylenetriamine was added. The reaction mixture was stirred and warmed in a 50°-60°C water bath for 20 min. After the ethanol was removed, 60 ml of benzene was added and the mixture was distilled azeotropically until all the water formed was removed. After removing the benzene by evaporation, 60 ml of cyclohexane was added. The mixture was heated to reflux and then filtered hot. The filtrate was allowed to stand at 5°C for 16 hr, and a finely crystalline product was obtained. The product was filtered out and vacuum dried under $P_2O_5$ at room temperature for 16 hr. 2.75 of Schiff base obtained, yield 81%.

$^1$H NMR (in $CDCl_3$): 8.52, (s, 2H, -CH=N-); 7.16, 7.09 (d, 4H, 4,5-H of pyridyl); 3.78 (t, 4H, =N-$CH_2$-); 3.03 (t, 4H, -$CH_2$-NH-$CH_2$-) ; 2.49 (s, 6H, methyl). $^{13}$C NMR (in $CDCl_3$): 167.9 (-CH=N-); 156.3, 148.8, 135.5, 126.2, 125.3 (2,3,4,5,6-carbon of pyridyl); 59.4 (=N-$CH_2$-); 49.6 (-$CH_2$-NH-$CH_2$-); 23.5 (methyl). Anal. Calcd. for $C_{18}H_{23}N_5O_2$: C, 63.34; H, 6.74; N, 20.53. Found: C, 63.93; H, 6.84; N, 20.73. FAB. M.S. $(M+H)^+$ = 342.

**N,N″-Bis(3-hydroxy-6-methyl-2-pyridylmethyl)diethylenetriamine, 9.** N,N″-Bis(3-hydroxy-6-methyl-2-pyridylmethylidene)diethylenetriamine, 2.75 g (0.0081 mole) was dissolved in 60 ml of absolute ethanol, to which 0.50 g of $NaBH_4$ was added portionwise at room temperature. The reaction mixture was stirred at room temperature for another hour, and the solvent was removed by evaporation. The residue was dissolved in 40 ml of water, and 2.5 M HCl was added to adjust the pH of the solution to 9.8. The solution was then evaporated to dryness. To the residue, 200 ml of benzene was added and the mixture was distilled azeotropically until no further water was removed. The hot benzene solution was filtered and the filtrate was concentrated to about 20 ml. A large amount of white precipitate separated and was filtered out. After

vacuum drying 2.15 g of pure product was obtained. From the filtrate, another 0.50 g of pure product was collected by evaporation. The total yield was 2.65, 95%.

$^1$H NMR ($CDCl_3$): 6.8-6.9 (d, 4H, 4,5-H of pyridyl); 3.9 (s, 4H, -$CH_2$- of pyridylmethyl); 2,6 (m, 8H, -$CH_2$-$CH_2$-NH-$CH_2$-$CH_2$); 2.4 (s, 6H, methyl). $^{13}$C NMR (in $CDCl_3$): 154.1 (3-carbon of pyridyl); 145.6, 145.0 (2,6-carbon of pyridyl); 124.6, 123.3 (4,5-carbon of pyridyl); 53.4 (-$CH_2$- of pyridylmethyl); 49.0, 48.5 (-$CH_2$-$CH_2$-NH-$CH_2$-$CH_2$-); 23.4 (methyl). FAB M. S. $(M+H)^+$ = 346.

**N,N″-Bis(3-hydroxy-6-methyl-2-pyridylmethyl)diethylenetriamine-N,N′,N″-triacetic Acid (DTTA-HP), 4.** 2.63 g (0.0076 mole) of N,N″-bis(3-hydroxy-6-methyl-2-pyridylmethyl)diethylenetriamine was dissolved in 55 ml of water containing 1.22 g of 50% NaOH solution (0.0152 mole). Bromoacetic acid, 3.48 g (0.025 mole), was dissolved in 35 ml of water in an ice-water bath. To this solution, 2.1 g (0.025 mole) of $NaHCO_3$ was added portionwise. The two solutions were mixed and the reaction mixture was heated to 40°C with a water bath while NaOH (50% solution) was used to maintain the pH of the solution at 11.8-12.0 for 6 hr. The reaction mixture was then allowed to stand at room temperature for 16 hr. 6N HCl was added to the reaction mixture to lower the pH to 4.5, and the water was removed by evaporation. To the pale yellow residue, 25 ml of methanol was added, and the insoluble inorganic salts were removed by filtration. The filtrate was concentrated to about 5 ml and was loaded on 80 g of silica gel 60 in a 70x55 mm (d/h) column which was then eluted with methanol. The first several collections (60 ml eluant each) contained inorganic salts, followed by some impurities of Rf = 0.54 and 0.39 (developed by methanol). The subsequent eluants which contained one spot of Rf = 0.28-0.29 on a TLC plate (developed by methanol) were combined and the resulting solution was concentrated to about 10 ml. After 30 ml of *i*-PrOH was added to this methanol solution, the product precipitated and was filtered off. After it was vacuum dried at 50°C, 0.1 mm Hg, for 5 hr, 3.0 g product was obtained, yield = 80%.

$^1$H NMR (in $D_2O$-DCl): 7.9, 7.7 (d, 4H, 4,5 protons of pyridyl); 4.29 (s, 4H, -$CH_2$- of pyridylmethyl); 4.3, 3.67 (s, 6H, -$CH_2$COO-); 3.3, 3.6 (t, 4H, 4H, the two ethylenes); 2.7 (s, 6H, methyl). $^{13}$C NMR (in $D_2O$-DCl): 176.7 (-COOH); 152.5 (3-C of pyridyl); 145.4 (2-C of pyridyl); 138.3 (4-C of pyridyl); 132.8 (6-C of pyridyl); 127.8 (5-C of pyridyl); 56.3 (-$CH_2$- of pyridylmethyl); 55.5, 53.8 (-$CH_2$- of acetate); 51.4, 50.6 (ethylene); 18.4 (methyl). Anal. Calcd. for $C_{24}H_{33}N_5O_5.H_2O$: C, 53.63; H, 6.52; N, 13.04. Found: C, 54.03; H, 6.65; N, 12 76. FAB M. S. $(M+H)^+$ = 520.

**N,N′,N″-Tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane (TACN-HP), 5.** To 1.04 g (0.008 mole) of 1,4,7-triazacyclononane in 20 ml of absolute ethanol solution, 2.12 g of 37% formaldehdye (J. T. Baker 2106-01) was added. Then, 2.6 g (0.024 mole) of 5-hydroxy-2-methylpyridine and 8 ml of absolute ethanol were added. This reaction mixture was heated to reflux under argon gas for 24 hr. The solvent was removed by evaporation at about 30 torr. The glassy orange residue (~4.9 g) which was obtained, was dissolved in 20 ml of chloroform, and the insoluble portion (~0.2 g of hydroxy-methylpyridine) was removed by filtration. The crude product was twice purified by flash chromatography with silica gel 60, by elution with $CHCl_3$:$CH_3OH$/9:1. After removal of the solvents and vacuum drying at 55°C, 0.1 mm Hg for 4

hr, 1.87 g pure product was obtained, yield = 46%. The product can be recrystallized from toluene.

$^1$H NMR ($D_2O$-DCl): 8.0 (d, 3H, arom.); 7.7 (d, 3H, arom.); 4.36 (s, 6H, -$CH_2$- of pyridylmethyl); 3.18 (s, 12H, -$CH_2$-$CH_2$- of triazacyclononane); 2.72 (s, 9H, methyl); $^{13}$C NMR (in $D_2O$-DCl): 153.6 (3-C of pyridyl); 146 (2-C of pyridyl); 135.4, 133.6, 129.3 (6,4,5-C of pyridyl); 51.1 (-$CH_2$- of pyridylmethyl); 49.4 (-$CH_2$-$CH_2$- of triazacyclononane); 18.3 (methyl). Anal. Calcd. for $C_{27}H_{36}N_6O_3.2.5H_2O$:C, 60.34; H, 7.64; N, 15.64. Found: C, 60.64; H, 6.84; N, 15.60. FAB M. S. $(M+H)^+$ = 493.

**Acknowledgement**. This work was supported by the National Cancer Institute, U. S. Public Health Service, under Contract No. CA-42925. The authors thank Dr. T. R. Sharp for fast atom bombardment mass spectral analysis. The R3m/V single-crystal X-ray diffraction and crystallographic computing system in the Crystal and Molecular Structures Laboratory of the Department of Chemistry, Texas A&M University, was purchased with funds provided by the National Science Foundation (CHE-8513273).

## References

1. Taliaferro, C. H.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1984**, *23*, 1188.

2. Motekaitis, R. J.; Yizhen Sun; Martell, A. E. *Inorg. Chim. Acta* **1989**, 159, 29.

3. Rocklage, S. M.; Cacheris, W. P.; Quay, S. C.; Hahn, F. E.; Raymond, K. N. *Inorg. Chem.* **1989**, 28, 477.

4. Green, M. A.; Welch, M. J.; Mathias, C. J.; Taylor, P.; Martell, A. E. *Int. J. Nucl. Med. Biol.* **1985**, *12(5)*, 381.

5. Perrin, D. D.; Armarego, W.L.F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd Ed. Pergamon Press, 1980.

6. Weis, C. D. *J. Heterocyclic Chem.* **1978**, *15*, 29.

7. Richman, J. K.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96(7)*, 2268.

8. Motekaitis, R. J.; Martell, A.E. to be submitted.

9. Harris, W. R.; Carrano, C. J.; Cooper, S. R.; Sofen, S. R.; Avdeef, A.; McArdel, J. V.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 6097.

10. Sun, Y.; Reibenspies, J.; Martell, A. E. to be submitted.

11. Auerbach, U.; Eckert, U.; Wieghardt, K.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1990**, *39*, 938.

12. Moore, D. A.; Fanwick, P. E.; Welch, M. J. *Inorg. Chem.* **1989**, *28*, 1504.

13. Wieghardt, K.; Bossek, U.; Chaudhuri, P.; Herrmann, W.; Menke, B.; Weiss, J. *Inorg. Chem.* **1982**, *21*, 4308.

14. Moore, D. A.; Fanwick, P. E.; Welch, M. J. *Inorg. Chem.* **1990**, *29*, 672.