Synthesis and Ligational Behavior toward Hydrogen and Copper(II) Ions of the Two New Oxa–Aza Macrocyclic Receptors 10,13,16-Trimethyl-1,4-dioxa-7,10,13,16,19-pentaazacyclohenicosane (Me_3[21]aneN_5O_2) and 13,16,19-Trimethyl-1,4,7-trioxa-10,13,16,19,22-pentaazacyclotetracosane (Me_3[24]aneN_5O_3)

Carla Bazzicalupi,[1a] Andrea Bencini,[1a] Antonio Bianchi,*[,1a] Vieri Fusi,[1a] Enrique Garcia-España,[1c] Piero Paoletti,*[,1a] Paola Paoli,[1b] and Barbara Valtancoli[1a]

Department of Chemistry, University of Florence, Via Maragliano 75/77, 50144 Florence, Italy, Department of Energetics, University of Florence, Santa Marta, Florence, Italy, and Department of Inorganic Chemistry, University of Valencia, C/Dr. Moliner 50, 46100 Burjassot (Valencia), Spain

Received April 7, 1993®

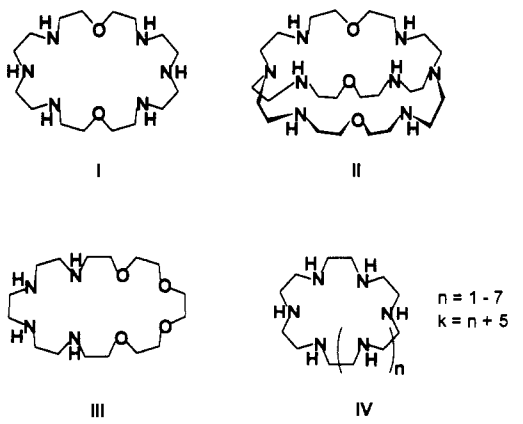
The synthesis and characterization of the two new oxa–aza macrocycles 10,13,16-trimethyl-1,4-dioxa-7,10,13,16,19-pentaazacyclohenicosane (Me_3[21]aneN_5O_2) and 13,16,19-trimethyl-1,4,7-trioxa-10,13,16,19,22-pentaazacyclotetracosane (Me_3[24]aneN_5O_3) are reported. Their basicity behavior in aqueous solution was investigated by means of potentiometric (298.1 ± 0.1 K, I = 0.15 mol dm^{-3}) and NMR (^{1}H and ^{13}C) techniques. ^{1}H–^{1}H and ^{1}H–^{13}C two-dimensional NMR experiments permitted the unequivocal assignment of all ^{1}H and ^{13}C resonances. Both of them behave as tetraprotic bases under the experimental conditions used. The protonation mechanism of these macrocyclic ligands was determined by means of ^{1}H and ^{13}C NMR spectra at various pH values. The thermodynamic parameters for the formation of 1:1 copper(II) complexes of both macrocycles were determined by potentiometry and microcalorimetry at 298.1 ± 0.1 K in 0.15 mol dm^{-3} $NaClO_4$. The involvement of all nitrogen donor atoms of the macrocycles in the coordination of the metal ion can be deduced, while the oxygens remain unbound. Furthermore mono- and diprotonated species are present at low pH. Crystal and molecular structures of the complexes $[Cu(Me_3[24]aneN_5O_3)](ClO_4)_2$ and $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)_2{\cdot}2H_2O$ were determined by single-crystal X-ray analysis. In $[Cu(Me_3[24]aneN_5O_3)](ClO_4)_2$ (space group $P2_1$, a = 8.371(2) Å, b = 11.781(2) Å, c = 14.390(3) Å, β = 96.90(2)°, V = 1408.8(5) Å^3, Z = 2, R = 0.047, R_w = 0.045) the metal ion is bound by the five nitrogens of the macrocyclic ligand, in a distorted square-pyramidal coordination geometry. In $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)_2{\cdot}2H_2O$ (space group $P\bar{1}$, a = 10.999(6) Å, b = 11.066(8) Å, c = 14.71(1) Å, α = 81.77(6), β = 80.46(5), γ = 61.68(5)°, V = 1550(2) Å^3, Z = 2, R = 0.052, R_w = 0.047) the copper(II) ion is coordinated by the three methylated nitrogen atoms of the ligand and two chloride anions, while the uncoordinated nitrogens are protonated. The resulting coordination polyhedron can be described as a trigonal bipyramid distorted toward a square pyramid with elongated axial distances. The latter crystal structure can give information on the topological features of protonated complexes of polyaza macrocyclic ligands.

Introduction

In the last few years the field of synthetic saturated oxa–aza macrocyclic compounds has undergone spectacular growth.[2]

Ditopic ligands with two N_3 binding subunits separated by $[CH_2]_2O[CH_2]_2$ (I in Chart I) or $[CH_2]_5$ bridges were investigated by Lehn's and Lippard's groups[3] in order to rationalize the formation, coordination geometries, and magnetic properties of polynuclear metal complexes. Lehn and co-workers also reported the synthesis of a macrobicycle with N_4 binding sites connected by similar bridges (II in Chart I).[4] The coordination tendencies toward transition metal ions of both these macrocycles have been studied by Martell and co-workers, with particular attention to the binding of anionic species by the metal centers.[5]

Chart I



* Abstract published in *Advance ACS Abstracts*, September 15, 1993.

(1) (a) Department of Chemistry, University of Florence. (b) Department of Energetics, University of Florence. (c) Department of Inorganic Chemistry, University of Valencia.

(2) (a) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721. (c) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475. (d) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (e) Christensen, J. J., Izatt, R. M., Eds. *Synthesis of Macrocycles, the Design of Selective Complexing Agents*; Wiley: New York, 1987. (f) Lindoy, L. F., Ed. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge Univ. Press: Cambridge, U.K., 1989. (g) Gokel, G. W. *Crown Ethers and Cryptands*; Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1992.

(3) (a) Coughlin, P. K.; Dewan, J. C.; Lippard, S. J.; Watanabe, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 265. (b) Coughlin, P. K.; Lippard, S. J.; Martin, A. E.; Bulkowski, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 7617. (c) Coughlin, P. K.; Lippard, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3228. (d) Comarmond, J.; Plumeré, P.; Lehn, J. M.; Agnus, Y.; Louis, R.; Weiss, R.; Kahn, O.; Morgenster-Badarau, I. *J. Am. Chem. Soc.* **1982**, *104*, 6330. (e) Lehn, J. M. *Pure Appl. Chem.* **1980**, *52*, 2441.

(4) Lehn, J. M.; Watanabe, E.; Pine, S. H.; Willard, A. K. *J. Am. Chem. Soc.* **1977**, *99*, 6766.

0020-1669/93/1332-4900$04.00/0

A great deal of interest in mixed oxa–aza macrocyclic receptors has been due to anion coordination by polyprotonated species of these ligands. Binding of simple anions by the hexaprotonated form of the macrocycles II, which can encapsulate halogenide ions,[6] as well as coordination of carboxylate anions[7] and of biologically relevant anionic substrates, such as ATP^{4-}, by the polyprotonated receptor I has been extensively studied.[8]

Furthermore, oxa–aza macrocycles with different kinds of molecular topology, such as "spherical" cryptands[2c,9] and "cylindrical" structures,[10] have been used to bind organic ammonium cations.

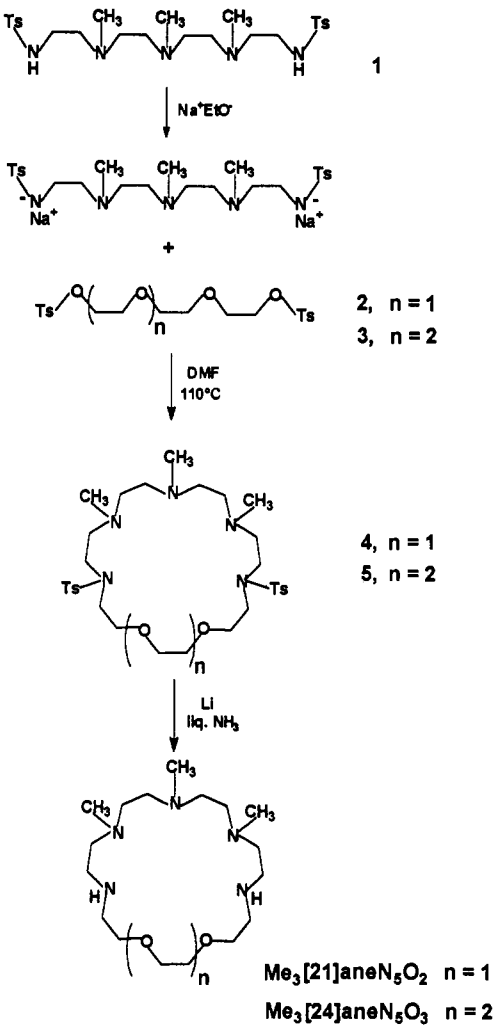
However, although a great variety of oxa–aza macrocyclic receptors have been examined in the search for synthetical host molecules, only few attempts have been devoted to the synthesis of macrocyclic structures containing both polyoxa and polyaza subunits as potentially hard and soft binding sites (III in Chart I).[11]

So far our own research interest has been devoted to large saturated aza macrocycles (IV in Chart I),[12] in order to analyze both metal ion coordination and the behavior of protonated species of these ligands as receptors for anionic species.[13] We are extending now our study to compartmental ligands presenting coordination sites with different characteristics having synthetized the two new macrocyclic receptors 10,13,16-trimethyl-1,4-dioxa-7,10,13,16,19-pentaazacyclohenicosane (Me_3[21]aneN_5O_2) and 13,16,19-trimethyl-1,4,7-trioxa-10,13,16,19,22-pentaazacyclotetracosane (Me_3[24]aneN_5O_3) displaying two different binding sites (one N_5 and one O_2 or O_3 subunits), located at opposite sides of the same macrocycle. In this paper we report on their synthesis and characterization as well as their ligational properties toward hydrogen (basicity) and copper(II) ions.

Experimental Section

Synthesis of the Compounds. The macrocycles Me_3[21]aneN_5O_2 and Me_3[24]aneN_5O_3 were obtained by following the synthetical procedure depicted in Scheme I. 1,13-Bis(*p*-tolylsulfonyl)-4,7,10-trimethyl-1,4,7,10,13-pentaazatridecane (**1**) was synthesized as reported in ref 14. Tetraethylene glycol bis(*p*-toluenesulfonate) (**2**) and triethylene glycol bis(*p*-toluenesulfonate) (**3**) were purchased from Aldrich Chemical Co.

Scheme I



10,13,16-Trimethyl-7,19-bis(*p*-tolylsulfonyl)-1,4-dioxa-7,10,13,16,19-pentaazacyclohenelcosane (4). All reaction were carried out in a nitrogen atmosphere. A solution of sodium (2.44 g, 0.105 mol) in dry ethanol (50 cm^3) was added to a hot solution of **1**·3HCl (13.1 g, 0.02 mol) in dry ethanol (100 cm^3). The resulting suspension was refluxed for *ca.* 30 min, and then the solvent was evaporated under reduced pressure. The solid residue was dissolved in dry DMF (100 cm^3), and to the resulting solution, heated at 110 °C, was added a solution of **2** (9.2 g, 0.02 mol) in 150 cm^3 of dry DMF, with stirring over a period of *ca.* 4 h. The reaction mixture was kept at 110 °C for a further 1.5 h. After cooling at room temperature, the resulting suspension was filtered and evaporated under reduced pressure to give a yellowish solid, which was dissolved in the minimum quantity of chloroform and chromatographed on neutral alumina (70–230 mesh, activity I), eluting with chloroform. The eluted fractions were collected and evaporated to dryness to obtain a colorless oil. Yield: 5.7 g (43%). Anal. Calcd for $C_{31}H_{51}N_5O_6S_2$: C, 56.94; H, 7.86; N, 10.76. Found: C, 56.7; H, 7.7; N, 10.6.

13,16,19-Trimethyl-1,4-dioxa-7,10,13,16,19-pentaazacyclohenelcosane (Me_3[21]aneN_5O_2). On a suspension of **4** (5.7 g, 0.009 mol) in diethyl ether (30 cm^3) and methanol (1 cm^3) cooled at −70 °C, ammonia (250 cm^3) was condensed. On addition of small bites of lithium (*ca.* 10 mg each piece), the reaction mixture became blue. The addition was continued until the suspension kept the blue color for at least 3 min. NH_4Cl (12 g, 0.2 mol) was added in small portions, and the reaction mixture was allowed to stand up to room temperature. Evaporation of

(5) (a) Motekaitis, R. J.; Martell, A. E.; Lehn, J. M.; Watanabe, E. *Inorg. Chem.* **1982**, *21*, 4253. (b) Motekaitis, R. J.; Martell, A. E.; Lecompte, J. P.; Lehn, J. M. *Inorg. Chem.* **1983**, *22*, 609. (c) Motekaitis, R. J.; Martell, A. E.; Dietrich, B.; Lehn, J. M. *Inorg. Chem.* **1984**, *23*, 1588. (d) Motekaitis, R. J.; Martell, A. E.; Murase, I. *Inorg. Chem.* **1986**, *25*, 938. (e) Motekaitis, R. J.; Martell, A. E. *J. Chem. Soc., Chem. Commun.* **1988**, 915. (f) Motekaitis, R. J.; Martell, A. E. *J. Am. Chem. Soc.* **1988**, *110*, 8059. (g) Motekaitis, R. J.; Martell, A. E.; Murase, I.; Lehn, J. M.; Hosseini, M. H. *Inorg. Chem.* **1988**, *27*, 3630. (h) Motekaitis, R. J.; Rudolf, P. R.; Martell, A. E.; Clearfield, A. *Inorg. Chem.* **1989**, *28*, 112. (i) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1992**, *31*, 5534 and references therein.

(6) Diederich, B.; Guilhem, J.; Lehn, J. M.; Pascard, C.; Sonveaux, E. *Helv. Chim. Acta* **1984**, *67*, 91.

(7) Diederich, B.; Hosseini, M. W.; Lehn, J. M.; Session, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282.

(8) (a) Hosseini, M. W.; Lehn, J. M.; Mertes, M. P. *Helv. Chim. Acta* **1983**, *66*, 2454. (b) Hosseini, M. W.; Lehn, J. M.; Maggiora, L.; Mertes; M. P.; Mertes, K. B. *J. Am. Chem. Soc.* **1985**, *107*, 909. (c) Hosseini, M. W.; Lehn, J. M.; Maggiora, L.; Mertes,; M. P.; Mertes, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 537. (d) Hosseini, M. W.; Lehn, J. M.; Jones, K. C.; Plute, K. E.; Mertes; M. P.; Mertes, K. B. *J. Am. Chem. Soc.* **1989**, *109*, 6330. (e) Mertes, M. P.; Mertes, K. B. *Acc. Chem. Res.* **1990**, *23*, 413 and references therein.

(9) Graf, E.; Kintzinger, J. P.; Lehn, J. M.; LeMoigne, J. *J. Am. Chem. Soc.* **1982**, *104*, 1672.

(10) (a) Kumar, A.; Mageswaran, S.; Sutherland, I. O. *Tetrahedron* **1986**, *42*, 3291. (b) Pratt, A. E.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 13. (c) Pascard, C.; Riche, C.; Cesario, M.; Kotzyba-Hibert, F.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 557.

(11) Sessler, J. L.; Sibert, J. W.; Hugdahl, J. D.; Lynch, V. *Inorg. Chem.* **1989**, *28*, 1417.

(12) (a) Bianchi, A.; Micheloni, M.; Paoletti, P. *Coord. Chem. Rev.* **1991**, *110*, 17. (b) Bencini, A.; Bianchi, A.; Paoletti, P.; Paoli, P. *Coord. Chem. Rev.* **1992**, *120*, 51. (c) Bencini, A.; Bianchi, A.; Paoletti, P.; Paoli P. *Pure Appl. Chem.* **1993**, *65*, 381.

(13) Bencini, A.; Bianchi, A.; Dapporto, P.; Garcia-España, E.; Micheloni, M.; Ramirez, J. A.; Paoletti, P.; Paoli, P. *Inorg. Chem.* **1992**, *31*, 1902 and references therein.

(14) Bencini, A.; Bianchi, A.; Garcia-España, E.; Fusi, V.; Micheloni, M.; Paoletti, P.; Ramirez, J. A.; Rodriguez, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1059.

ammonia gave a white solid residue, which was treated with 3 mol dm^3 HCl (300 cm^3). The resulting suspension was washed with chloroform (3 × 100 cm^3), and the aqueous layer filtered and evaporated to dryness under reduced pressure to give a white solid. This product was dissolved in the minimum amount of water, and the resulting solution was made alkaline with concentrated NaOH. This solution was extracted with CH_2Cl_2 (6 × 100 cm^3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, affording the macrocycle Me_3[21]aneN_5O_2 as a colorless oil. Yield: 1.6 g (54%). Anal. Calcd for $C_{17}H_{39}N_5O_2$: C, 59.09; H, 11.38; N, 20.27. Found: C, 59.0; H, 11.5; N, 20.4.

Me_3[21]aneN_5O_2·4$HClO_4$. The tetraperchlorate salt was obtained in a quantitative yield by adding 70% $HClO_4$ to an ethanolic solution containing the free amine. The white solid formed was filtered off and recrystallized from methanol. Anal. Calcd for $C_{17}H_{43}N_5O_{15}Cl_4$: C, 27.32; H, 5.80; N, 9.37. Found: C, 27.2; H, 5.8; N, 9.3.

13,16,19-Trimethyl-10,22-bis(*p*-tolylsulfonyl)-1,4,7-trioxa-10,13,16,19,22-pentaazacyclotetracosane (5). This compound was synthesized from **1** (13.1 g, 0.02 mol) and **3** (10.0 g, 0.02 mol) by following the procedure reported for **4**. Yield: 5.2 g (37%). Anal. Calcd for $C_{33}H_{55}N_5O_7S_2$: C, 56.79; H, 7.94; N, 10.03. Found: C, 56.7; H, 8.0; N, 9.9.

13,16,19-Trimethyl-1,4,7-trioxa-10,13,16,19,22-pentaazacyclotetracosane (Me_3[24]aneN_5O_3). This macrocycle was obtained from **5** as described for Me_3[21]aneN_5O_2. Yield: 2 g (68%). Anal. Calcd for $C_{19}H_{43}N_5O_3$: C, 58.58; H, 11.12; N, 17.98. Found: C, 58.5; H, 11.0; N, 17.9.

Me_3[24]aneN_5O_3·5HNO_3. The nitrate salt was synthesized in a quantitative yield by adding 65% HNO_3 to an ethanolic solution containing the free amine. The pentanitrate salt precipitated was filtered off and recrystallized from an 2:1 ethanol/water mixture. Anal. Calcd for $C_{19}H_{48}N_{10}O_{18}$: C, 32.39; H, 6.86; N, 19.88. Found: C, 32.3; H, 6.9; N, 19.8.

[Cu(Me_3[21]aneN_5O_2)](ClO_4)$_2$. A solution of $Cu(ClO_4)_2$·$6H_2O$ (37.2 mg, 0.1 mmol) in methanol (5 cm^3) was added to a methanolic solution (5 cm^3) of Me_3[21]aneN_5O_2 (34.5 mg, 0.1 mmol). To the resulting blue solution was added butanol (10 cm^3) until the precipitation of a blue solid, which was filtered off, washed with a 1:1 methanol/butanol mixture, and dried in vacuum. Yield: 60 mg (83%). Anal. Calcd for $C_{17}H_{39}N_5O_{10}Cl_2Cu$: C, 33.58; H, 6.46; N, 11.52. Found: C, 33.5; H, 6.3; N, 11.6. *Caution: Perchlorate salts of metal complexes with organic ligands are potentially explosive; these compound must be handle with great caution!*

[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)$_2$·2H_2O. An aqueous solution (5 cm^3) of $Cu(ClO_4)_2$·$6H_2O$ (37.2 mg, 0.1 mmol) was added to an aqueous solution (5 cm^3) of Me_3[21]aneN_5O_2 (34.5 mg, 0.1 mmol). The pH of the solution was adjusted at 5 by adding small amounts of diluted HCl. Crystals of the complex suitable for X-ray analysis were obtained by slow evaporation at room temperature of the resulting solution. Yield: 27 mg (37%). Anal. Calcd for $C_{17}H_{46}N_5O_{12}Cl_4Cu$: C, 28.48; H, 6.33; N, 9.77. Found: C, 28.5; H, 6.3; N, 9.7.

[Cu(Me_3[24]aneN_5O_3)](ClO_4)$_2$. The complex [Cu(Me_3[24]aneN_5O_3)](ClO_4)$_2$ was obtained by mixing a solution of Me_3[24]aneN_5O_3·5HNO_3 (70.5 mg, 0.1 mmol) in 5 cm^3 of 0.2 mol dm^{-3} NaOH and an aqueous solution (5 cm^3) of $Cu(ClO_4)_2$·$6H_2O$ (37.2 mg, 0.1 mmol). By slow evaporation of the resulting solution crystals of the complex, suitable for X-ray analysis, grew. Yield: 43 mg (66%). Anal. Calcd for $C_{19}H_{43}N_5O_{11}Cl_2Cu$: C, 35.00; H, 6.65; N, 10.74. Found: C, 34.9; H, 6.6; N, 10.6.

Emf Measurements. All the potentiometric measurements were carried out in 0.15 mol dm^{-3} $NaClO_4$ or NEt_4ClO_4 at 298.1 ± 0.1 K, by using the equipment that has been already described.[15] The reference electrode was an Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2-free NaOH solutions and determining the equivalent point by Gran's method,[16] which allows one to determine the standard potential $E°$, and the ionic product of water. At least three measurements were performed for each system. The computer program SUPERQUAD[17] was used to calculate both protonation and stability constants from emf data. The titration curves for each system were treated either as a single set or as separated entities without significant variations in the values of the stability constants.

Microcalorimetry. The enthalpy changes for the reaction of Cu^{2+} with Me_3[21]aneN_5O_2 and Me_3[24]aneN_5O_3 were determined by means of an LKB Batch Model 10700-2 microcalorimeter in aqueous solution at 298.1 ± 0.1 K in 0.15 mol dm^{-3} $NaClO_4$. The direct reaction of the metal ion with the two ligands is fast. The heat of reaction was measured by mixing aqueous solutions of Cu^{2+} and of the free ligand; the only significant species present at equilibrium before and after mixing were the free polyamine and the unprotonated complex.

NMR Spectroscopy. The 200.0-MHz ^1H NMR and 50.32-MHz ^{13}C spectra in D_2O solutions at different pH values were recorded at 298 K in a Bruker AC-200 spectrometer. In ^1H NMR spectra peak positions are reported relative to HOD at 4.75 ppm. Dioxane was used as reference standard in ^{13}C NMR spectra (δ = 67.4 ppm). Small amounts of NaOD or DCl were added to a solution of Me_3[21]aneN_5O_2 or Me_3[24]aneN_5O_3 to adjust the pD. The pH was calculated from the measured pD values using the following relationship:[18]

$$pH = pD - 0.40$$

Electronic Spectroscopy. The electronic spectra were recorded on a Perkin-Elmer Lambda 9 spectrophotometer equipped with a 1-cm cell thermostated at 298 K.

X-ray Structure Analysis. Analyses on single crystals of [Cu(H_2Me_3-[21]aneN_5O_2)Cl_2](ClO_4)$_2$·2H_2O and [Cu(Me_3[24]aneN_5O_3)](ClO_4)$_2$ were carried out with an Enraf-Nonius CAD4 X-ray diffractometer that uses an equatorial geometry; a summary of the crystallographic data is reported in Table I. A prismatic green crystal of [Cu(H_2Me_3[21]-aneN_5O_2)Cl_2](ClO_4)$_2$·2H_2O and a prismatic blue crystal of [Cu(Me_3-[24]aneN_5O_3)](ClO_4)$_2$ of approximate dimensions 0.4 × 0.4 × 0.3 mm and 0.3 × 0.2 × 0.1 mm, respectively, were mounted on the diffractometer and used for data collection at room temperature with graphite-monochromated Mo Kα radiation.

Cell parameters for both compounds were determined by least-squares refinement of diffractometer setting angles for 25 carefully centered reflections. The intensities of two standard reflections were monitored periodically during data collection: no loss of intensities was recognized. A total of 5653 and 2702 reflections were collected for [Cu(H_2Me_3[21]-aneN_5O_2)Cl_2](ClO_4)$_2$·2H_2O and [Cu(Me_3[24]aneN_5O_3)](ClO_4)$_2$, respectively, up to 2θ = 50°. Intensity data were corrected for Lorentz and polarization effects, and an absorption correction was applied once the structures were solved by the Walker and Stuart method.[19]

The structures were solved by the heavy-atom technique, which showed the copper atoms and some chlorine atoms. Subsequent fourier maps showed all the non-hydrogen atoms in both structures.

Table I. Crystallographic data for [Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)$_2$·2H_2O (**a**) and [Cu(Me_3[24]aneN_5O_3)](ClO_4)$_2$ (**b**)

	a	**b**
chem formula	$C_{17}H_{45}Cl_4CuN_5O_{12}$	$C_{19}H_{43}Cl_2CuN_5O_{11}$
fw	716.95	652.03
space group	$P\bar{1}$	$P2_1$
a, Å	10.999(6)	8.371(2)
b, Å	11.066(8)	11.781(2)
c, Å	14.710(10)	14.390(3)
α, deg	81.77(6)	90.0
β, deg	80.46(5)	96.90(2)
γ, deg	61.68(5)	90.0
V, Å^3	1550(2)	1408.8(5)
Z	2	2
D_c, g cm^{-3}	1.54	1.54
radiation (λ, Å)	graphite-monochromated Mo Kα (0.7107)	
μ, cm^{-1}	11.1	10.3
T, °C	25	25
R^a	0.052	0.047
R_w^b	0.047	0.045

^{a} $R = \sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$.

(15) Bianchi, A.; Bologni, L.; Dapporto, P.; Micheloni, M.; Paoletti, P. *Inorg. Chem.* **1984**, *23*, 1201.
(16) (a) Gran, G. *Analyst (London)* **1952**, *77*, 661. (b) Rossotti, F. J.; Rossotti, H. *J. Chem. Educ.* **1965**, *42*, 375.
(17) Gans, P.; Sabatini, A.; Vacca, A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195.
(18) Covington, A. K.; Paabo, M.; Robinson, R. A.; Bates, R. G. *Anal. Chem.* **1968**, *40*, 700.
(19) Walker, N.; Stuart, D. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 158.

Table II. Positional Parameters (×10⁴) for $C_{17}H_{45}Cl_4CuN_5O_{12}$ and Equivalent Temperature Factors (×10³), with Esd's in Parentheses

atom	x/a	y/b	z/c	U_{eq}, Å²
Cu	2529(1)	815(1)	2189(1)	31(1)
Cl1	4395(1)	889(1)	1260(1)	41(1)
Cl2	3969(1)	−472(1)	3461(1)	39(1)
Cl3	8100(2)	3550(2)	127(1)	59(1)
Cl4	7622(2)	3774(1)	5348(1)	51(1)
O31	7408(8)	2864(7)	635(4)	184(7)
O32	8055(5)	4501(4)	665(4)	116(4)
O33	7604(7)	4091(6)	−701(4)	160(6)
O34	9429(6)	2512(6)	−37(4)	176(5)
O41	7556(5)	4954(4)	4823(3)	97(4)
O42	6909(6)	3267(5)	4942(4)	137(5)
O43	7151(6)	4014(5)	6262(3)	129(4)
O44	8996(5)	2734(5)	5287(4)	137(4)
O3	4108(4)	4287(4)	6732(2)	64(3)
O4	5759(5)	3699(5)	2311(3)	103(4)
N1	4682(4)	2037(5)	3279(3)	40(3)
N2	1646(4)	2943(3)	2309(3)	35(2)
N3	607(3)	1065(4)	2780(3)	35(2)
N4	2613(3)	−850(3)	1540(2)	33(2)
N5	5997(4)	−2269(5)	1772(3)	37(3)
O1	8192(3)	−2993(3)	2778(2)	50(2)
O2	7495(3)	−230(3)	3458(2)	47(2)
C1	3145(5)	2895(5)	3446(3)	48(3)
C2	2489(5)	3543(5)	2561(3)	42(3)
C3	387(5)	3308(5)	2973(3)	45(3)
C4	−366(5)	2540(5)	2783(4)	49(3)
C5	167(5)	392(5)	2185(3)	46(3)
C6	1357(5)	−993(5)	1984(3)	46(3)
C7	3774(5)	−2274(4)	1609(3)	42(3)
C8	5194(4)	−2513(5)	1158(3)	42(3)
C9	7395(5)	−2513(5)	1324(3)	46(3)
C10	8098(5)	−2146(5)	1949(3)	50(3)
C11	8741(5)	−2691(5)	3488(4)	55(3)
C12	7702(5)	−1478(5)	4001(3)	51(3)
C13	6895(5)	947(5)	3976(3)	48(3)
C14	5362(5)	1581(5)	4152(3)	45(3)
C15	1243(5)	3574(5)	1381(3)	49(3)
C16	657(5)	424(5)	3737(3)	49(3)
C17	2464(5)	−369(5)	549(3)	44(3)
H011	4761(43)	1232(47)	3028(30)	55(15)
H012	5063(44)	2416(44)	2875(30)	46(14)
H051	5968(52)	−2568(54)	2338(37)	72(19)
H052	5266(56)	−1164(62)	1943(37)	117(20)

Refinements were performed by means of the full-matrix least-squares method. In both cases the function minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = a/\sigma^2(F)$, where a is an adjustable parameter.

All calculations, carried out on an IBM PS/2 Model 80 computer, were performed with the SHELX-76[20] set of programs which use the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms from ref 21.

$[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)_2 \cdot 2H_2O$. Crystals of the compound belong to the triclinic family, space group $P\bar{1}$ ($Z = 2$), lattice constants $a = 10.999(6)$ Å, $b = 11.066(8)$ Å, $c = 14.71(1)$ Å, $\alpha = 81.77(6)°$, $\beta = 80.46(5)°$, and $\gamma = 61.68(5)°$.

All the non-hydrogen atoms were refined using anisotropic thermal parameters, while the hydrogen atoms bound to the carbon atoms of the ligand were included in calculated positions and their coordinates refined in agreement with those of the linked atoms, with a temperature factor U of 0.05 Å². The hydrogen atoms of the secondary nitrogen atoms N1 and N5 were found in a ΔF map carried out in the last refinement step and successfully refined with isotropic thermal parameters. The final agreement factors were $R = 0.052$ and $R_w = 0.047$ for 368 refined parameters and 4864 unique observed reflections having $I > 3\sigma(I)$. Table II shows the final coordinates with estimated standard deviations.

$[Cu(Me_3[24]aneN_5O_3)](ClO_4)_2$. The compound crystallizes in the monoclinic family, space group $P2_1$ ($Z = 2$), cell dimensions $a = 8.371(2)$ Å, $b = 11.781(2)$ Å, $c = 14.390(3)$ Å, and $\beta = 96.90(2)°$.

The hydrogen atoms were introduced in calculated position, with an overall thermal parameter U of 0.05 Å² and their positional parameters refined accordingly to those of the bound atoms. Anisotropic thermal parameters were used with all the other atoms.

In this case the final agreement factors were $R = 0.047$ and $R_w = 0.045$. The number of refined parameters was 342 for 2429 independent observed reflections with $I > 3\sigma(I)$. The absolute structure has been determined by performing two separate refinements for the two enantiomorphs. The correct one gave $R = 0.047$ and $R_w = 0.045$, whereas for the other these values were 0.049 and 0.048, respectively.

The final atomic coordinates are reported in Table III.

Table III. Positional Parameters (×10⁴) and Equivalent Thermal Parameters (×10³) for $C_{19}H_{43}Cl_2CuN_5O_{11}$, with Esd's in Parentheses

atom	x/a	y/b	z/c	U_{eq}, Å²
Cu	612(1)	0	2506(1)	30(1)
Cl1	5966(2)	215(2)	5310(2)	51(1)
O11	7500(8)	−268(10)	5579(5)	101(7)
O12	5021(10)	73(15)	6009(6)	142(8)
O13	5269(9)	−274(9)	4482(6)	114(7)
O14	6151(12)	1366(8)	5145(7)	117(8)
Cl2	5632(3)	6212(3)	646(2)	66(2)
O21	5262(22)	6319(16)	1454(9)	272(18)
O22	5421(13)	5193(13)	408(13)	232(15)
O23	7241(12)	6425(9)	689(9)	149(10)
O24	4843(19)	7173(17)	145(10)	224(14)
N1	−964(7)	1407(6)	2420(4)	38(4)
N2	−363(8)	−196(6)	1152(4)	38(4)
N3	2356(8)	−1189(7)	2142(5)	41(4)
N4	13(8)	−1555(6()	3458(5)	43(4)
N5	1830(7)	431(5)	3787(4)	34(3)
O1	2488(7)	1976(5)	2331(4)	41(3)
O2	410(9)	3756(6)	1700(5)	67(4)
O3	−1140(7)	3532(5)	3276(4)	53(4)
C1	−1847(11)	1454(8)	1505(6)	52(5)
C2	−801(12)	947(9)	808(6)	53(6)
C3	931(10)	−644(8)	648(6)	50(5)
C4	1768(11)	−1596(8)	1181(6)	57(6)
C5	2451(13)	−2148(9)	2800(7)	58(7)
C6	834(11)	−2518(8)	3067(7)	53(6)
C7	725(12)	−1298(8)	4403(6)	54(5)
C8	971(9)	−26(10)	4537(5)	46(4)
C9	2231(10)	1664(7)	3949(5)	39(5)
C10	3293(10)	2095(8)	3242(6)	43(5)
C11	2913(12)	2876(10)	1727(7)	68(7)
C12	2050(16)	3938(9)	1865(7)	78(8)
C13	−545(20)	4603(11)	2027(9)	153(13)
C14	−1156(18)	4549(10)	2808(10)	100(10)
C15	−2533(11)	2900(8)	3139(7)	58(6)
C16	−2021(11)	1667(8)	3166(7)	47(5)
C17	−1726(11)	−986(9)	1033(7)	55(6)
C18	3989(10)	−679(8)	2122(7)	61(6)
C19	−1716(13)	−1866(10)	3462(7)	66(7)

Results and Discussion

Synthesis. Compounds **4** and **5** were synthesized by means of well-known procedures.[2c,22] The subsequent removal of the protecting tosyl groups was carried out by employing Li in liquid NH_3[23] as the cleavage of ether linkages could take place by using alternative acidic detosylation methods.[22]

Both macrocycles are extremely versatile precursor molecules from a synthetical point of view. One of the goals of macrocyclic chemistry is the construction of highly organized structures with branches or connections that allow the arrangement of several binding sites and reactive functions.[24] Thus, a significant step in aza macrocycle synthesis is specific functionalization of amino groups. In both $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ the presence of three tertiary and only two secondary amino groups allows for the insertion in the macrocyclic framework of two "side arms" containing functional groups or bridging connections, in order to perform more structured receptors.

(20) Sheldrick, G. M. *SHELX-76, Program for Crystal Structure Determination*; University of Cambridge: Cambridge, England, 1976.
(21) *International Tables for X-ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.
(22) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268.
(23) Lehn, J. M.; Montavon, F. *Helv. Chim. Acta* **1976**, *59*, 1566.
(24) (a) Pilichowski, J. F.; Lehn, J. M.; Sauvage, J. P.; Gramain, J. C. *Tetrahedron* **1985**, *41*, 1959. (b) Hosseini, M. W.; Lehn, J. M.; Duff, S. R.; Gu, K.; Mertes, M. P. *J. Org. Chem.* **1987**, *52*, 909.

Table IV. Logarithms of the Protonation Constants of $Me_3[21]andN_5O_2$ and $Me_3[24]aneN_5O_3$ in 0.15 mol dm^{-3} $NaClO_4$ and 0.15 mol dm^{-3} NEt_4ClO_4 Aqueous Solution at 298.15 K

	log K			
	L = $Me_3[21]aneN_5O_2$		L = $Me_3[24]aneN_5O_3$	
reacn	$NaClO_4$	NEt_4ClO_4	$NaClO_4$	NEt_4ClO_4
$L + H^+ = LH^+$	9.31(1)[a]	9.26(1)	9.32(1)	9.41(3)
$L + 2H^+ = LH_2^{2+}$	17.89(1)	17.66(2)	17.91(1)	17.89(2)
$L + 3H^+ = LH_3^{3+}$	25.39(1)	24.95(2)	25.48(1)	25.43(3)
$L + 4H^+ = LH_4^{4+}$	27.87(1)		28.26(1)	27.62(5)
$LH^+ + H^+ = LH_2^{2+}$	8.58	8.40	8.59	8.48
$LH_2^{2+} + H^+ = LH_3^{3+}$	7.50	7.29	7.57	7.54
$LH_3^{3+} + H^+ = LH_4^{4+}$	2.48		2.78	2.19

[a] Values in parentheses are standard deviations on the last significant figure.

Protonation. The behavior of both $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ toward protonation was studied in 0.15 mol dm^{-3} $NaClO_4$ or 0.15 mol dm^{-3} NEt_4ClO_4 solutions at 298.1 ± 0.1 K in the pH range 2.5–11.5. The values of the basicity contants obtained in both media are presented in Table IV. Under the experimental conditions employed both macrocycles behave as tetraprotic bases. For each ligand the protonation constants are very similar in the two ionic media (0.15 mol dm^{-3} $NaClO_4$ or NEt_4ClO_4), especially in the first steps of protonation, according to a negligible interaction between the macrocycles and Na^+. However, a slight difference is observed for $Me_3[24]aneN_5O_3$ in the fourth protonation step, while, in the case of $Me_3[21]aneN_5O_2$, the value of the fourth basicity constant in 0.15 mol dm^{-3} NEt_4ClO_4 solution is too small to be confidently determined by potentiometry.

The basicity features of the two macrocycles are almost identical, the first two protonation constants being equal within the experimental error. Only in the fourth protonation step $Me_3[24]aneN_5O_3$ exhibits a basicity constant somewhat larger than that of $Me_3[21]aneN_5O_2$.

By using these equilibrium data, the distributions of the species of $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ formed as a function of pH were calculated, and the results, in the case of $Me_3[24]aneN_5O_3$, are reported in Figure 1.

The values of the basicity constants of $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ are lower than those reported for the corresponding protonation steps of the dimensionally analogous polyazacycloalkanes [21]$aneN_7$ and [24]$aneN_8$ (Chart I, $n = 2$ and $n = 3$, respectively, in ligand drawing IV),[12a] in which all the donors are secondary nitrogen atoms. This could be explained considering the methylation of some nitrogen atoms even if statistical effects, due to the presence in [21]$aneN_7$ of a larger number of nitrogens available for protonation, can contribute to lower the basicity.[25] Indeed, it has been observed[14] that [18]$aneN_6$ is more basic than the tetramethylated analogous Me_4-[18]$aneN_6$, which contains a $NMe-(CH_2)_2-NMe-(CH_2)_2-NMe$ chain, similarly to $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$.

Also of interest is the sharp decrease in basicity between the third and fourth stepwise constants of both these oxa–aza macrocycles: in the case of $Me_3[21]aneN_5O_2$, the difference between the first and the third protonation constants is only 1.81 logarithm units, while that between the third and the fourth ones is 5.02. Similar values can be calculated for $Me_3[24]aneN_5O_3$. As previously reported, this behavior can be rationalized considering the minimization of electrostatic repulsion between positive charges in protonated species of polyaza macrocycles.[12a] In $Me_3[24]aneN_5O_3$ the first three protons can occupy alternate positions in the macrocycle, separated by an unprotonated amino group, while in the tetraprotonated ligand two or more protonated nitrogens are necessarily contiguous (*vide infra*).

(25) For [18]$aneN_6$: log K_1 = 10.15, log K_2 = 9.18, log K_3 = 8.89, log K_4 = 4.27, log K_5 = 2.21, log K_6 = 1; for 1,4,7,13-tetramethyl-1,4,7,10,-13,16-hexazacyclooctadecane (Me_4[18]$aneN_6$): log K_1 = 9.75, log K_2 = 9.11, log K_3 = 7.53, log K_4 = 2.59; for [21]$aneN_7$: log K_1 = 9.76, log K_2 = 8.63, log K_3 = 8.63, log K_4 = 6.42, log K_5 = 2.13, log K_6 = 2.0; for [24]$aneN_8$: log K_1 = 9.65, log K_2 = 9.33, log K_3 = 8.76, log K_4 = 7.87, log K_5 = 4.55, log K_6 = 3.42, log K_7 = 2.71, log K_8 = 1.95.

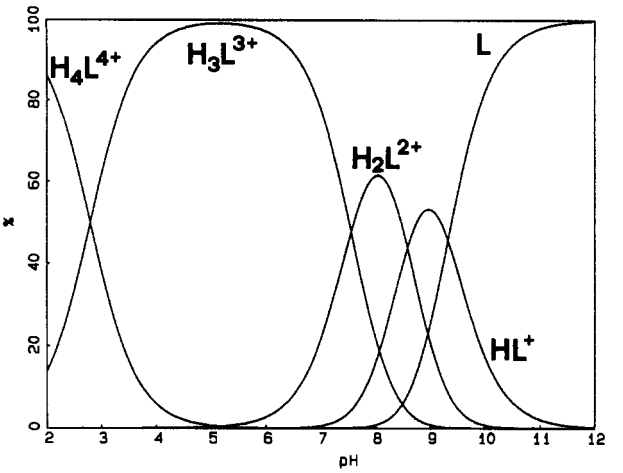


Figure 1. Distribution diagram of the species formed as a function of pH in the system $H^+/Me_3[24]aneN_5O_3$ in 0.15 mol dm^{-3} $NaClO_4$ solution at 298.15 K. [$Me_3[24]aneN_5O_3$] = 1 × 10^{-3} mol dm^{-3}.

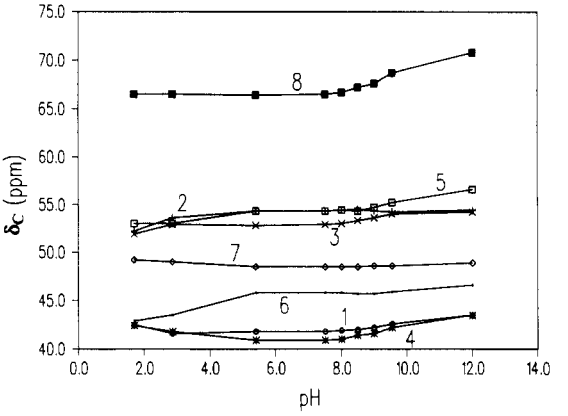


Figure 2. Experimental ^{13}C NMR chemical shifts of $Me_3[24]aneN_5O_3$ as a function of pH. Labels are reported as for $Me_3[24]aneN_5O_3$. The chemical shifts of the signals of the carbon atoms C9 and C10 do not change appreciably in the pH range investigated (δ_{C9} = 70.9–71.1 ppm, δ_{C10} = 70.7–70.9 ppm) and are not reported for clarity.

In order to get further information on the protonation mechanism of these cyclic polyamines, ^1H and ^{13}C spectra at different pH values were recorded.

The ^{13}C spectrum of $Me_3[24]aneN_5O_3$ at pH 12, where the free amine predominates (Figure 1), consists of nine signals at 71.1, 70.8, 70.7, 56.6, 54.4, 54.2, 48.9, 46.5, and 43.4 ppm. The resonances at 71.1, 70.8, and 70.7 ppm can be attributed to the carbon atoms near the oxygens (C8, C9, C10), while the peak at 43.4 ppm can be assigned to the carbon atoms of the methyl groups (C1, C4). The ^1H NMR spectrum exhibits two singlets at 3.79 and 3.78 ppm (attributed to the hydrogens of C9 and C10) and two singlets at 2.36 and 2.35 ppm (the hydrogens of the methyl groups). The hydrogen atoms of the ethylenic chains C7–C8 display an A_2B_2 spin system (ν_A = 3.73 ppm, ν_B = 2.88 ppm, J_{AB} = 4.6 Hz), while those of the remaining ethylenic chains give rise to a complex pattern of signals in the range 2.85–2.65 ppm.

Figures 2 and 3 show respectively the ^{13}C and ^1H NMR chemical shifts of $Me_3[24]aneN_5O_3$ as a function of pH. As far the ^{13}C NMR spectra are concerned, in all the pH range investigated the number of signals does not exceed half of the overall carbon atoms of this molecule indicating a C_{2v} time-

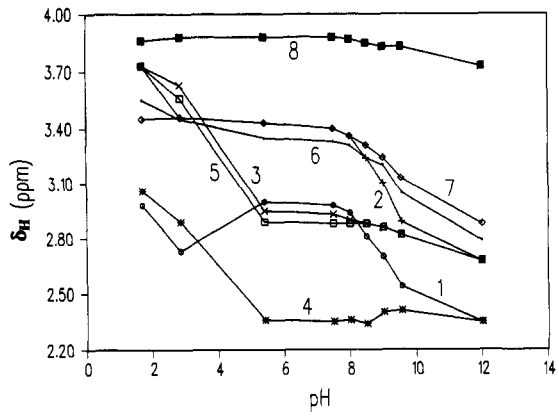


Figure 3. Experimental ^1H NMR chemical shifts of $Me_3[24]aneN_5O_3$ as a function of pH. Labels refer to the carbon atoms as reported for $Me_3[24]aneN_5O_3$. The chemical shifts of the signals for the hydrogens of C9 and C10 do not change appreciably in the pH range investigated (δ_9 = 3.76–3.80 ppm, δ_{10} = 3.76–3.80 ppm) and are not reported for clarity.

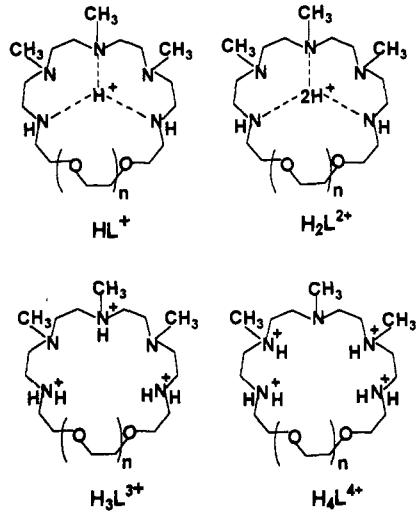
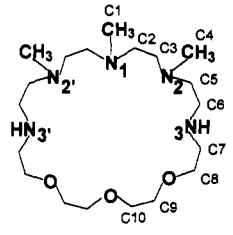


Figure 4. Suggested protonation mechanism.

averaged symmetry. All ^{13}C and ^1H resonances were assigned on the basis of ^1H–^{13}C heteronuclear and ^1H–^1H homonuclear correlations.



At pH 9, where $(HMe_3[24]aneN_5O_3)^+$ prevails in solution, the resonances of the hydrogens of C6 and C7, in α-position with respect to the secondary amino groups, as well as those of the hydrogens of C2 and C1, in α-position with respect to the methylated nitrogen N1, bear a remarkable downfield shift, while the signal of the hydrogens of the methyl group C4 does not shift appreciably. This suggests that the first proton binding the macrocycle is shared by the two secondary nitrogen atoms (N3 and N3′) and the methylated N1 (Figure 4). This hypothesis is confirmed by the spectral features of the ^{13}C spectrum recorded at this pH: the signals of the carbon atoms C3, C5, and C8 shift upfield (Figure 2), in good agreement with the β-shift reported for protonation of polyamines.[26]

The same trend is shown by the ^1H and ^{13}C NMR spectra recorded at pH 8, where $Me_3[24]aneN_5O_3$ is mainly in its diprotonated form, until pH 5.5, where the only species present in solution is the triprotonated $(H_3Me_3[24]aneN_5O_3)^{3+}$ (Figure 1). In other words, in the pH range 12–5.5, the first three protonation steps involve only the secondary amino groups and the nitrogen atom N1, as reported in Figure 4. Since the protons occupy alternate positions, such as disposition would mean a minimum in electrostatic repulsions.

As seen in the distribution diagram (Figure 1), $Me_3[24]aneN_5O_3$ is mainly in its tetraprotonated form at pH < 2.6. Figure 3 shows that the signal of the hydrogens of the methyl group C4 does not shift appreciably until pH 5.5, indicating that the nitrogen atoms N2 and N2′ are not involved in proton binding at least in the first three protonation steps. In the ^1H spectrum recordered at pH 2.5, this signal bears a clear downfield shift, while the signal of the hydrogen atoms of the methyl group C1 shifts upfield. A downfield shift is also observed for the resonances of the hydrogens of C3 and C5, in α-position with respect to N2. These spectral features indicate that in $[H_4Me_3[24]aneN_5O_3]^{4+}$ species the four protons are located on the secondary amino groups N3 and N3′ and on the methylated nitrogens N2 and N2′, while N1 remains unprotonated (Figure 4). This protonation pattern agrees with the upfield shifts experienced in the ^{13}C NMR spectra by the resonance of C6, in β-position with respect to N2. Obviously, the fifth protonation site is N1. The potentiometric study has not evidenced the formation of the $[H_5Me_3[24]aneN_5O_3]^{5+}$ species in the pH range 2.5–11.5; however, in the ^1H spectrum at pH 1.7 the sharp downfield shift experienced by the hydrogen atoms of C1 and C2 can be explained with the presence at this pH of the pentaprotonated form of the macrocycle.

As far as the ligand $Me_3[21]aneN_5O_2$ is concerned, the same protonation mechanism can be deduced from the analysis of ^1H and ^{13}C spectra recorded at different pH values.

Description of the Structures. $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)_2\cdot 2H_2O$. The molecular structure consists of $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2]^{2+}$ cations, ClO_4^- anions, and lattice water molecules.

The copper(II) ion is coordinated by the three methylated nitrogens of the ligand N2, N3, and N4 and by two chloride ions; the Cu–N bonds range from 2.052(4) to 2.151(5) Å, while the Cu–Cl distances are 2.298(2) and 2.474(2) Å, for Cl1 and Cl2, respectively. Figure 5 reports an ORTEP[27] view of the complex. Distances and angles for the metal's coordination are listed in Table V. The arrangement of the five donor atoms around the metal ion does not result in a regular polyhedron. The geometry of the coordination sphere can be described as trigonal bipyramid remarkably distorted toward a square pyramid, N3 and Cl1 being in the axial positions of the bipyramid and Cl2 in the apical position of the square pyramid. In fact the three equatorial bond angles show a significant distortion from an idealized trigonal bipyramidal geometry, the equatorial angles being N2–Cu–Cl2 = 110.2(1)°, N2–Cu–N4 = 148.6(2)°, and N4–Cu–Cl2 = 100.6(1)°. Furthermore the distance of the Cl2 atom from the metal ion (Cu–Cl2 = 2.474(2) Å), which is opposite to the larger equatorial angle N2–Cu–N4 is significantly longer than the analogous Cu–Cl1 (2.298(2) Å). An elongation of the axial distance is usually found in square pyramidal complexes of Cu(II).[28] The hydrogen atoms located on N1 and N5 form both intramolecular and intermolecular hydrogen bonds. Particularly in the complexed cation the chloride ions Cl1 and Cl2 are involved in the following network of hydrogen bonds with the hydrogen

(26) Sarnessky, J. E.; Surprenant, H. L.; Molen, F. K.; Reilley, C. N. *Anal. Chem.* **1975**, *47*, 2116.
(27) Johnson, C. K. *ORTEP*. Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN, 1971.
(28) Hatfield, W. E.; Whyrnam, R. *Trans. Met. Chem.* **1969**, *5*, 47.

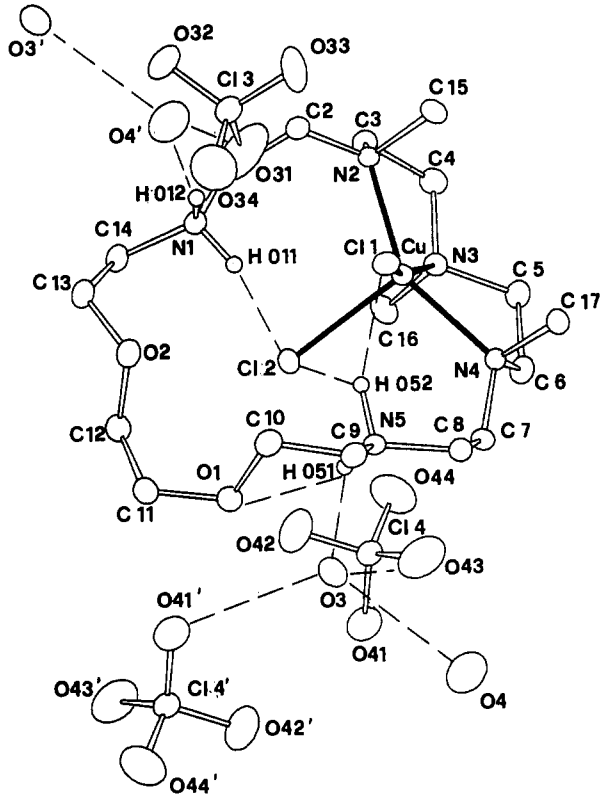


Figure 5. ORTEP drawing showing the intramolecular hydrogen bonds and some intermolecular contacts in the $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2](ClO_4)_2 \cdot 2H_2O$ species.

Table V. Selected Bond Distances (Å) and Angles (deg) for $C_{17}H_{45}Cl_4CuN_5O_{12}$, with Esd's in Parentheses

		Distances	
Cu–Cl1	2.298(2)	Cu–N4	2.151(5)
Cu–Cl2	2.474(2)	Cu–N3	2.052(4)
Cu–N2	2.101(4)		
		Angles	
N4–Cu–N3	84.7(2)	Cl2–Cu–N2	110.2(1)
N2–Cu–N3	83.8(2)	Cl1–Cu–N3	166.7(2)
N2–Cu–N4	148.6(2)	Cl1–Cu–N4	95.2(2)
Cl2–Cu–N3	101.4(1)	Cl1–Cu–N2	89.6(2)
Cl2–Cu–N4	100.6(1)	Cl1–Cu–C12	91.7(1)

atoms of the ammonium groups: H052···Cl1 = 2.17(6), H052···C12 = 2.45(5), H011···Cl2 = 2.40(6) Å. Finally H051 interacts with the oxygen atom O1 of the macrocyclic framework (H051···O1 2.44(6) Å). Furthermore, very strong intermolecular hydrogen bonds are present between H012, on N1, and the oxygen O4 of a water molecule (1.94(5) Å) and between H051, on N5, and the other water molecule (H051···O3 = 2.21(6) Å).

The oxygen atom O4 of a water crystallization molecule is 2.793(8) Å apart from O31 of a perchlorate counterion and 2.873(8) Å from the oxygen atom O3 belonging to the other water molecule. This one bridges two perchlorate ions, being 2.944(7) and 3.179(8) Å apart from O41 and O43, belonging to two symmetry-related counterions. Thus, the water molecules have a fundamental role in the crystal packing arrangement.

$[Cu(Me_3[24]aneN_5O_3)](ClO_4)_2$. The molecular structure consists of $[Cu(Me_3[24]aneN_5O_3]^{2+}$ cations and perchlorate ions. Figure 6 shows an ORTEP drawing of the complexed cation. Table VI lists bond distances and angles around the metal ion.

The coordination geometry determined by the five nitrogen atoms around the copper(II) can be described as a distorted square pyramid, with the copper ion 0.2249(8) Å above the mean basal plane, shifted toward N4 which occupies the apical position at 2.377(7) Å. This distance is significantly longer than those involving the nitrogen atoms of the basal plane (Table VI). To

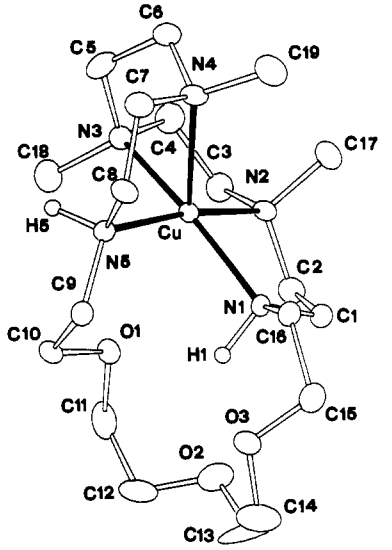


Figure 6. ORTEP drawing of the $[Cu(Me_3[24]aneN_5O_3)]^{2+}$ cation.

Table VI. Selected Bond Distances (Å) and Angles (deg) for $C_{19}H_{43}Cl_2CuN_5O_{11}$ with Esd's Parentheses

		Distances	
Cu–N1	2.113(6)	Cu–N4	2.377(7)
Cu–N2	2.032(6)	Cu–N5	2.061(6)
Cu–N3	2.133(7)		
		Angles	
N4–Cu–N5	77.9(2)	N2–Cu–N3	84.2(3)
N3–Cu–N5	95.8(2)	N1–Cu–N5	95.6(2)
N3–Cu–N4	80.4(3)	N1–Cu–N4	117.7(2)
N2–Cu–N5	169.8(3)	N1–Cu–N3	160.3(3)
N2–Cu–N4	112.1(2)	N1–Cu–N2	81.8(2)

our knowledge, few Cu^{2+} complexes structures of this type of ligands have been reported. The closest comparisons are in the copper(II) complex of the macrocycle 1,4,7,10-tetraoxa-13,16,19,22-tetraazacyclotetracosane[11] ([24]aneN$_4$O$_4$, III in Chart I), where the Cu^{2+} is coordinated by a N_4O donor set of the macrocycle. The axial position in the square-pyramidal coordination polyhedron of the metal ion is occupied by an oxygen atom of the macrocyclic framework adjacent to the N_4 subunit. Instead, in $[Cu(Me_3[24]aneN_5O_3]^{2+}$, the Cu^{2+} ion prefers the available N_5 set of donors, the apical position being occupied by the nitrogen atom N4 of the $(-CH_2-NMe-CH_2-)_3$ moiety. However, in both cases the resulting geometry is axially elongated. As far as the nitrogen donors on the basal plane are concerned, in our structure the distances Cu–N, which span from 2.032(6) to 2.133(7) Å, are longer than those of the above $[Cu([24]aneN_4O_4)]^{2+}$ complex (1.95–2.05 Å).

Because N3, N4, and N5 belong to adjacent ethylenic bits, the axial bond N4–Cu significantly deviates from perpendicularity, with respect to the coordination plane. In fact the angles N4–Cu–N5 and N4–Cu–N3 are 77.9(2) and 80.4(3)°, respectively, while N4–Cu–N1 and N4–Cu–N2 are much larger, being 117.7(2) and 112.1(2)°, respectively.

The conformation of the uncoordinated moiety of the ligand appears to be determined by the presence of intramolecular contacts via hydrogen bonds between the secondary nitrogen atoms and the three ethereal oxygens (N1···O1 = 2.984(8), N1···O2 = 3.22(1), N1···O3 = 2.801(9) Å). In fact the oxygen atoms of the macrocyclic framework point toward the hydrogen H1 (Figure 6). On the other hand, there is likely the presence of an hydrogen bond between H5, located on the N5 secondary nitrogen, and an oxygen atom of a perchlorate anion (N5···O13 = 3.05(1) Å).

Copper(II) Complexes Formation. The stability constants in 0.15 mol dm^{-3} $NaClO_4$ aqueous solution at 298.1 ± 0.1 K for the equilibrium reactions of $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ with Cu^{2+} are reported in Table VII. The metal ion forms CuL^{2+}

Table VII. Logarithms of the Formation Constants of Cu^{2+} Complexes of $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$ in 0.15 mol dm^{-3} $NaClO_4$ Aqueous Solution at 298.1 ● 0.1 K

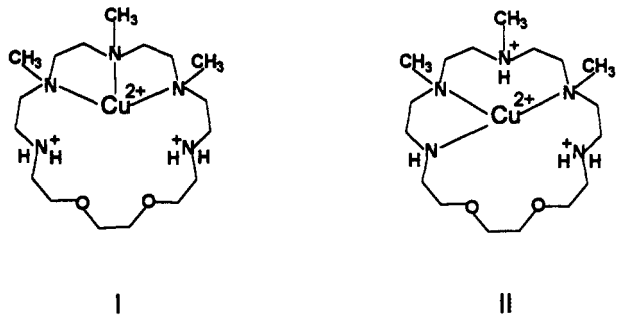
	log K	
reacn	L = $Me_3[21]aneN_5O_2$	L = $Me_3[24]aneN_5O_3$
$Cu^{2+} + L = CuL^{2+}$	17.66(1)[a,b]	17.30(1)[c]
$Cu^{2+} + L + H^+ = CuHL^{3+}$	21.92(1)	22.50(1)
$Cu^{2+} + L + 2H^+ = CuH_2L^{4+}$	24.31	25.01(2)
$CuL^{2+} + H^+ = CuHL^{3+}$	4.26	5.20
$CuHL^{3+} + H^+ = CuH_2L^{4+}$	2.39	2.51

[a] Values in parentheses are standard deviations on the last significant figure. [b] $\Delta H^\circ = -13.1(1)$ kcal mol^{-1}; $T\Delta S^\circ = 11.0(1)$ kcal mol^{-1}. [c] $\Delta H^\circ = -12.8(1)$ kcal mol^{-1}, $T\Delta S^\circ = 10.8(1)$ kcal mol^{-1}.

complexes with both ligands, the stability constants being very similar. Furthermore, it can be noted that Cu^{2+}, at least under the experimental conditions employed, forms complexes with mono- and diprotonated species of $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$. However, the CuL^{2+} complexes present a low tendency to bear protonation (for the first protonation log K = 4.26 for L = $Me_3[21]aneN_5O_2$ and 5.20 for $Me_3[24]aneN_5O_3$) and therefore they remain the largely predominating species from acidic to alkaline solutions. Such low values of the protonation constants of polyamine complexes have been attributed to the involvement of amino groups coordinated to the metal centers.[12a] This is consistent with a metal–ligand interaction determined by the coordination of all five nitrogen atoms of the macrocycles. The crystal structure of the complex $[Cu(Me_3[24]aneN_5O_3)](ClO_4)_2$ (Figure 5), in which the Cu^{2+} ion is five-coordinated by the nitrogen donors of the receptor, gives confidence to this hypothesis. Furthermore, the analogy of coordination spheres in the solid state and in solution is confirmed by the similarity of the electronic spectra of this complex in 0.01 mol dm^{-3} NaOH aqueous solution (a broad band with λ_{max} = 650 nm, ϵ = 60 dm^3 mol^{-1} cm^{-1}) and in the solid state (λ_{max} = 640 nm). As far as $Me_3[21]aneN_5O_2$ is concerned, the analogous complex $[Cu(Me_3[21]aneN_5O_2)](ClO_4)_2$ was isolated as a solid, and its electronic spectra show similar features (λ_{max} = 660 nm, ϵ = 57 dm^3 mol^{-1} cm^{-1} in 0.01 mol dm^{-3} NaOH aqueous solution, λ_{max} = 630 nm in the solid state). From these thermodynamic and spectral data it can be concluded that for both macrocycles the complex CuL^{2+} is characterized in aqueous solution by the involvement of all the five amino groups in the coordination of the metal ion.

The formation constants of the complexes CuL^{2+} are by far lower than those reported for $[Cu([15]aneN_5)]^{2+}$ (log K = 28.3), in which the involvement of all the nitrogens in the coordination of the Cu^{2+} has been demonstrated.[29] Such a decrease in stability can be ascribed to both the formation of large chelate rings containing the oxygen atoms (11 and 14 terms in the case of $[Cu(Me_3[21]aneN_5O_2)]^{2+}$ and $[Cu(Me_3[24]aneN_5O_3)]^{2+}$, respectively and to the presence of tertiary amino groups. The lower stability shown by these complexes with respect to $[Cu[15]aneN_5]^{2+}$ is due mainly to the enthalpic contribution (ΔH°_{CuL} = −13.1(1) kcal mol^{-1}, $T\Delta S^\circ$ = 11.0(1) kcal mol^{-1} and ΔH°_{CuL} = −12.8(1) kcal mol^{-1}, $T\Delta S^\circ$ = 10.8(1) kcal mol^{-1} for L = $Me_3[21]aneN_5O_2$ and $Me_3[24]aneN_5O_3$, respectively, while ΔH°_{CuL} = −32.9 kcal mol^{-1} and $T\Delta S^\circ$ = 5.7 kcal mol^{-1} for $[15]aneN_5$).

The ligand $[21]aneN_7$ (Chart I, n = 2 in ligand drawing IV), which can be considered the macrocycle dimensionally analogous to $Me_3[21]aneN_5O_2$ among the $[3k]aneN_k$ polyazacycloalkanes, gives rise in aqueous solution to both mono- and binuclear complexes with Cu^{2+}.[12a] For the species $[Cu([21]aneN_7)]^{2+}$ (log K = 24.4) a pentacoordination of the metal ion was proposed, suggesting the presence of either two 8-membered or one 11-membered chelate ring. Different contributions can be invoked to explain the higher formation constant for this complex, with respect to $[Cu(Me_3[21]aneN_5O_2)]^{2+}$: (i) absence of nitrogens bearing methyl groups; (ii) the ability of $[21]aneN_7$ in better organizing the chelate rings, reducing the macrocycle strain in the complex; (iii) statistical effects, due to a larger number of nitrogen donors in $[21]aneN_7$. As a matter of fact, $[18]aneN_6$ (Chart I, n = 1 in ligand drawing IV) gives rise to a Cu^{2+} complex more stable than that formed by is four-methylated analogous $Me_4[18]aneN_6$ (log K_{CuL} = 24.40[30] and 20.49,[31] respectively), supporting the idea that electronic and steric effects due to the presence of some methylated amino groups affect remarkably the formation constants of Cu^{2+} complexes with polyaza macrocycles.



I II

Figure 7. Proposed structures for the $[Cu(H_2Me_3[21]aneN_5O_2)]^{4+}$ cation in solution.

In spite of diprotonated species of such complexes are present at equilibrium in very small amounts, a solid with stoichiometry $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2][ClO_4]_2 \cdot 2H_2O$ was isolated. Although methylation appears to decrease the binding ability of the macrocycle in these complexes, it can be noted that, in $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2]^{2+}$, at least in the solid state (Figure 6), the Cu^{2+} is coordinated by the tertiary nitrogen donors, while the secondary amino groups are protonated. It is extremely difficult to rationalize the role played by each nitrogen donor in determining the overall binding properties of the whole ligand in such a complex. In fact many factors can be suggested to explain the main characteristics of this species. By adoption of such a disposition, the complex can achieve the minimization of the electrostatic repulsion between the metal ion and the two protonated nitrogens, located at opposite sides of the macrocycle; furthermore, the balance between σ-donor and basicity properties of secondary and tertiary amino groups, as well as the steric effects due to the presence of methyl groups, has to be taken into account. It seems likely that this structure is maintained also in solution. The reaction of complex formation is a competition with the protonation of the ligand, and as it has been shown by the NMR study, the secondary amino groups participate in the first steps of protonation together with the central tertiary nitrogen. Effectively two different structures could be proposed for the diprotonated complex (Figure 7). Both of them account for a reduced electronic repulsion and for the above mentioned basicity properties of the different nitrogens. However, the coordination environment presented by complex I in Figure 7 could give rise to a larger stability due to the presence of just one large chelate ring. As evidenced by the crystal structure, the Cu^{2+} ion completes its coordination sphere by binding two Cl^- anions; the subsequent decrease of the overall charge of the complex and the formation of $Cl\cdots H_2^+-N$ hydrogen bonds allow this species to achieve a larger stability in the solid state. The reflectance spectrum of $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2][ClO_4]_2 \cdot 2H_2O$ exhibits a broad band with λ_{max} = 730 nm, showing a shift toward lower energy

(29) Kodama, M.; Kimura, E. *J. Chem. Soc., Dalton Trans.* **1978**, *104*. [15]aneN$_5$: 1,4,7,10,13-cyclopentaazadecane (Chart I, n = 0 in ligand drawing IV).

(30) Bencini, A.; Bianchi, A.; Micheloni, M.; Paoletti, P.; Garcia-España, E.; Niño, M. A. *J. Chem. Soc., Dalton Trans.* **1991**, 1171.

(31) Bencini, A.; Bianchi, A.; Dapporto, P.; Fusi, V.; Garcia-España, E.; Micheloni, M.; Paoletti, P.; Paoli, P.; Rodriguez, A.; Valtancoli, B. *Inorg. Chem.* **1993**, *32*, 2753.

with respect to the spectrum of $[Cu(Me_3[21]aneN_5O_2)][ClO_4]_2$, which can reasonably be ascribed to the replacement of two amino groups with the chloride ions in the coordination environment of the metal ion.

Conclusions. Although the presence of three tertiary amino groups seems to affect strictly the protonation behavior of such receptors, lowering their basicity, NMR measurements have shown the first protonation steps involve at least one (N_1) of the nitrogens bearing methyl groups.

Both ligands give rise to a rather weak overall interaction with Cu^{2+}, with respect to other polyazacycloalkanes. Both thermodynamic and structural data indicate all nitrogen donors are coordinated to the metal ion in the CuL^{2+} species, while the oxygens remain unbound. The low enthalpic effect for the reaction $Cu^{2+} + L = CuL^{2+}$ suggests that methylation reduces the overall interaction between the ligand and the metal ion, even if the formation of large chelate rings in metal ion binding also contributes in lowering the stability of such complexes. On the other hand, in the solid state, the crystal structure of $[Cu(H_2Me_3[21]aneN_5O_2)Cl_2]^{2+}$ reveals that Cu^{2+} is coordinated by the three tertiary nitrogen donors, completing its coordination environment by two chloride anions. This results from the balance of steric and electronic effects due to the presence of methyl groups, Coulombic repulsion and $Cl\cdots H_2^+-N$ hydrogen bond formation. We are currently analyzing the role played by nucleophilicity and basicity of nitrogen donors as well as by steric hindrance of the N-substituent in determining the binding ability of macrocyclic receptors.

Acknowledgment. Financial support by the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (quota 60%) and Progetto Finalizzato di Chimica Fine e Secondaria of the Italian Research Council (CNR) and by the Spanish Comisión de Ciencia y Tecnologia (Proyecto PB90-0567) is gratefully acknowledged. We are also indebted to Mr. M. Fontanelli, Dr. P. Mariani, and Dr. S. Seniori Costantini for technical assistance.

Supplementary Material Available: Tables of crystallographic parameters, anisotropic and isotropic thermal parameters, positional parameters for the hydrogen atoms, and complete bond lengths and angles (11 pages). Ordering information is given on any current masthead page.