Inorg. Chem. **1993,** *32,* 3320–3326

Stabilities of Divalent and Trivalent Metal Ion Complexes of Macrocyclic Triazatriacetic Acids

Rita Delgado,[†] Yizhen Sun, Ramunas J. Motekaitis, and Arthur E. Martell*

Department of Chemistry, Texas A&M University, College Station, Texas 77843-3255

Received January 28, 1993

Potentiometric methods have been used to determine the stability constants of complexes of trivalent metal ions of Al^{3+}, Fe^{3+}, Ga^{3+}, In^{3+}, and Gd^{3+} with the ligands 1-oxa-4,7,10-triazacyclododecane-*N,N′,N″*-triacetic acid, **1**, 1,7-dioxa-4,10,13-triazacyclopentadecane-*N,N′,N″*-triacetic acid, **2**, and 1,7,13-trioxa-4,10,16-triazacyclooctadecane-*N,N′,N″*-triacetic acid, **3**, and of divalent metal ions of Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} with ligands **2** and **3**. To these data are added the stability constants of complexes formed by divalent metal ions with **1** and of complexes of divalent and trivalent metals ions with 1,4,7-triazacyclononane-*N,N′,N″*-triacetic acid, **4**. The metal ion affinities of the series of four triazamacrocyclic ligands with three pendant acetate donor groups are compared. The effects of the metal ions on the stabilities are discussed, and the trends in the stability constants resulting from changing the macrocyclic ring size from 9 to 18 atoms and the change in the number of donor atoms of the ligand from six to nine are described.

Introduction

The objective of this research is to determine the stability constants of complexes of some di- and trivalent metal ions with a series of macrocyclic ligands having acetate groups as N-pendant arms, **1–3** (Chart I). All the ligands have three nitrogen atoms in a macrocyclic ring with acetate groups linked to each of them, forming a series with an increasing number of ether oxygen atoms forming from 12-membered to 18-membered macrocylic rings with an increasing number of donor atoms, from seven to nine. This series of ligands provides an opportunity to study the influence of the size of the macrocyclic ring and the increasing number of donor atoms on the stability and selectivity of metal complexes. The metal ions studied includes the divalent metal ions, such as Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, and trivalent metal ions, Al^{3+}, Ga^{3+}, Fe^{3+}, In^{3+}, and Gd^{3+}. This series of ligands also provides an opportunity to compare the affinities of the metal ions studied here with those of the parent *N,N′,N″*-triazacyclononanetriacetic acid, NOTA, **4**, especially those reported by Clarke and Martell[1] and by Hama and Takamoto.[2]

Some of the ligands and metal complexes formed are of potential interest in several medical applications, such as the removal of Fe^{3+} in the treatment of Cooley's anemia,[3–5] treatment of aluminum intoxication,[6] use of In^{3+} and Ga^{3+} as imaging agents,[7] and use of complexes of lanthanides^{3+}, especially Gd^{3+}, as NMR imaging agents.[8]

The ligand N-ac$_3$[12]aneN$_3$O has been studied previously,[9,10] and in this work only the stability constants of some trivalent metal ions (Al^{3}, Ga^{3+}, Fe^{3+}, In^{3+}, and Gd^{3+}) were determined. The ligand N-ac$_3$[15]aneN$_3$O$_2$ was synthesized earlier[11] but only some semiquantitative experiments with its ^{90}Y complex were made; later the parent amine was synthesized by a simpler procedure,[12] and in this work another method of alkylation was used with good yield. The ligand N-ac$_3$[18]aneN$_3$O$_3$ was also prepared previously, although only the crystal structure of its Gd^{3+} complex was described.[13]

Experimental Section

Synthesis and Characterization of the Ligands. Materials and Methods. Bromoacetic acid, benzyl bromoacetate, benzyl alcohol, palladium on activated carbon (10%), Dowex 1 × 8-50 ion exchange resin, silica gel (200–400 mesh, 60 Å) were obtained from Aldrich Chemical Co. and were used as supplied without further purification (Dowex 1 × 8-50 resin was treated with 2M NaOH to convert it to the OH$^-$ form).

Ligand **1** and 1,7-dioxa-4,10,13-triazacyclopentadecane trihydrobromide were prepared by previously reported procedures.[9–12]

1,7,13-Trioxa-4,10,16-triazacyclooctadecane trihydrobromide was prepared by the condensation of 1,11-bis(*p*-toluenesulfonyloxy)-6-(*p*-toluenesulfonyl)-3,9-dioxa-6-azaundecane[12] and 1,5-bis(*p*-toluenesulfonylamino)-3-oxapentane,[14,15] followed by detosylation.

Ligands **2** and **3** were prepared by improvements of the procedures previously reported.[11,13]

The proton and carbon-13 NMR were recorded on 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 our departmental VG Analytical 70S high-resolution double-focusing magnetic sector spectrometer with attached VG Analytical 11/250J data system. The C, H, N, and Cl analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Synthetic Procedures. 1,7-Dioxa-4,10,13-triazacyclopentadecane-*N,N′,N″*-triacetic Acid, 2. Ground KOH pellets, 0.77 g (87%, 0.012 mol), were added to a suspension of 1.84 g (0.004 mol) of 1,7-dioxa-4,10,13-triazacyclopentadecane trihydrobromide ([15]aneN$_3$O$_2$·3HBr) and 40 mL of absolute ethanol, and this mixture was stirred at room temperature for 1 h. The KBr was removed by filtration, and the solvents were removed by vacuum distillation. The white residue obtained was dissolved in 20 mL of water. Bromoacetic acid, 1.85 g (0.0132 mol), was dissolved in 20 mL of ice cold water (1–2 °C). A solution of 1.7 g of KOH (87%) in 20 mL of water was added dropwise to form potassium

---

[†] Permanent address: Centro de Quimica Estrutural, IST, Lisbon, Portugal.

(1) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1991**, *181*, 273.

(2) Hama, H.; Takamoto, S. *Nippon Kagaku Kaishi* **1975**, *7*, 1182.

(3) Martell, A. E.; Motekaitis, R. J.; Murase, I.; Sala, L. F.; Stoldt, R.; Ng, C. Y.; Rosenkrantz, H.; Metterville, J. J. *Inorg. Chim. Acta* **1987**, *138*, 215.

(4) Martell, A. E.; Motekaitis, R. J.; Clarke, E. T.; Sun, Y. *Drugs Today* **1992**, *28*, 11.

(5) Pitt, C. G.; Martell, A. E. *ACS Symp. Ser.* **1980**, *140*, 279.

(6) Martell, A. E.; Motekaitis, R. J. In *The Environmental Chemistry and Toxicology of Aluminum*; Lewis, T. E., Ed.; Lewis Publishers: Chelsea, MI, 1989; p 3.

(7) Riesen, A.; Kaden, T. A.; Ritter, W.; Macke, H. R. *J. Chem. Soc., Chem. Commun.* **1989**, 460. Schwarz, S. W.; Mathias, C. J.; Sun, Y.; Dilley, W. G.; Wells, S. A., Jr.; Martell, A. E.; Welch, M. J. *Nucl. Med. Biol.* **1991**, *18*, 477.

(8) Lauffer, R. C. *Chem. Rev.* **1987**, *87*, 901.

(9) Amorim, M. T. S.; Delgado, R.; Frausto da Silva, J. J. R.; Vaz, M. C. T. A.; Vilhena, M. F. *Talanta* **1988**, *35*, 741.

(10) Amorim, M. T. S.; Ascenso, J. R.; Delgado, R.; Frausto da Silva, J. J. R. *J. Chem. Soc., Dalton Trans.* **1990**, 3449.

(11) 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**, 87.

(12) Sun, Y.; Martell, A. E.; Welch, M. J. *Tetrahedron* **1991**, *47*, 8863.

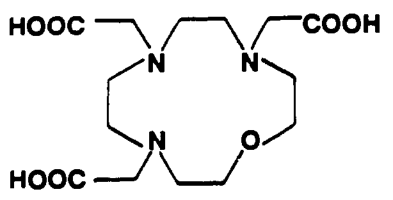
(13) Chen, D.; Squattrito, P. J.; Martell, A. E.; Clearfield, A. *Inorg. Chem.* **1990**, *29*, 4366.

(14) Bogatskii, N. G.; Luk'yanenko, N. G.; Kivichenko, T. I. *Zh. Org. Khim.* **1980**, *16*, 1301.

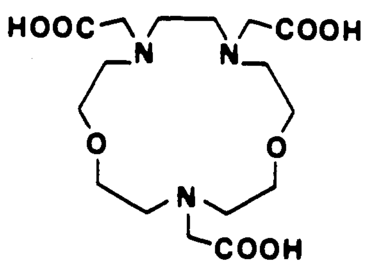
(15) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1975**, *96*, 2268.

0020-1669/93/1332-3320$04.00/0

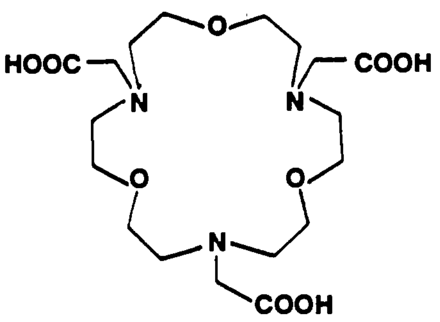
Chart I



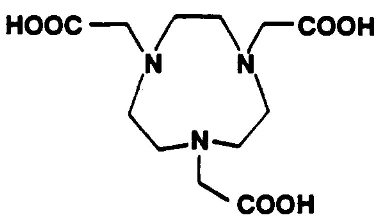
1 1-oxa-4,7,10-triazacyclodocecane-N,N′,N″-triacetic acid, N-ac$_3$[12]aneN$_3$O



2 1,7-dioxa-4,10,13-triazacyclopentadecane-N,N′,N″-triacetic acid, N-ac$_3$[15]aneN$_3$O$_2$



3 1,7,13-trioxa-4,10,16-triazacyclooctadecane-N,N′,N″-triacetic acid, N-ac$_3$[18]aneN$_3$O$_3$



4 1,4,7-triazacyclononane-N,N′,N″-triacetic acid, N-ac$_3$[9]aneN$_3$

bromoacetate at 2–5 °C until the pH of the solution became 12. The [15]aneN$_3$O$_2$ and BrCH$_2$COOK solutions were mixed and heated to 40–42 °C. The rest of the KOH aqueous solution described above was used to maintain the pH of the reaction solution at 11.5–12.0. The reaction solution was kept at 40–42 °C for 5 h and then at room temperature for 16 h. It was neutralized to pH 9.0 with 6 M HCl, and then concentrated to 5–10 mL. The resulting solution was loaded on a Dowex 1 × 8-50 ion exchange resin in the OH$^-$ form in a 20 × 230 mm ($d \times h$) column. The column was eluted successively with 200 mL of water, 200 mL of 0.01 M HCl, and 300 mL of 0.1 M HCl. The eluant with pH = 3 contained 0.78 g of the pure ligand 2. After elution with 100 mL of 0.2 M HCl, another 0.2 g of the tri-HCl salt was obtained; total yield 60%. ^{1}H NMR (in D$_2$O–NaOD, pD = 13.2, *t*-BuOH = 1.29 ppm): δ 3.57 (t, 8H, –CH$_2$–O–CH$_2$–), 3.23 and 3.15 (two singlets, 6H, –CH$_2$–COO–), 2.73 (two triplets, 8H, –O–CH$_2$–*CH$_2$*–N–), 2.64 (s, 4H, –N–CH$_2$–CH$_2$–N–). ^{13}C NMR (in D$_2$O–NaOD, pD = 13.2, *t*-BuOH = 31.1 ppm): δ 181.3 and 181.6 (carbonyls), 68.9 and 68.8 –CH$_2$–O–CH$_2$–), 61.2, 60.7 (–*CH$_2$*–COO–), 57.1 (–N–CH$_2$CH$_2$–N–), 55.3 and 55.0 (–O–CH$_2$–*CH$_2$*–N–). FAB MS: (M + H)$^+$ = 392. Anal. Calcd for $C_{16}H_{29}N_3O_8\cdot 3HCl\cdot 1^1/_2H_2O$: C, 36.40; H, 6.64; N, 7.96; Cl, 20.19. Found: C, 36.16; H, 6.43; N, 7.74; Cl, 19.90.

1,7,13-Trioxa-4,10,16-triazacyclooctadecane-*N,N′,N″*-triacetic Acid, 3. To a suspension of 1.008 g (0.002 mol) of 1,7,13-trioxa-4,10,16-triazacyclooctadecane trihydrobromide ([18]aneN$_3$O$_3$·3HBr) in 25 mL of benzyl alcohol 1.27 g (0.012 mol) anhydrous Na$_2$CO$_3$ was added. After the mixture was stirred at room temperature for 30 min, 1.512 g (0.0066 mol) of benzyl bromoacetate was added. The reaction mixture was heated to 90–95 °C (bath temperature) for 24 h. After the solution was cooled, 25 mL of chloroform was added. The inorganic salts were removed by filtration and the solvents were removed by vacuum distillation. To the white oily residue 25 mL of ethyl ether was added and the crude product was isolated as a white solid. This crude product was dissolved in CH$_2$Cl$_2$ and was purified by flash chromatography with silica gel 60. The eluants (CHCl$_3$:MeOH/98:2) containing one spot of R_f = 0.39 (developed by CHCl$_3$:MeOH = 9:1) were pooled. After concentration and cooling, 0.73 g of colorless crystals was obtained; yield 52%. ^{1}H NMR (CDCl$_3$): δ 7.33 (m, 15H, aromatic); 5.12 (s, 6H, –CH$_2$ of benzyl), 3.51 (t, 12H, –CH$_2$–O–CH$_2$–), 3.55 (s, 6H, *CH$_2$*-COOBz), 2.92 (t, 12H, –CH$_2$–N–CH$_2$–). Anal. Calcd for $C_{39}H_{51}N_3O_9\cdot NaBr$: C, 57.93; H, 6.31; N, 5.19. Found: C, 57.52; H, 6.76; N, 5.07.

To the above tribenzyl ester 1.14 g (0.0016 m), 7 mL of methanol and 0.7 g of Pd–C (10%) were added. This mixture was reacted with H$_2$ at room temperature and 1 atm of pressure. The hydrogenolysis was complete within 2 h. After the product was vacuum dried at room temperature over P$_2$O$_5$ (0.1 mmHg) for 24 h, 0.66 g of a white solid was obtained; yield 94%. ^{1}H NMR (D$_2$O-NaOD): δ 3.38 (t, 12H, –CH$_2$–O–CH$_2$–), 2.94 (s, 6H, –*CH$_2$*–COO–), 2.6 (t, 12H, –CH$_2$–N–CH$_2$–). Anal. Calcd for $C_{18}H_{33}N_3O_9\cdot NaBr\cdot 6H_2O$: C, 33.44; H, 6.96; N, 6.50. Found: C, 33.62; H, 6.90; N, 6.10.

Other Reagents and Standard Solutions. Metal ion solutions were prepared at about 0.025 M from the analytical grade of chloride or nitrate salts with demineralized water and were standardized by titration with Na$_2$H$_2$EDTA (disodium salt of ethylenedinitrilotetraacetic acid).[16] For Ga^{3+} and Al^{3+}, a back-titration with a standard solution of ZnSO$_4$ was made.[16] The Ga^{3+}, Fe^{3+}, and Al^{3+} solutions were stored with a small excess of hydrochloric acid in order to prevent hydrolysis of the metal ions. The exact amount of excess acid was checked by titration of 1:1 ratios of those metal ions with EDTA. The amount of KOH consumed in excess of the amount needed to neutralize all of the ligand protons represents the excess of HCl.

Carbonate-free solutions of the titrant, KOH, were prepared by dilution of a commercial ampoule of "Dilut-It" (obtained from J. T. Baker Chemical Co.) analytical concentrate with dimineralized water under a stream of purified N$_2$ purge gas. The solutions were standardized by potassium acid phthalate (dried powder), and the extent of the carbonate accumulation was checked periodically by titration with a standard hydrochloric acid solution and discarded when the percentage of carbonate reached about 2% of the KOH present.[17]

Potentiometric Equipment and Measurements. For the potentiometric titrations a Corning Ion Analyzer 250 instrument was used together with a Model S-30050-15D Sargent Welch glass electrode and a Corning 476 002 reference electrode. A 100-mL glass-jacketed titration cell completely

---

(16) Schwarzenbach, G.; Flaschka, H.; *Complexometric Titrations*; Methuen & Co.: London, 1969.

(17) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*, 2nd ed.; VCH: New York, 1992.

sealed from the atmosphere was used, and the temperature was controlled with a Haake thermostat (25.0 ± 0.1 °C) by circulation of thermostated water through the jacket. Atmospheric CO$_2$ was excluded from the cell during the titration by passing purified Ar across the top of the experimental solution in the reaction cell. The standard base (or acid) was added through a capillary tip at the surface of the solution attached to a 10-mL capacity Metrohm piston-type burette.[17]

Prior to each potentiometric equilibrium study a calibration of the pH meter and electrode system was made using standard dilute HCl solutions at an ionic strength adjusted to 0.10 M with KCl in the thermostated cell at 25.0 °C, so as to read hydrogen ion concentrations directly. Thus, the term p[H] in this work is defined as $-\log [H^+]$. The value of K_W = ([H$^+$][OH]) used in the computations was $10^{-13.78}$.[17]

The potentiometric equilibrium measurements were made on 20.00 mL of ligand solutions $\simeq 2.50 \times 10^{-3}$ M diluted to a final volume of 50.00 mL, first in the absence of metal ions and then in the presence of each metal ion for which the m_L:m_M ratios were 1:1 (for the divalent metal ions, a ratio of 1:2 was also used). The p[H] data were taken after additions of 0.050- or 0.100-mL increments of standard 0.1094 M KOH solution, and after stabilization in this direction, equilibrium was then approached from the other direction by adding 0.1021 M standard acid.

When the degree of formation of the metal complexes, even at low pH, was too high for the use of the direct potentiometric method, ligand–ligand competition titrations were performed. This was the case for Ga^{3+}, Fe^{3+}, In^{3+}, and Gd^{3+} with the ligand N-ac$_3$[12]aneN$_3$O, and for Cu^{2+}, Fe^{3+}, and In^{3+} with the ligand N-ac$_3$[15]aneN$_3$O$_2$. In all cases, except for Ga^{3+}, the ligand used for the competition was EDTA. Other ligands tried were CDTA (*trans*-1,2-cyclohexylenedinitrilotetraacetic acid) and *meso*-EHPG (ethylenediiminobis[(2-hydroxyphenyl)acetic acid] in the first system studied in the present work (In^{3+}/N-ac$_3$[12]aneN$_3$O). EDTA was chosen for two reasons: (1) the time necessary to attain the equilibrium after each addition of titrant was shorter than with the other ligands, although still slow in some cases requiring the batch method described below, and (2) the stability constants with the metal ions studied are well-known.[18] Usually the ratio m_L:$m_{L'}$:m_M = 1:1:1 was used (L being the ligand for which the stability constant of the metal complex is to be determined and L′ being the reference ligand for which the stability constant of the complex of the same metal is known). In two cases other ratios were necessary to achieve a better competition reaction, whereby concentrations of all the complexed species exist in solution to at least 30% of the total metal ion concentration. This was the case for the system N-ac$_3$[12]aneN$_3$O–EDTA–Gd^{3+} where a molar ratio of 1:1.5:1 was used, and the case of N-ac$_3$[15]aneN$_3$O$_2$–EDTA–Fe^{3+} where a 1:0.6:1 molar ratio was used.

The competition reaction can be written by the following equilibrium:

$$ML' + H_nL \rightleftharpoons ML + (n - m)H^+ + H_mL'$$

The potentiometric studies of the Ga^{3+} complexes provide two different types of experimental data. In the case of the ligand N-ac$_3$[12]aneN$_3$O, the gallium(3+) is 100% complexed at low p[H], and the stability constants were calculated at higher pH values by relying on the following competition or displacement:[19]

$$GaL + 3OH^- \rightleftharpoons Ga(OH)_4^- + HL^{2-}$$

In the other two cases, where Ga^{3+} complexation was not complete, the low pH values were used in the determination of the stability constants.

The equilibration of the ligands N-ac$_3$[15]aneN$_3$O$_2$ and N-ac$_3$[18]aneN$_3$O$_3$ with the divalent metal ions was fairly rapid. The only case where the equilibrium is slowly attained involved Ni(II) complex formation. For both ligands with this metal ion it was necessary to wait about 30 min for each point of the titration in the p[H] region where the complex was forming.

The complexation reactions of the trivalent metal ions with all the three ligands were found to be, in general, very slow: Ga^{3+} with N-ac$_3$[12]aneN$_3$O needing 40 min for each point of the titration, Gd^{3+} with N-ac$_3$[15]aneN$_3$O$_2$ and N-ac$_3$[18]aneN$_3$O$_3$ needing 30 min, and Fe^{3+} with N-ac$_3$[15]aneN$_3$O$_2$ needing about 20 min. When the p[H] of the solutions prepared for titrations (with a specific ligand and metal ion) did not stabilize in 1 h for each point of the titration, a batch technique was performed. In this procedure, sets of solutions were prepared in individual vials (containing equimolar amounts of metal and ligand, sufficient potassium chloride for a 0.10 M solution, water to the appropriate volume and the amount of base required to achieve a specific p[H] value), each solution corresponding to a single point in a normal titration. This technique was used for the 1:1 titration of Gd^{3+} and Al^{3+} with N-ac$_3$[12]aneN$_3$O (the p[H] values were read 7 days after preparation of the solutions and confirmed later as stabilized), for Ga^{3+} with N-ac$_3$[15]aneN$_3$O$_2$ (8 days were needed for stabilization), with the ligand N-ac$_3$[18]aneN$_3$O$_3$ (3 days for the stabilization) and for Fe^{3+} with this last ligand (6 days were needed). The reactions involving competition with EDTA were also slow: N-ac$_3$[12]aneN$_3$O with Gd^{3+} (6 days of stabilization) and with Fe^{3+} (12 days of stabilization). Faster kinetics in the competition reactions with EDTA were found with In^{3+} where, in general, 15 min were enough for each point, for both ligands (N-ac$_3$[12]aneN$_3$O and N-ac$_3$[15]aneN$_3$O$_2$), and also for Fe^{3+} with N-ac$_3$[15]aneN$_3$O$_2$.

NMR Titration. Proton NMR spectra were recorded with a Varian Unity 300 spectrometer at probe temperature. The adjustment in pD for the NMR titration was made with an Orion 420 A instrument fitted with a combined Ingold microelectrode. The $-\log [D^+]$ measurements were made directly in the NMR tube, after the calibration of the microelectrode with buffered aqueous solutions and the final pD was calculated by the equation pD = pH + 0.40.[20] Solutions of the ligand N-ac$_3$[15]aneN$_3$O$_2$ for the NMR measurements ($\simeq$0.01 M) were made up in D$_2$O and the pD was adjusted by adding DCl or CO$_2$-free KOD. Sodium 3-(trimethylsilyl)propane-1-sulfonate was used as an internal reference.

Calculation of Equilibrium Constants. Protonation constants ($K_i^H = [H_iL]/[H_{i-1}L][H]^i$) were calculated by fitting the potentiometric data to the PKAS program.[17]

The stability constants of the various species formed in the aqueous solution were obtained from the experimental data with the aid of the BEST program.[17] The initial computations were obtained in the form of overall stability constants or β values: $\beta = [M_mL_lH_h]/[[M]^m[L]^l[H]^h$. Differences between the various log β's provide the stepwise formation and protonation reaction constants.

For the determination of species distributions the program SPE was used.[17]

Hydrolytic Species of the Trivalent Metal Ions. Some of the trivalent metal ions used in the present work form several hydrolytic species in aqueous solution, whose constants have some discrepancies in the literature. The values listed below are considered reliable:[18,21,22]

quotient	Al^{3+}	Ga^{3+}	Fe^{3+}	In^{3+}	Gd^{3+}
$[MOH]/[M][OH]$	8.47	10.87	11.27	9.5	5.38
$[M(OH)_2]/[M][OH]^2$	16.8	20.95	21.7	18.2	
$[M(OH)_3]/[M][OH]^3$	24.7	30.33			
$[M(OH)_4]/[M][OH]^4$	31.5	38.34		33.9	
$[M_2(OH)_2][M]^2[OH]^2$			24.8		
$[M_3(OH)_4]/[M]^3[OH]^4$	42.0				
$[M_4(OH)_4]/[M]^4[OH]^4$				47.8	

Results and Discussion

Synthetic Methods. All the ligands studied in the present work were synthesized previously. With N-ac$_3$[12]aneN$_3$O, **1**, some work has been carried out on the determination of protonation constants and stability constants of several divalent metal ions in aqueous solution with 0.1 M (Me)$_4$NNO$_3$ as ionic medium,[9] and a NMR study has been accomplished on the sequence of protonation of the ligand.[10] A synthetic route for N-ac$_3$[18]aneN$_3$O$_3$, **3**, and the crystal structure of its Gd^{3+} complex was published.[13] In the Experimental Section an improved and simpler route of the synthetic procedure is described in detail. Parker and co-workers[11] published a synthetic procedure for N-ac$_3$[15]aneN$_3$O$_2$, **2**, which was used for some qualitative studies as the ^{90}Y complex in a competition reaction with DTPA (diethylenetriaminepentaacetic acid). A new and simpler synthesis for the parent amine of this ligand was performed ([15]aneN$_3$O$_2$·

---

(18) Smith, R. M.; Martell, A. E. *Critical Stability Constants*, Plenum Press: New York, 1974–1989; Vols. 1, 2, 5, and 6.

(19) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1980**, *19*, 1646.

(20) Delgado, R.; Frausto da Silva, J. J. R.; Amorim, M. T. S.; Cabral, M. F.; Chaves, S.; Costa, J. *Anal. Chim. Acta* **1991**, *245*, 271.

(21) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1976; Vol. 4.

(22) Baes, C. F.; Mesmer, R. E. *The Hydrolysis of Cations*, John Wiley & Sons, Inc.: New York, 1976.

Table I. Protonation (log K_i^H) Constants of Triacetate Derivatives of Polyoxa-Polyaza Macrocyclic Ligands

equilibrium quotient	log K_i^H 0.100 M KCl, 25.0 °C	log K_i^H 0.100 M $(Me)_4NNO_3$, 25.0 °C
	N-ac$_3$[12]aneN$_3$O	
[HL]/[L][H]	11.24(2)	11.61[a]
[H$_2$L]/[HL][H]	7.76(3)	7.70[a]
[H$_3$L]/[H$_2$L][H]	4.00(4)	4.05[a]
[H$_4$L]/[H$_3$L][H]	2.59(3)	2.77[a]
	N-ac$_3$[15]aneN$_3$O$_2$	
[HL]/[L][H]	9.55(1)	
[H$_2$L]/[HL][H]	8.92(1)	
[H$_3$L]/[H$_2$L][H]	4.51(3)	
[H$_4$L]/[H$_3$L][H]	1.59(2)	
	N-ac$_3$[18]aneN$_3$O$_3$	
[HL]/[L][H]	9.57(2)	
[H$_2$L]/[HL][H]	8.15(3)	
[H$_3$L]/[H$_2$L][H]	7.67(1)	
[H$_4$L]/[H$_3$L][H]	2.05(3)	
[H$_5$L]/[H$_4$L][H]	1.07(2)	
	N-ac$_3$[9]aneN$_3$	
[HL]/[L][H]	11.96[b]	12.00[c]
[H$_2$L]/[HL][H]	5.65[b]	5.65[c]
[H$_3$L]/[H$_2$L][H]	3.17[b]	3.19[c]

[a] Reference 9. [b] Reference 1; KCl. [c] Reference 1; $(Me_4)_4NCl$.

3HBr),[12] which makes possible the preparation of this macrocycle in large quantities. The alkylation of the parent amine was accomplished in good yield by condensation with potassium bromoacetate in basic aqueous solution, instead of the use of a benzyl ester (to avoid the formation of lactam).

Protonation Constants. In the present study KCl is used as the ionic medium at 0.10 M ionic strength. The values of the protonation constants obtained can be seen in Table I, together with the values determined in the previous work for N-ac$_3$[12]aneN$_3$O[9,10] and for N-ac$_3$[9]aneN$_3$.[1,2] In the case of N-ac$_3$[12]aneN$_3$O the first protonation constant is lower in KCl than in Me$_4$NNO$_3$ medium because this ligand forms complexes with K$^+$. The correction due to the formation of potassium complexes was made in this work.

For the 12-membered macrocycle, **1**, NMR spectroscopy titration has shown[10] that the two higher values of the protonation constants correspond to the protonation of nitrogen atoms, but the third and fourth correspond to the protonation of the carboxylate groups.

In the ligand N-ac$_3$[18]aneN$_3$O$_3$ the nitrogen atoms are separated by longer chains (–CH$_2$CH$_2$OCH$_2$CH$_2$–) and the ring is less rigid because of the larger size of the macrocycle, when compared with the 12-membered macrocyclic derivative. All the nitrogen atoms are protonated before the carboxylate groups, as the electrostatic repulsions between the positive charges on the nitrogen atoms are weaker than those of the 12-membered macrocycle. As usual the protonation of carboxylate groups linked to protonated nitrogen atoms corrresponds to log *K*'s of around 2 or less.

The behavior of ligand N-ac$_3$[15]aneN$_3$O$_2$ is similar to that of N-ac$_3$[18]aneN$_3$O$_3$, in that the protonation of all the nitrogen atoms occurs before that of the carboxylate groups, although this conclusion cannot be inferred from the potentiometric determinations alone. A ^{1}H NMR titration of this ligand is shown in Figure 1, together with an NMR spectrum obtained at p[D] = 1.3. The NMR spectra exhibit seven resonances, some of which overlap in certain regions of pD: three singlets (c–e) and four triplets (a, a′, b, and b′). The assignment of the resonances was made by double-resonance experiments (for the assignment of the triplets), differences in area (assignment of resonance e), and the profile of the titration curve.[10] It can be seen (Figure 1) that at high values of pD (between 11 and 8) all the resonances move downfield but resonances b and e undergo the largest shift, showing that protonation occurs on nitrogen N^1 (Figure 1) and also 50% on each of the other undistinguishable nitrogen atoms N^2. The number of protonated centers in this pD region (two) is known from the potentiometric titration. Between pD 6 and 4, all the resonances shift downfield except b and e, corresponding to the protonation of the last nitrogen atom (50% of N^2). The protonation of the carboxylate groups occurs at low pD values (below pD = 3). In this region resonances a and a′ do not shift, but the shift of resonances d and e is seen to occur. The values of the first two protonation constants of this ligand are similar to those found for N-ac$_3$[18]aneN$_3$O$_3$, as the protonations occur on nitrogen atoms separated by a long chain (–CH$_2$CH$_2$OCH$_2$CH$_2$–). However, log K_3 is lower than that of the 18-membered derivative since the third nitrogen of N-ac$_3$[15]aneN$_3$O$_2$ is separated by an ethylene group from the other protonated nitrogen. The value of this constant is similar in magnitude to the analogous constant in N-ac$_3$[12]aneN$_3$O. However, in this last case the third constant corresponds to the protonation of a carboxylate group and not a nitrogen of the ring, as is the case for the 15-membered macrocycle. The protonation of two nitrogen atoms separated by ethane chains can occur in the ring of N-ac$_3$[15]aneN$_3$O$_2$ because of the larger size of the cavity of this ligand, so that the greater flexibility of the ring can minimize the repulsion. This cannot happen in the more rigid ring of the 12-membered macrocycle.

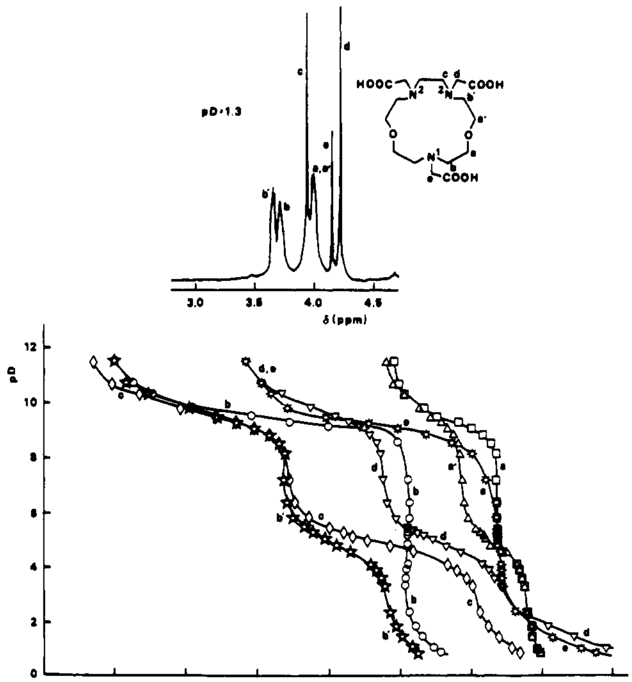


Figure 1. ^{1}H NMR spectrum of ligand N-ac$_3$[15]aneN$_3$O$_2$ at pD = 1.3 and titration curve pD *vs* δ (ppm).

In this series of macrocycles N-ac$_3$[18]aneN$_3$O$_3$ has the highest overall basicity because in the triprotonated form the positive nitrogen centers are farthest apart and are subject to the least Coulombic repulsion.

Stability Constants. Divalent Metal Ions. In Table II are shown the stability constants for the complexes of the divalent metal ions studied in the present work (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}) with N-ac$_3$[15]aneN$_3$O$_2$ and N-ac$_3$[18]aneN$_3$O$_3$. In this table the published values for the same set of metal ions with ligands N-ac$_3$[12]aneN$_3$O[9] and N-ac$_3$[9]aneN$_3$[2] are also indicated for comparison. The two ligands form several complex species, according to the constants calculated by the Best program:[17] all of them form ML, some form protonated and hydroxo complex species, and in most cases some binuclear species are also formed.

Table II. Stability Constants^a for the Metal Complexes of Triacetate Derivatives of Polyoxo–Polyaza Macrocyclic Ligands with Several Di- and Trivalent Metal Ions (t = 25.0 °C; μ = 0.100 M KCl)

		stability const			
cation	quotient	N-ac$_3$[9]aneN$_3$	N-ac$_3$[12]aneN$_3$O	N-ac$_3$[15]aneN$_3$O$_2$	N-ac$_3$[18]aneN$_3$O$_3$
Co^{2+}	$[ML]/[M][L]$	17.5^b	19.54^c	16.38	9.33
	$[MHL]/[ML][H]$		2.64^c	3.73	7.53
	$[M_2L]/[M]^2[L]$			18.11	12.10
	$[M_2HL]/[M_2L][H]$				6.57
	$[ML]/[MLOH][H]$			11.20	10.38
Ni^{2+}	$[ML]/[M][L]$		18.04^c	14.94	9.84
	$[MHL]/[ML][H]$		3.66^c	4.78	7.46
	$[M_2L]/[M]^2[L]$			16.29	12.95
	$[ML]/[MLOH][H]$			11.01	10.84
Cu^{2+}	$[ML]/[M][L]$	19.8^b, 21.63^d	20.17^c	17.54	14.88
	$[MHL]/[ML][H]$	2.74^d	3.10^c	5.63	8.14
	$[MH_2L]/[MHL][H]$			1.49	2.27
	$[M_2L]/[M]^2[L]$				20.10
	$[M_2HL]/[M_2L][H]$				5.41
	$[M_2L]/[M_2LOH][H]$				6.57
	$[M_2LOH]/[M_2L(OH)]_2[H]$				5.76
	$[ML]/[MLOH][H]$			11.91	10.81
	$[M_3L]/[M]^3[L]$				22.37
Zn^{2+}	$[ML]/[M][L]$	18.3	18.66^c	16.38	9.89
	$[MHL]/[ML][H]$		2.85^c	3.73	8.14
	$[MH_2L]/[MHL][H]$				4.36
	$[M_2L]/[M]^2[L]$			18.52	13.63
	$[M_2HL]/[M_2L][H]$				6.36
	$[M_2L]/[M_2LOH][H]$				7.18
	$[M_2LOH]/[M_2L(OH)]_2[H]$				8.12
	$[ML]/[MLOH][H]$			10.68	10.84
Cd^{2+}	$[ML]/[M][L]$	16.0^b	19.25^e	16.97	12.42
	$[MHL]/[ML][H]$			3.56	6.06
	$[M_2L]/[M][L]$			19.03	14.83
	$[M_2HL]/[M_2L][H]$				5.81
	$[ML]/[MLOH][H]$			10.95	10.87
Pd^{2+}	$[ML]/[M][L]$	16.6^b	19.27^e	16.58	15.82
	$[MHL]/[ML][H]$		3.48^e	4.88	4.47
	$[MH_2L]/[MHL][H]$			2.18	
	$[M_2L]/[M]^2[L]$			19.82	19.39
	$[M_2HL]/[M_2L][H]$				2.53
	$[M_2L]/[M_2LOH][H]$				10.98
	$[ML]/[MLOH][H]$			10.77	11.54
Al^{3+}	$[ML]/[M][L]$		12.5		
	$[MHL]/[ML][H]$		3.28		
Ga^{3+}	$[ML]/[M][L]$	30.98^f	21.3	17.1	19.2
	$[MHL]/[ML][H]$		2.66	3.48	
	$[ML]/[MLOH][H]$		7.84		
Fe^{3+}	$[ML]/[M][L]$	28.3^f	26.8	19.82	22.5
	$[MHL]/[ML][H]$		2.17	2.65	3.65
	$[ML]/[MLOH][H]$		7.75	6.15	
In^{3+}	$[ML]/[M][L]$	26.2^f	25.48	23.56	
	$[MHL]/[ML][H]$		1.8	2.49	
	$[ML]/[MLOH][H]$		9.59		
Gd^{3+}	$[ML]/[M][L]$		21.6	17.23	18.02
	$[MHL]/[ML][H]$		1.45	2.32	
	$[ML]/[MLOH][H]$		10.35	10.79	

[a] Estimated errors for constants reported in this research are one digit or less in the last decimal number shown. [b] Reference 2; μ = 0.10 M KNO$_3$. [c] Reference 9; μ = 0.10 M (Me$_4$)NNO$_3$. [d] Reference 25; μ = 1.0 M NaNO$_3$. [e] Reference 35; μ = 0.10 M (Me$_4$)NNO$_3$. [f] Reference 1; μ = 0.10 M KCl.

For all the ML complexes (and also for the M$_2$L complexes) formed with divalent metal ions the values of stability constants decrease with increase of ring size, in spite of the increase of the potential number of donor atoms and the increase of the overall basicity. This is also true for the 12-membered macrocycle, **1**, but not for the 9-membered ligand (NOTA) which will be analyzed later. However a tendency for the reversal of this trend is found for the complexes of Cd^{2+} and especially of Pb^{2+} with N-ac$_3$[18]aneN$_3$O$_3$, which have stability constants higher than expected (Figure 2). The increase in stability for these two complexes can be interpreted as due to a more favorable adjustment of the ligand to the larger metal ions and/or to the increase of the number of donor atoms. The larger metal ions Cd^{2+} and Pb^{2+}, which have less stereochemical requirements for specific coordination geometries than do the transition metal ions, allow a more favorable adjustment of the ligand to the metal ion. This leads to more favorable heats of reaction at the expense of configurational entropy changes.[23] The complexes formed with the transition metal ions and zinc ion have stability constants with the three ligands for which, although decreasing with the size of the ring, the differences in stability constants are larger. These metal ions involving more covalent interactions have stricter stereochemical demands for specific geometries, and therefore the adjustment of the ligand to the metal ion is more difficult, with the result that probably some of the donor atoms are not involved in the coordination to the metal ion. The values of the stability constants do not provide enough information to indicate more detail about the nature of the complexes formed. The determination of the thermodynamic functions, enthalpic and

---

[23] Delgado, R.; Frausto da Silva, J. J. R.; Vaz, M. C. T. A.; Paoletti, P.; Micheloni, M. *J. Chem. Soc., Dalton Trans.* **1989**, 133.

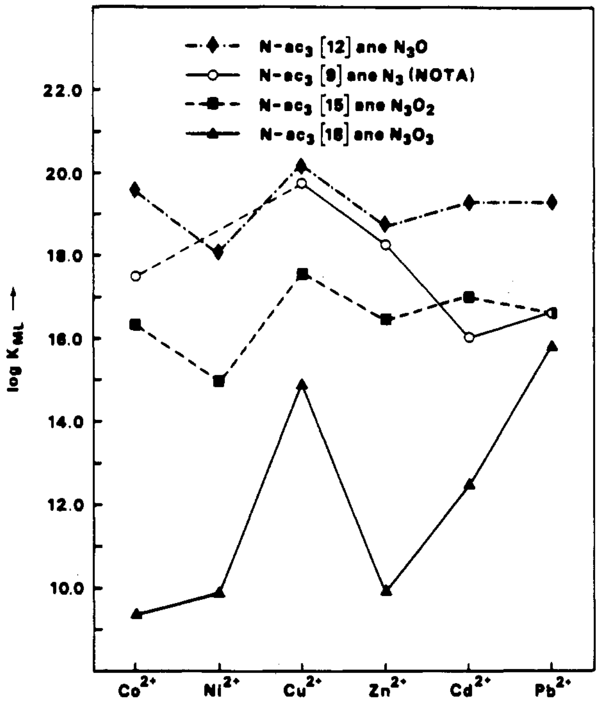


Figure 2. Variation of the stability constants K_{ML} of the complexes N-ac$_3$[12]aneN$_3$O, NOTA, N-ac$_3$[15]aneN$_3$O$_2$, and N-ac$_3$[18]aneN$_3$O$_3$ with the atomic number of the metal.

entropic variations, and some X-ray structures would be necessary to provide further insights.

For the protonated complexes, MHL, corresponding to the equilibrium MHL $\rightleftharpoons$ ML + H$^+$ the trend in pK's observed for the various divalent metal ions with the increase of the size of the macrocycle is reversed from that observed for the ML and M$_2$L complexes. This means that the higher protonation constants are found for the complexes of the 18-membered ligand. However the increase in protonation constants for the complexes Cd^{2+} and Pb^{2+} with this ligand are considerably lower than the increase in protonation constants observed for the complexes of the smaller metal ions. The value for the Pb^{2+} complex of N-ac$_3$[18]aneN$_3$O$_3$ is lower than the protonation constant of the Pb^{2+} complex with the 15-membered macrocycle. The tendency to form protonated complexes increases with the size of the ring for the same metal ion but the increase is less for the larger metal ions. The protonation constants for the smaller transition metal ions are generally higher than the protonation constants of the larger metal ions, Cd^{2+} and Pb^{2+}. This seems to corroborate our hypothesis that for the transition metal ions the complexes formed with the ligands with larger ring size do not use all the potential donor atoms of the ligand for coordination. The higher basicities of the larger ligand is manifested in the higher affinity for hydrogen ions.

Another effect that can be observed in the trend shown in Figure 2 is that the Irving–Williams order of stability is not obeyed for the complexes formed with the ligand N-ac$_3$[15]aneN$_3$O$_2$, as the Ni^{2+} complex has a stability constant lower than that of the Co^{2+} complex. A similar trend was observed for the ligand N-ac$_3$[12]aneN$_3$O[9] and other cyclic complexones like N-ac$_2$[15]aneN$_2$O$_3$[23] and even for some macrocycles without acetate pendant arms.[24] This anomalous behavior was tentatively discussed in previous publications.[9,23]

NOTA, **4**, is anomalous in its interactions with divalent metal ions when compared with the three studied herein. The trend presented by this ligand is probably a result of the restricted size of the triazacyclononane ring and its tendency to form octahedral complexes with the three nitrogen atoms of the ring occupying facial sites[26] with very efficient packing around small metal ions.[27]

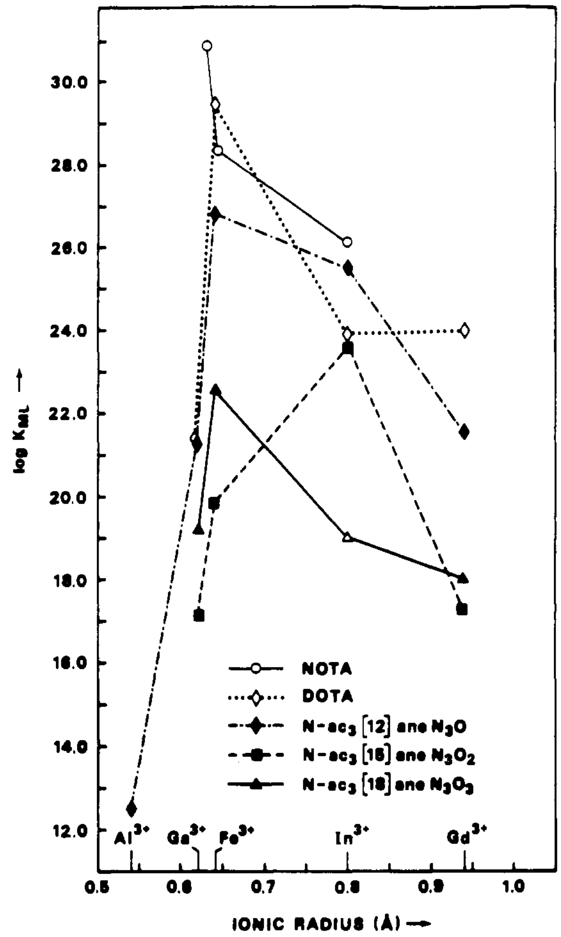


Figure 3. Variation of the stability constants (K_{ML}) of the complexes NOTA, DOTA, N-ac$_3$[12]aneN$_3$O, N-ac$_3$[15]aneN$_3$O$_2$, and N-ac$_3$[18]aneN$_3$O$_3$ with the ionic radius of the trivalent metal ions.

Trivalent Metal Ions. The stability constants of the complexes formed by the ligands (**1**–**3**) with Ga^{3+}, Fe^{3+}, In^{3+} and Gd^{3+} have been determined (with the N-ac$_3$[12]aneN$_3$O the Al^{3+} ion was also studied), in 0.100 M KCl ionic medium at 25.0 °C. The values obtained can be seen in Table II. Generally only ML and MHL complexes were found, but in some cases MLOH species were also postulated for better fit of the experimental data according to the BEST program. Most of the constants were obtained by competition reactions with EDTA. As the kinetics of the competition is usually slow only one ratio was tried. For Al^{3+} only the constant with N-ac$_3$[12]aneN$_3$O was determined because the complexation reaction with this metal ion is very slow and even with the most effective ligand the stability was relatively small.

The complexes formed by N-ac$_3$[12]aneN$_3$O and N-ac$_3$[18]aneN$_3$O$_3$ with the various trivalent metal ions studied show the usual stability trend already discussed for other polyamino polycarboxylate ligands[28–33] (Figure 3). A steep increase of

---

(24) Luboch, E.; Cygan, A.; Biernat, J. F. *Inorg. Chim. Acta* **1983**, *68*, 201. Arnaud-Neu, F.; Spiess, B.; Schwing-Weill, M. J. *Helv. Chim. Acta* **1977**, *60*, 2633.

(25) Bevilacqua, A.; Gelb, R. I.; Hebard, W. B.; Zompa, L. J. *Inorg. Chem.* **1987**, *26*, 2699.

(26) Craig, A. S.; Parker, D.; Adams, H.; Bailey, N. A.; *J. Chem. Soc., Chem. Commun.* **1989**, 1793.

(27) van der Merwe, M. J.; Boeyens, J. C. A.; Hancock, R. D. *Inorg. Chem.* **1985**, *24*, 1208.

(28) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1991**, *190*, 37.

(29) Motekaitis, R. J.; Sun, Y.; Martell, A. E. *Inorg. Chem.* **1991**, *30*, 1554.

(30) Motekaitis, R. J.; Martell, A. E.; Welch, M. J. *Inorg. Chem.* **1990**, *29*, 1464.

(31) Bannochie, C. J.; Martell, A. E. *Inorg. Chem.* **1991**, *30*, 1385.

(32) Bannochie, C. J.; Martell, A. E. *J. Am. Chem. Soc.* **1989**, *111*, 4735.

(33) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.

stabilities from Al^{3+} to Fe^{3+}, a small decrease for In^{3+} and a more pronounced decrease for Gd^{3+}. The much larger ionic radius (smaller charge/radius ratio) of Gd^{3+}, is reflected in lower values of stability constants, as one would predict for mainly electrostatic complexes. Similarly, it was expected from the effective ionic radii to obtain values for the stability constants of In^{3+} complexes considerably lower than those of Ga^{3+} and Fe^{3+}, as is found for "harder" ligands (like some phenol-containing donor ligands).[29–32] However, with the polyamino polycarboxylate ligands the situation is usually reversed, with the In^{3+} chelates considerably more stable than those of Ga^{3+}.[28,29,31,32] This is the case not only for some linear amino polycarboxylate ligands such as NTA (nitrilotriacetic acid), EDTA and DTPA,[18] but also for some tetraacetate tetraazamacrocyclic ligands, DOTA (1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid), TRITA (1,4,7,10-tetraazacyclotridecane-*N,N′,N″,N‴*-tetraacetic acid), and TETA (1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid).[28] This reversal may be rationalized by the fact that the carboxylate donor groups are considerably softer than the phenolate groups for the coordination of metal ions.[30] The lower Ga^{3+} affinities relative to those of Fe^{3+} may be attributed to the greater covalent character of the Fe^{3+} coordinate bonds[29] but also to the conformation of the ligands.

However, the complexes formed by the N-ac$_3$[15]aneN$_3$O$_2$ with the trivalent metal ions have an unusual trend with a maximum for the indium(3+) complex. In fact the In^{3+} complex of this 15-membered ligand is very stable compared to the stability of the other trivalent metal ion complexes of this ligand. It is more stable than that of the Fe^{3+} complex, with a value of stability constant that is only slightly lower than that of the DOTA complex.[28] Also, the In(III) complex of the 12-membered macrocyclic ligand is more stable than that of DOTA. On the other hand, the complexes formed with the ligand N-ac$_3$[18]aneN$_3$O$_3$ are more stable than those of N-ac$_3$[15]aneN$_3$O$_2$, except for the In^{3+} complex. In fact, it was even impossible to determine the constant for the In^{3+} complex with the ligand N-ac$_3$[18]aneN$_3$O$_3$, because a precipitate was formed at the beginning of the titration, at p[H] about 3.2. Even by a batch procedure, it was impossible to have a clear solution. With a back titration of this complex, beginning at p[H] 5, it was possible to obtain some points without precipitation and to calculate an approximate constant which seems to be about 19 log units.

NOTA[1] is also anomalous in its interactions with trivalent metal ions when compared with the three ligands studied herein and even with DOTA. The Al^{3+} complex was not reported, and the value for Gd^{3+} comes from another author[34] and was only marked in a figure. However, when the values shown for NOTA in Table I are entered in Figure 3, it becomes clear that the small, compact NOTA ligand is superior in its affinity for the trivalent ions investigated, except for the larger Gd^{3+} ion. While the Fe^{3+} to In^{3+} trend is parallel to the behavior shown for N-ac$_3$[12]aneN$_3$O and N-ac$_3$[18]aneN$_3$O$_3$ derivatives, the Ga^{3+} and Fe^{3+} trend is the reverse for all three ligands of this study. The high stability in acid solution of the gallium complex of NOTA had already attracted the attention of Parker and co-workers.[26]

In conclusion it can be stated that the ligands studied in the present work form, in general, stable complexes with the trivalent metal ions. The N-ac$_3$[12]aneN$_3$O ligand with the 12-membered macrocyclic ring forms a very stable complex with In^{3+}, with a stability constant which is higher than that of DOTA, and forms a Ga^{3+} complex which has a stability of the same order of magnitude as that formed with the tetraaza derivative (DOTA). When the ring size of the macrocycle increases, all the stability constants decrease, but the decrease is larger for the 15-membered macrocycle than for N-ac$_3$[18]aneN$_3$O$_3$, except for the In^{3+} complex where the situation is reversed.

It is suggested that the behavior of these complexes of the trivalent metal ions can be rationalized in the same way as was done before for the complexes formed by these ligands with divalent metal ions: the number of donor atoms involved in the coordination and/or the adjustment of the ligand to the metal ions. It seems that the more rigid macrocyclic ligand, N-ac$_3$[12]aneN$_3$O, and also NOTA make possible a good adjustment (a favorable cage structure) of these trivalent metal ions (except for Al^{3+} which probably is too small for the cage) to all donor atoms of the ligand. When the size of the macrocycle increases from a 12- to a 15-membered ring there is a drop in stability for all metal ions in spite of the introduction of only one additional donor atom in the ring. However, another increase of the ring with one oxygen atom more to form the 18-membered ring brings a slight increase of the stability constants except for In^{3+}. This probably means that the first increase of the size of the ring leads to a ligand which cannot place all the donor atoms in the right position for coordination, but the larger ligand which is more flexible seems to adapt better to the size of the metal ions and to bring the donor atoms near to the metal ions. The crystal structure of the gadolinium complex of N-ac$_3$[18]aneN$_3$O$_3$[13] seems to confirm this hypothesis; in fact, in the solid state the gadolinium atom lies within the macrocycle and is 9-coordinate, being bound to all the donor atoms of the macrocycle.

Acknowledgment. R.D. acknowledges the Fundacao Calouste Gulbenkian and Fundacao Luso-Americana para o Desenvolvimento for travel funds. Partial support was provided by Grant No. CA-42925, National Cancer Institute, U.S. Public Health Service.

---

(34) Cacheris, W. P.; Nickle, S. K.; Sherry, A. D. *Inorg. Chem.* **1987**, *26*, 958.

(35) Cabral, M. F.; Costa, J.; Delgado, R.; Frausto da Silva, J. J. R.; Vilhena, M. F. *Polyhedron* **1990**, *9*, 2847.