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Synthesis and co-ordination of 1,4,7,10-tetraazacyclododecanes disubstituted with imidazole and pyrazole

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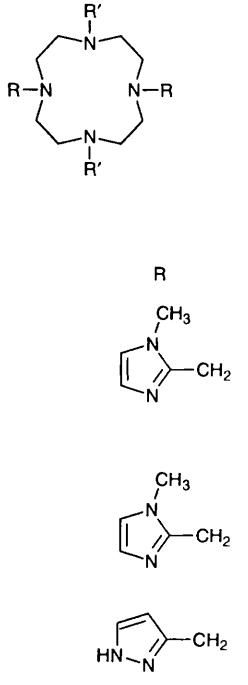
The potentially hexadentate ligands 1,7-bis(1-methylimidazol-2-ylmethyl)- (L^1), 1,7-dimethyl-4,10-bis(1-methylimidazol-2-ylmethyl)- (L^2) and 1,7-dimethyl-4,10-bis(pyrazol-3-ylmethyl)-1,4,7,10-tetraazacyclododecane (L^3) have been synthesized and their basicity constants determined by potentiometry at 25 °C in 0.15 mol dm $^{-3}$ $NaClO_4$. Nickel(II) and zinc(II) complexes with the three compounds have been prepared and characterized. The structures of $[NiL^1][BPh_4]_2$ and $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ have been determined by single-crystal X-ray analyses. In both complex cations the metal ion is co-ordinated by the six nitrogen donor atoms of the ligand.

In recent years considerable attention has been addressed to metal complexes of 1,4,7,10-tetraazacyclododecane bearing co-ordinating pendant groups.[1] Such complexes, because of their favourable thermodynamic and kinetic stability, are widely studied for potential applications in diagnostic[2] and therapeutic medicine.[3] The compound Na[Gd(dota)(H_2O)] (H_4dota = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid) has been exploited as a magnetic resonance imaging (MRI) contrast agent in clinical practice.[4]

Most of the ligands which have been used up to now present four identical groups attached to the nitrogen atoms,[5] whereas tetrasubstituted derivatives with different pendant groups have received limited attention, probably owing to difficulties in their synthesis. Heterosubstituted derivatives have been mainly obtained through two successive steps, the first leading to a partially (homo-)substituted macrocycle and the second to the (hetero-)tetrasubstituted macrocycle. The first step, which requires an efficient regioselective derivatization, is difficult to perform and constitutes the main obstacle to the synthesis of the fully substituted derivatives. The partially substituted derivatives described up to now have been obtained through selective protection of some (two or three) nitrogens,[6] followed by removal of the protecting group(s) under relatively harsh conditions. Such conditions, however, make the above synthetic route efficient for ligands with scarcely reactive pendant groups. The selective partial N-substitution of polyazamacrocycles accordingly presents an interesting synthetic challenge. Furthermore, the basicity properties of compounds bearing co-ordinating pendant groups may be intriguing, because of the proximity of many donor atoms as well as of the geometric constraints imposed on their environments by the molecular framework.[7]

In recent years we have investigated the co-ordination chemistry of tri- and tetra-azamacrocycles functionalized with such residues as imidazole and pyrazole, which are relevant for biomimetic purposes.[8,9] The compounds have been synthesized under mild and controlled conditions, due to the well known reactivity of the synthons of the above heterocycles which are employed for the derivatization of the macrocycles Such compounds have been found to possess interesting co-ordinating properties[8] and chemical reactivity.[9]

Therefore, it appeared worthwhile pursuing the investigations on the synthesis of derivatives formed by 1,4,7,10-tetraazacyclododecane partially substituted with groups like imidazole and pyrazole. We report herein the synthesis and characterization of 1,7-bis(1-methylimidazol-2-ylmethyl)- (L^1), 1,7-dimethyl-4,10-bis(1-methylimidazol-2-ylmethyl)- (L^2) and 1,7-dimethyl-4,10-bis(pyrazol-3-ylmethyl)-1,4,7,10-tetraazacyclododecane (L^3). Compounds L^2 and L^3, obtained by functionalization of the methylated macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane, have been synthesized mainly to tune the basicity of the macrocycle N-donors and to study the possible steric effects on co-ordination due to the methyl substituents. The basicity of the compounds has been determined and their co-ordinating properties toward nickel(II) and zinc(II) have been investigated. The crystal structures of nickel derivatives of L^1 and L^2 have been determined.



Experimental

All reagents were reagent grade; solvents, when required by the synthetic procedures, were dried according to standard methods just before use. Electronic spectra were recorded in the range 300–2500 nm with a Perkin-Elmer Lambda 9 spectrometer. The concentration of the solutions in water was about 10^{-3} mol dm^{-3}. The ^{13}C NMR spectra of all compounds were obtained with a Varian CFT 80 spectrometer operating at 20.00 MHz, from solutions in deuteriated chloroform,

acetonitrile or water. Chemical shifts are reported in ppm downfield with respect to the internal standard $SiMe_4$. The intermediate compounds 1,4,7,10-tetraazacyclododecane[10] 1,7-dimethyl-1,4,7,10-tetraazacyclododecane,[11] 2-(chloromethyl)-1-methylimidazole hydrochloride[12] and 3-(chloromethyl)pyrazole hydrochloride[13] were prepared according to published procedures. Hydrated nickel(II) and zinc(II) perchlorates were prepared by standard methods. Free 3-(chloromethyl)pyrazole was obtained by slow addition of the stoichiometric amount of ethyldiisopropylamine (Aldrich) in diethyl ether to a suspension of 3-(chloromethyl)pyrazole hydrochloride in the same solvent. When the reaction was complete the solution was filtered and the solvent removed by rotary evaporation to give a sticky colourless oil which was satisfactorily employed in subsequent synthesis. ^{13}C NMR ($CDCl_3$): δ 146.6 (C^3), 104.9 (C^4, C^5), 131.2 (C^5, C^4) and 37.5 (CH_2 bridge). 2-(Chloromethyl)-1-methylimidazole was freed in solution by slow addition of a stoichiometric amount of the 'proton sponge' 1,8-bis(dimethylamino)naphthalene (Aldrich) (19.72 g, 0.092 mol) in MeCN (100 cm^3) to a suspension of 2-(chloromethyl)-1-methylimidazole hydrochloride (17.37 g, 0.092 mol) in MeCN (160 cm^3). The resulting suspension was stirred overnight at 4 °C and filtered. The solution was satisfactorily used for subsequent synthesis. If the solvent is removed from the above solution a sticky oil is obtained which yields a, presumably polymeric, solid in a short time even at low temperature. Alternatively 2-(chloromethyl)-1-methylimidazole may be obtained in diethyl ether solution by treating a suspension of the hydrochloride with the stoichiometric amount of ethyldiisopropylamine and working up the suspension as described for the MeCN solution.

CAUTION: free 3-(chloromethyl)pyrazole has been found to be an irritant even in very low concentration in the gas phase. In addition, perchlorate salts of metal complexes with organic ligands are potentially explosive. For this reason the drying temperature was kept below 50 °C and small amounts of sample were handled at a time.

Macrocycle synthesis

The reactions of the macrocycles (1,4,7,10-tetraazacyclododecane or 1,7-dimethyl-1,4,7,10-tetraazacyclododecane) with potassium and with the chlorides [3-(chloromethyl)pyrazole or 2-(chloromethyl)-1-methylimidazole] were carried out under a moisture-free atmosphere. All successive manipulations were performed in the air.

1,7-Bis(1-methylimidazol-2-ylmethyl)-1,4,7,10-tetraazacyclododecane, L^1. Solutions of 2-(chloromethyl)-1-methylimidazole (0.092 mol) in MeCN (260 cm^3) and proton sponge (10 g, 0.047 mol) in MeCN (50 cm^3) were slowly added to a stirred solution of 1,4,7,10-tetraazacyclododecane (3.96 g, 0.023 mol) in dimethylformamide (dmf) (150 cm^3) at 4 °C. The resulting solution was stirred at room temperature for 3 d. The yellowish solid which separated was collected, washed with diethyl ether and dried. It was dissolved in methanol–chloroform (1 : 1) and eluted through a silica column with the same mixture. 1,7-Bis-(1-methylimidazol-2-ylmethyl)-1,4,7,10-tetraazacyclododecane trihydrochloride was obtained as a hygroscopic white solid by removing the solvent under reduced pressure (yield 35%). ^{13}C NMR (D_2O): δ 146.4 (C^2), 126.8 (C^4, C^5), 123.6 (C^5, C^4), 51.1 (CH_2 of macrocycle) 50.8 (CH_2 bridge), 45.4 (CH_2 of macrocycle) and 33.4 (CH_3 of imidazole) (Found: C, 46.1; H, 7.60; N, 23.7. Calc. for $C_{18}H_{35}Cl_3N_8$: C, 46.0; H, 7.50; N, 23.8%). A solution of the trihydrochloride (1 g, 2.13 mmol) dissolved in water (20 cm^3) was adjusted to pH 13 with 5 mol dm^{-3} NaOH and extracted twice with chloroform (20 cm^3). 1,7-Bis(1-methylimidazol-2-ylmethyl)-1,4,7,10-tetraazacyclododecane (0.23 g, 0.64 mmol; yield 30%), obtained by removing the solvent, may be recrystallized from acetone and hexane. ^{13}C NMR (CD_3CN): δ 145.6 (C^2), 126.6 (C^4, C^5), 121.9 (C^5, C^4), 52.3 (CH_2 bridge), 51.9 (CH_2 of macrocycle), 46.8 (CH_2 of macrocycle) and 32.7 (CH_3 of imidazole).

1,7-Dimethyl-4,10-bis(1-methylimidazol-2-ylmethyl)-1,4,7,10-tetraazacyclododecane, L^2. *Method A.* Solutions of 2-(chloromethyl)-1-methylimidazole (48 mmol) in MeCN (70 cm^3), prepared as described above, and of proton sponge (8.56 g, 40 mmol) in MeCN (20 cm^3) were slowly added to 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (4.0 g, 20 mmol) dissolved in MeCN (60 cm^3) and the solution was stirred at room temperature for 24 h at 4 °C. The solvent was then removed under reduced pressure. The remaining solid was dissolved in water (20 cm^3) and the solution adjusted to pH 13 with 5 mol dm^{-3} NaOH. The suspended solid (proton sponge) was extracted twice with diethyl ether (50 cm^3). The aqueous layer was separated and extracted four times with chloroform (50 cm^3); the solvent of the organic phase was then removed under reduced pressure. The remaining sticky oil was dissolved in chloroform and eluted through a neutral alumina column with chloroform. Crystals were obtained by adding hexane to the chloroform solution (1.1 g, 2.8 mmol; yield 14%), m.p. 118–120 °C. ^{13}C NMR ($CDCl_3$): δ 145.6 (C^2), 126.6 (C^4, C^5), 121.2 (C^5, C^4), 55.5 (CH_2 of macrocycle), 53.0 (CH_2 bridge), 52.4 (CH_2 of macrocycle), 42.8 (CH_3 of macrocycle) and 32.8 (CH_3 of imidazole). The elemental analysis was performed on the hexahydrochloride $L^2 \cdot 6HCl$ obtained by bubbling HCl through a solution of L^2 in water–ethanol (Found: C, 39.7; H, 7.15; N, 18.5. Calc. for $C_{20}H_{42}Cl_6N_8$: C, 39.6; H, 6.95; N, 18.5%).

Method B. Potassium (0.78 g, 0.020 mol) was added in small amounts to a refluxing solution of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (1.0 g, 0.005 mol) dissolved in tetrahydrofuran (70 cm^3) and the resulting suspension was refluxed for 3 h, then filtered. 2-(Chloromethyl)-1-methylimidazole (0.024 mol) in diethyl ether, prepared as described above, was slowly added to the above solution maintained at 4 °C with an ice-bath. The resulting slurry was stirred overnight and the solvent removed under reduced pressure. The remaining solid was extracted with a small amount of chloroform and eluted through a silica column with a mixture of chloroform and methanol (4%). The solid obtained by removing the solvent was characterized as pure according to its ^{13}C NMR spectrum and on the basis of the elemental analysis of the hexahydrochloride (yield 35%).

1,7-Dimethyl-4,10-bis(pyrazol-3-ylmethyl)-1,4,7,10-tetraazacyclododecane, L^3. Solutions of 3-(chloromethyl)pyrazole (0.029 mol) in MeCN (50 cm^3), prepared as previously described, and of proton sponge (6.2 g, 0.029 mol) in MeCN (50 cm^3) were simultaneously added to a solution of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (2.4 g, 0.012 mol) in dmf (50 cm^3), maintained at 4 °C. The resulting solution was worked up as described for the synthesis of L^2 to yield a sticky oil (yield 18%). ^{13}C NMR ($CDCl_3$): δ 149.7 (C^3), 129.3 (C^4, C^5), 103.0 (C^5, C^4), 53.7 (CH_2 of macrocycle), 51.8 (CH_2 of macrocycle), 47.0 (CH_2 bridge) and 43.2 (CH_3 of macrocycle) (Found: C, 59.8; H, 7.70; N, 23.7. Calc. for $C_{18}H_{32}N_8$: C, 60.0; H, 7.50; N, 23.8%).

Synthesis of the complexes $[ML]Y_2$ ($M = Ni^{2+}$ or Zn^{2+}; L = L^1, L^2 or L^3; $Y = ClO_4^-$; $M = Ni^{2+}$, $L = L^1$, $Y = BPh_4^-$)

The nickel(II) and zinc(II) complexes were prepared by mixing warm solutions (20 cm^3) of the appropriate macrocycle in methanol and the hydrated nickel(II) or zinc(II) perchlorates in ethanol in 1 : 1 molar ratio. The solutions were concentrated to a small volume until crystalline products were obtained. The complex $[NiL^1][BPh_4]_2$ was isolated by adding the stoichiometric amount of $NaBPh_4$ dissolved in ethanol to $[NiL^1][ClO_4]_2$

dissolved in warm methanol; crystals suitable for X-ray investigation were obtained by slow evaporation at room temperature of a dimethylformamide–butanol solution. The crystals of $[NiL^2][ClO_4]_2$ used for X-ray analysis (see below) were found to contain a small amount of solvate water. The complexes are soluble in water and warm methanol.

$[NiL^1][ClO_4]_2$ (Found: C, 34.9; H, 5.20; N, 17.9. Calc. for $C_{18}H_{32}Cl_2N_8NiO_8$: C, 35.0; H, 5.20; N, 18.1); $[NiL^1][BPh_4]_2$ (Found: C, 74.8; H, 7.00; N, 10.6. Calc. for $C_{66}H_{72}B_2N_8Ni$: C, 74.9; H, 6.95; N, 10.6); $[ZnL^1][ClO_4]_2$ (Found: C, 34.5; H, 5.10; N, 17.8. Calc. for $C_{18}H_{32}Cl_2N_8O_8Zn$: C, 34.6; H, 5.15; N, 17.9); $[NiL^2][ClO_4]_2$ (Found: C, 37.0; H, 5.55; N, 17.2. Calc. for $C_{20}H_{36}Cl_2N_8NiO_8$: C, 37.2; H, 5.60 N, 17.3); $[ZnL^2][ClO_4]_2$ (Found: C, 36.7; H, 5.60; N, 17.0. Calc. for $C_{20}H_{36}Cl_2N_8O_8Zn$: C, 36.8; H, 5.55; N, 17.2); $[NiL^3][ClO_4]_2$ (Found: C, 34.9; H, 5.20; N, 18.0. Calc. for $C_{18}H_{32}Cl_2N_8NiO_8$: C, 35.0; H, 5.20; N, 18.1); $[ZnL^3][ClO_4]_2$ (Found: C, 34.5; H, 5.10; N, 17.7. Calc. for $C_{18}H_{32}Cl_2N_8O_8Zn$: C, 34.6; H, 5.15; N, 17.9%).

Significant absorptions in the UV/VIS spectra of the nickel complexes are [λ_{max}/nm (ε/cm^2 mmol^{-1}); concentration of the solutions in water *ca.* 10^{-3} mol dm^{-3}]: $[NiL^1]Y_2$ (Y = ClO_4^- or BPh_4^-), diffuse reflectance, 380, 550, 630 (sh) and 1020; solution, 365 (45), 560 (22), 625 (sh) and 1020 (33); $[NiL^2][ClO_4]_2$, diffuse reflectance, 380, 555, 630 (sh) and 1030; solution, 380 (42), 555 (24), 625 (sh) and 1025 (31); $[NiL^3][ClO_4]_2$, diffuse reflectance, 380, 555, 615 (sh) and 1035; solution, 375 (24), 560 (22), 620 (sh) and 1020 (38). ^{13}C NMR (CD_3CN): $[ZnL^1][ClO_4]_2$, δ 147.2 (C^2), 126.7 (C^4, C^5), 124.0 (C^5, C^4), 52.3 (CH_2 of macrocycle), 50.4 (CH_2 bridge), 45.8 (CH_2 of macrocycle) and 33.3 (CH_3 of imidazole); $[ZnL^2][ClO_4]_2$, δ 147.5 (C^2), 125.6 (C^4, C^5), 124.3 (C^5, C^4), 55.0 (CH_2 of macrocycle), 52.6 (CH_2 of macrocycle), 51.2 (CH_2 bridge), 45.1 (CH_3 of macrocycle) and 32.7 (CH_3 of imidazole); $[ZnL^3][ClO_4]_2$, δ 149.8 (C^3), 133.7 (C^4, C^5), 104.5 (C^5, C^4), 53.6 (CH_2 of macrocycle), 50.1 (CH_2 of macrocycle), 50.7 (CH_2 bridge) and 43.7 (CH_3 of macrocycle).

Electromotive force measurements

Deionized water was purified with a MilliQ-Reagent system to produce water with a resistivity greater than 15 MΩ cm. The salt $NaClO_4 \cdot H_2O$ (Merck, analytical grade) was purified by double recrystallization from ethanol–water mixtures. Commercial HCl and NaOH as standard 0.100 mol dm^{-3} solutions (Fluka) were stored under nitrogen and their concentration checked before and after each emf titration by conventional calibration methods. The ionic strength was adjusted to 0.15 mol dm^{-3} with $NaClO_4$. Although some weak interactions between Na^+ and the macrocycles could not be ruled out in solution. $NaClO_4$ was used in order to obtain protonation data comparable with those of other cyclic compounds the equilibria of which have been studied in such an electrolytic medium.[7]

Potentiometric titrations were carried out using a Crison Micro pH 2002 potentiometer fitted with a Metrohm combined electrode (model 6.0204.000) in conjunction with a Hamilton Microlab M motor-driven syringe under the control of an appropriate program running on an IBM PS/2 model 20 computer.[14] Titration solutions were magnetically stirred and thermostatted at 298.2 ± 0.1 K in a water-jacketted vessel. A stream of pre-saturated nitrogen gas was passed over the solution in order to avoid contamination by atmospheric carbon dioxide. The instrumentation was calibrated by titration of 0.100 mol dm^{-3} NaOH (about 1 cm^3) from the syringe against 15 mmol dm^{-3} HCl ($\approx$20 cm^3).

The potentiometric experiments were performed by adding a 0.100 mol dm^{-3} NaOH solution to a solution containing the macrocycle ($\approx$1 mmol dm^{-3}) in the acidic form. In the case of L^3 a 0.100 mol dm^{-3} HCl solution was first added to a solution of the macrocycle ($\approx$1 mmol dm^{-3}) and the final solution was back titrated with standard NaOH solution. Data were collected in the range pH 2.5–11.0; 179 data points were used for L^1, 101 for L^2 and 125 for L^3.

Crystallography

Crystal data and refinement parameters for the compounds $[NiL^1][BPh_4]_2$ **1** and $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ **2** are given in Table 2. All operations were performed at 293 K using an Enraf-Nonius CAD4 diffractometer and graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å) (**1**) or Cu-Kα (λ = 1.5418 Å) radiation (**2**). Unit-cell parameters were obtained for each compound from the settings of 24 reflections having $16 < \theta < 17$ (**1**) and $31 < \theta < 34°$ (**2**). The ω–2θ scan mode was used. The intensities of standard reflections monitored periodically during the data collections did not reveal any crystal decay. An empirical absorption correction was applied to all data after structure solution at isotropic convergence.[15] The principal computer programs used in the crystallographic calculations are listed in refs. 15–19. Atomic scattering factors were from refs. 17 (C, H, B, Cl, N and O) and 20 (Ni), the latter being corrected for anomalous dispersion.[21]

Both structures were solved by direct[16] and heavy-atom methods. The asymmetric unit of complex **1** contains half a formula unit, with the metal atom lying on a two-fold axis. The content of the asymmetric unit of **2** corresponds to one formula unit, with the water molecule lying on a two-fold axis. In the final refinement cycles performed on *F* in one block for each structure all non-hydrogen atoms were assigned anisotropic thermal parameters. The hydrogen atoms of **1** were assigned an overall thermal parameter and their positions were refined. Those of **2** were included in calculated positions (except for the hydrogens of the water molecule, which were not located), at 0.96 Å from the respective C atom, with $U_H = 1.2\ U_C^{eq}$, where U_C^{eq} is the equivalent isotropic thermal parameter of the carrier atom. Since **2** appeared to belong to one of two enantiomorphic space groups, $P4_12_12$ (no. 92) or $P4_32_12$ (no. 96), the absolute configuration was assigned by refining both enantiomeric models and found to be consistent with the former (*R* 0.056 *vs.* 0.066).

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/71.

Results and Discussion

Synthesis of the macrocyles

1,4,7,10-Tetraazacyclododecane was treated with 2-(chloromethyl)-1-methylimidazole (in 1:4 molar ratio) in an ice-cooled dmf–MeCN solution for 3 d. The resulting solid, purified by silica gel column chromatography with $CHCl_3$–MeOH (1:1) as eluent, afforded a white hygroscopic solid which was characterized as $L^1 \cdot 3HCl$. Extraction with chloroform of a water solution of the trihydrochloride adjusted to pH 13 yielded pure L^1. The neutralization of the trihydrochloride and the successive extraction resulted in a significant decrease in yield. 1,7-Dimethyl-1,4,7,10-tetraazacyclododecane was treated with 2-(chloromethyl)-1-methylimidazole or 3-(chloromethyl)pyrazole (in 1:2.4 molar ratio) in an ice-cooled MeCN solution for 1 d. The reaction mixture was purified by alumina column chromatography with $CHCl_3$–MeOH (100:4) as eluent. The compounds L^2 and L^3 may be recrystallized from acetone and hexane. The former was obtained in higher yield by treating a solution of the macrocycle after reaction with potassium, with 2-(chloromethyl)-1-methylimidazole (in 1:5 molar ratio). The reaction mixture was

Table 1 Stepwise basicity constants of the macrocycles at 298.2 K in 0.15 mol dm $^{-3}$ $NaClO_4$ [a]

Macrocycle	log K_1	log K_2	log K_3	log K_4
1,4,7,10-Tetrazacyclododecane [b]	10.6	9.6	< 2	
L^1	9.55 ± 0.09	8.1 ± 0.1	5.9 ± 0.1	3.80 ± 0.09
L^2	11.47 ± 0.04	8.28 ± 0.02	5.29 ± 0.02	3.42 ± 0.02
L^3	10.42 ± 0.02	8.97 ± 0.02	2.87 ± 0.02	< 1.5

[a] The error limits are three standard deviations. [b] Ref. 24.

purified by alumina column cromatography with $CHCl_3$–MeOH (100:4) as eluent. Such a route for the functionalization of macrocycles has been recently employed to obtain triazacyclononane derivatives.[22] Treatment of L^1 and L^2 with alkaline solution (pH *ca.* 13) results in significant decomposition.

Acid-base equilibria

The data were processed using the program HYPERQUAD.[23] The refined protonation constants for L^1–L^3 and for 1,4,7,10-tetraazacyclododecane are given in Table 1.

When the hydrogen atoms of two secondary amino groups of the 1,4,7,10-tetraazacyclododecane are substituted with pendant arms bearing imidazole groups, the first two (stepwise) protonation constants are lowered by more than one logarithmic unit. A similar substantial decrease is also observed with respect to 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (log K_1 = 10.76 and log K_2 = 9.41)[11] which exhibits similar protonation constants. The next two protons are presumably attached to the basic nitrogen atoms of the imidazole substituents. Owing to the presence of positively charged centres on the diprotonated macrocyclic ring, the equilibrium constants for protonation of these nitrogen atoms are much lower than that of 1-methylimidazole (log K = 7.1).[25]

The value of log K_1 for L^2 is higher than the corresponding values for L^1 and 1,4,7,10-tetraazacyclododecane. This result apparently contradicts the well known rule that tertiary amines are less basic than secondary amines, but it is known that this trend may be reversed in macrocyclic polyamines.[7] Also in this case, after two protons have been added to the macrocyclic ring, protonation occurs on the pendant imidazole substituents. The compound L^3 is less basic than the imidazole homologue, the differences being particularly evident in the last two protonation steps. This may be ascribed to the fact that the pyrazole nitrogen atoms have a lower proton affinity than those of imidazole.

Metal complexes

The reaction of $M(ClO_4)_2$ (M = Ni or Zn) and the partially protonated form of L^1, L^2 or L^3 in a water–ethanol mixture gives the $[ML][ClO_4]_2$ (M = Ni or Zn; L = L^1, L^2 or L^3) complexes. The solid-state structures of the nickel complexes with L^1 and L^2 have been established by X-ray diffraction methods.

The electronic spectra of the nickel complexes are typical of octahedral high-spin chromophores, exhibiting three band maxima at *ca.* 380, 560 and 1020 nm. The ^{13}C NMR spectra of $[ZnL]^{2+}$ (L = L^1, L^2 or L^3) in CD_3CN display a single signal for equivalent carbon atoms of the pendant groups and two signals for the carbon atoms of the macrocycle; such data are compatible with a geometry of the complex cation similar to that found for the nickel derivatives.

Crystal structures. The structure of the compound $[NiL^1][BPh_4]_2$ **1** consists of isolated $[NiL^1]^{2+}$ complex cations and tetraphenylborate anions. The cation possesses a crystallographic two-fold symmetry axis passing through the metal atom position and the asymmetric unit contains one half

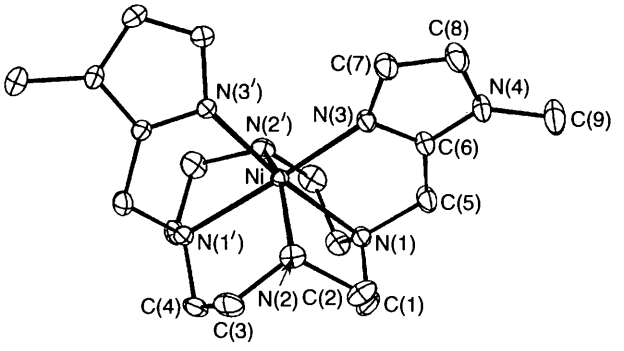


Fig. 1 A view of the cation in the structure of $[NiL^1][BPh_4]_2$ **1**, with 20% probability ellipsoids. Primed atoms are related to unprimed ones by a two-fold axis

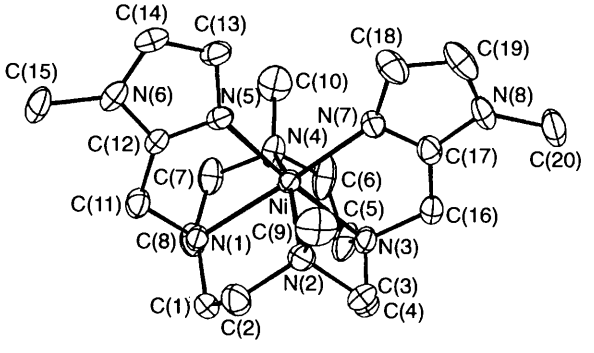


Fig. 2 A view of the cation in the structure of $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ **2**, with 20% probability ellipsoids

of the above formula unit. The structure of $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ **2** contains $[NiL^2]^{2+}$ cations, perchlorate anions and water molecules. Such molecules lie on two-fold axes and are linked to the anions through hydrogen bonds [O(9) ••• O(4) 2.90(1) Å]. The co-ordination geometry is similar for the two cations (Figs. 1 and 2, Tables 3 and 4), with the metal atom in a distorted-octahedral environment formed by the four macrocycle N atoms and the N donors of the two dangling imidazole groups. The macrocycle spans two faces of the octahedron. The co-ordination is similar to that previously found[9] for the two nickel(II) derivatives $[NiL^4]I_2$ **3** and $[NiL^{4'}][BPh_4]_2$ **4** where the L^4 ligand is formed by the present tetraazamacrocycle functionalized with four pyrazole groups, two of which are unco-ordinated, and the $L^{4'}$ ligand is obtained from L^4 through the substitution of a pyrazole by an ethoxo group. The cation in **3** has C_2 symmetry as in **1**. Detailed comparisons between the geometries of the compounds **1**–**4** reveal significant differences in the Ni–N distances formed by the two macrocycle nitrogens which are unsubstituted (**1**), or methyl substituted (**2**), or bear larger unco-ordinating groups (**3** and **4**). The mean values increase from 2.11 (**1**), to 2.14 (**2**), to 2.19 (**3**) and 2.20 Å (**4**), probably as a consequence of the increasing size of the substituents. The other two macrocycle Ni–N distances, on the other hand, exhibit the opposite trend, decreasing from the present compounds (2.20 Å, mean in **1** and **2**), to the previous ones [2.13 (**3**) and 2.15 Å (**4**)], possibly due to geometric requirements of the macrocycle, compensating for the

Table 2 Crystallographic data for $[NiL^1][BPh_4]_2$ **1** and $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ **2**

	1	**2**
Formula	$C_{66}H_{72}B_2N_8Ni$	$C_{20}H_{37}Cl_2N_8NiO_{8.5}$
M	1057.69	655.18
Crystal system	Monoclinic	Tetragonal
Space group	$C2/c$ (no. 15)	$P4_12_12$ (no. 92)
a/Å	17.743(3)	12.364(2)
b/Å	11.950(2)	12.364(2)
c/Å	27.836(6)	37.001(4)
β/°	104.96(2)	
U/Å^3	5702(2)	5656(1)
Z	4	8
D_c/g cm^{-3}	1.232	1.538
$F(000)$	2248	2744
Crystal size/mm	0.35 × 0.40 × 0.40	0.30 × 0.40 × 0.40
μ/mm^{-1}	0.39	3.27
Range of correction factor for absorption[a]	1.11–0.95	1.13–0.75
Scan width[b]/°	0.90	1.00
Scan speed/° min^{-1}	2–8	1.5–5
Collection range/°	$5 \leqslant 2\theta \leqslant 44$	$6 \leqslant 2\theta \leqslant 124$
Data collected[c]	$\pm h, \pm k, +l$	$+h, +k, +l$
No. unique data	3394	4307
No. observed data[d]	2865	3928
No. parameters	457	369
g[e]	0.0015	0.0040
R[f]	0.042	0.056
R'[g]	0.057	0.068
Maximum, minimum electron density/e Å^{-3}	0.4, −0.3	0.6, −0.4

[a] Empirical absorption corrections applied (**1**, Mo-Kα; **2**, Cu-Kα), see text. [b] Value of the a parameter in the formula $(a + b\tan\theta)°$ [b = 0.35 **1**, 0.14 **2**] for the scan width. [c] Data collected in triclinic **1** and orthorhombic **2** settings: 6760 and 5046 reflections measured; internal R values 0.03 and 0.05. [d] Reflections with $I > 3\sigma_I$ **1** and $I > 2\sigma_I$ **2**. [e] In the weighting scheme $w^{-1} = \sigma^2(F_o) + gF_o^2$. [f] $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. [g] $[\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{\frac{1}{2}}$. [h] Residual density in the final Fourier-difference map.

Table 3 Selected bond distances (Å) and angles (°) for $[NiL^1][BPh_4]_2$ **1** *

Ni–N(1)	2.202(3)	Ni–N(3)	2.053(2)
Ni–N(2)	2.110(3)		
N(1)–Ni–N(2)	82.0(1)	N(2)–Ni–N(3)	94.2(1)
N(1)–Ni–N(3)	79.5(1)	N(2)–Ni–N(2′)	152.4(1)
N(1)–Ni–N(1′)	106.1(1)	N(2)–Ni–N(3′)	104.3(1)
N(1)–Ni–N(2′)	81.5(1)	N(3)–Ni–N(3′)	95.4(1)
N(1)–Ni–N(3′)	172.2(1)		

* Symmetry operation: ′ $-x, y, \frac{3}{2} - z$.

Table 4 Selected bond distances (Å) and angles (°) for $[NiL^2][ClO_4]_2 \cdot 0.5H_2O$ **2**

Ni–N(1)	2.223(4)	Ni–N(4)	2.106(5)
Ni–N(2)	2.170(5)	Ni–N(5)	2.054(4)
Ni–N(3)	2.180(4)	Ni–N(7)	2.068(4)
N(1)–Ni–N(2)	81.5(2)	N(2)–Ni–N(7)	97.0(2)
N(1)–Ni–N(3)	104.6(2)	N(3)–Ni–N(4)	82.9(2)
N(1)–Ni–N(4)	82.9(2)	N(3)–Ni–N(5)	175.7(2)
N(1)–Ni–N(5)	79.5(2)	N(3)–Ni–N(7)	79.9(2)
N(1)–Ni–N(7)	174.9(2)	N(4)–Ni–N(5)	96.5(2)
N(2)–Ni–N(3)	82.3(2)	N(4)–Ni–N(7)	100.0(2)
N(2)–Ni–N(4)	155.1(2)	N(5)–Ni–N(7)	96.0(2)
N(2)–Ni–N(5)	99.7(2)		

lengthening of the other two distances, and/or to a stronger *trans* influence of the co-ordinating imidazole nitrogens in the present compounds than that of the (less basic) pyrazole nitrogens in the previous ones. Overall, the mean of the six Ni–N distances is essentially constant, in the range 2.12–2.13 Å for the four compounds, also due to the substantial constancy of the distances formed by the heterocyclic donors.

While the two chelate rings formed by the pendant arms in complex **2** are almost coplanar, with a 3.2(2)° angle between the normals to the best planes through the five atoms forming the rings, and also the imidazole planes in that compound are not far from coplanarity, forming a 12.2(3)° angle, such angles are larger in **1** [9.7(1) and 27.5(2)°, in the above order] and are still larger in the two compounds with pyrazole substituents [12.8(2) and 37.0(3) in **3** and 16.8(2) and 36.7(2)° in **4**]. Actually the nearest metal atom environment approaches C_{2v} symmetry in **2**, whereas it possesses crystallographic (**1** and **3**) or approximate C_2 symmetry (**4**) in the other cases, with increasing deviations from the former geometry on going from **1** to the pyrazole-substituted compounds (**3** and **4**). Such a trend could hardly be ascribed to the effects of intermolecular contacts, in view of the different site symmetries involved. It is also unlikely that it originates from different geometric requirements of the chelate rings formed by pendant arms bearing different types (imidazole or pyrazole) of substituents. Although the two types of chelate rings have different sequences of C and N atoms, in these compounds their bites are all in the narrow range 2.71–2.74 Å. The chelate rings deviate from planarity to various extents, the largest being exhibited by those formed with the pyrazole rather than the imidazole substituents: 0.29 Å in **4** and 0.25 Å in **3**, to be compared with 0.18 Å in **1** and 0.04 Å in **2**. The extents of these deviations essentially parallel those of the cations from idealized C_{2v} symmetry but are probably a consequence, rather than being the cause, of the arrangement attained by the outer parts of the ligands. This is also suggested by the different deviations from planarity of the chelate rings in **1** and **2**, both formed by imidazole-bearing pendant arms. It appears that the detailed conformations attained by the ligands are ultimately determined by the effects of intramolecular contacts. Effects of this sort were found to direct the orientation of the unco-ordinated pyrazole groups in **3** and **4**.[9] In all of the compounds **1**–**4** short contacts also exist between atoms of the co-ordinating imidazole or pyrazole groups. These, however, cannot be the main cause of the above deviations from C_{2v} symmetry, because the shortest contacts of this type are found for the most regular ($\approx C_{2v}$) cation among those being compared: *e.g.* C(13)···C(18) 3.45(1) Å in **2** *vs.* 3.47(1) Å in **1** and contacts ⩾3.55 Å in **3** and **4**. A special role seems to be played by the presence of the methyl substituents on the aminic

nitrogens in the L^2 ligand of compound **2**. These methyl groups in staggered orientation with respect to the N–C bonds of the macrocycle (orientation substantially confirmed by a Fourier-difference map) contribute to an overall symmetric environment of the metal atom through their repulsions with the imidazole groups. Stabilizing interactions of this sort are absent in **2** and the nature of the substituents on the unco-ordinating arms in **3** and **4** is not such as to favour the most regular arrangement about the metal atom. In the latter cases the repulsions between the co-ordinating heterocyclic groups probably prevail, switching on the decrease in symmetry from C_{2v}. In conclusion, it appears that the role of all intramolecular repulsions should be carefully considered when the conformations of complexes formed by ligands of this type are investigated.

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