Hexaaza and octaaza macrocycles with 2-hydroxy-3,5-dimethylbenzyl pendant arms

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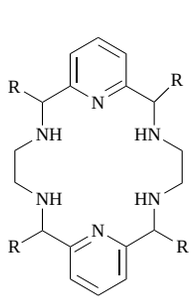
New 18-membered hexaaza (3 and 4) and 24-membered octaaza (7 and 8) macrocycles with 2-hydroxy-3,5-dimethylbenzyl pendant arms have been prepared *via* a Mannich type reaction of the corresponding macrocycles [(1 and 2) and (5 and 6) respectively] with 2,4-dimethylphenol in the presence of methanal in a methanolic solution. X-Ray structure analysis shows the tetramethyl substituted hexaaza macrocycle with 2-hydroxy-3,5-dimethylbenzyl pendant arms 4 and its precursor $[H_4\mathbf{2}]^{4+}$ both have centrosymmetric molecules with step conformation. Differences in conformation arise from hydrogen bonding interactions; in $[H_4\mathbf{2}]^{4+}$ bonding between amino nitrogen atoms and water molecules appears to tie the backbone chain of the macrocycle together, and in 4 strong intramolecular hydrogen bonding with each 2-hydroxybenzylamino unit dictates the orientation of the pendant arms.

The increasing interest in the molecular recognition and complexing properties of naturally occurring macrocycles has attracted much attention in the design and synthesis of new cyclic polyaza and polyoxa compounds.[1] The cavity size, the rigidity and the donor type of a macrocycle is important in governing the host–guest interactions and the selectivity of metal ions.[2] The incorporation of functionalised pendant coordinating arms on cyclic polyoxa and polyaza compounds can provide additional coordinating functions and hence enhance the complexing stability. Functionalities used include methylenecarboxylate,[3–5] methylenepyridyl,[6–9] hydroxyalkyl,[10–12] methylenephosphonate[13–15] and methylenephosphinate.[16,17] Previously for tetraaza macrocycles a wide variety of pendant arms containing hydroxy functional groups, such as 2-hydroxyethyl,[18] 2-hydroxybenzyl,[19] 3-*tert*-butyl-2-hydroxybenzyl[19] and 3,5-dimethyl-2-hydroxybenzyl,[20] have been attached to the secondary amine nitrogen atom. In this study, as part of our programme to design better ligands for use in magnetic resonance imaging agents, we report the details of the syntheses of the first hexaaza and octaaza macrocycles with pendant arms incorporating phenolic group, the macrocycles **3**, **4**,[21] **7** and **8**. The crystal structures of the hexaaza macrocycle **4** and its precursor $[H_4\mathbf{2}]Br_4$ confirm the formulation, and show similar step conformations.



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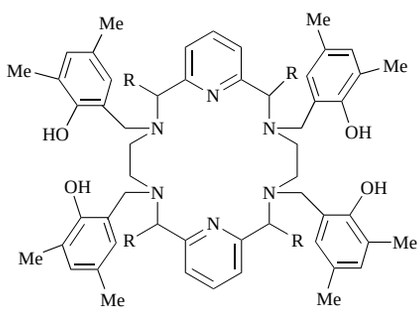
2 R = Me



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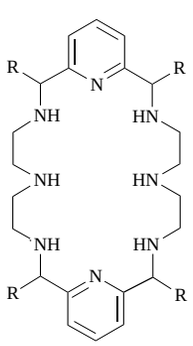

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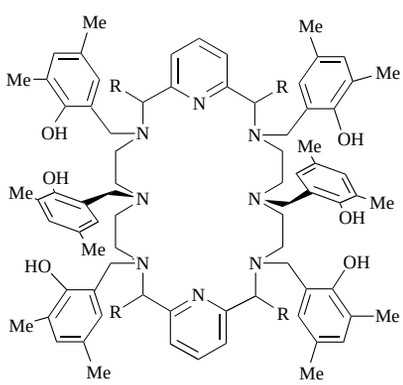
6 R = Me



7 R = H
8 R = Me

Results and discussion

Synthesis

The preparation of each of the pendant arm macrocycles **3** and **4** (hexaaza), and **7** and **8** (octaaza) involves a three-stage synthesis. The initial Schiff-base condensation reaction and the subsequent borohydride reduction reaction were carried out using a similar procedure to that previously reported by Jackels and co-workers.[22] Compounds **1** and **2** were isolated as hydrobromide salts, and **5** and **6** as hydrochloride salts. The final stage of the synthesis involved the reaction of the four free macrocyclic amines with 2,4-dimethylphenol and aqueous methanal in a methanolic solution giving the macrocycles **3**, **4**, **7** and **8** with 2-hydroxy-3,5-dimethylbenzyl pendant arms. Attempts to carry out this stage using the salt of the amine only results in the isolation of the starting material.

The final stage of the synthesis presented some difficulties, and the order in which the reactant was added proved to be important. Reactions based on the literature procedures for smaller macrocycles,[23,24] *i.e.* refluxing the amine with methanal followed by the addition of 2,4-dimethylphenol, did not work. The method developed, *i.e.* the slow addition of methanal to the refluxing 2,4-dimethylphenol and amine solution, gives an immediate white flocculent solid in relatively good yield during reflux. The yields are in the range 32–47% and their solubilities were limited in dichloromethane, acetone, toluene and warm DMSO.

Mass spectra

The liquid secondary ion (LSI) mass spectra of the macrocycles

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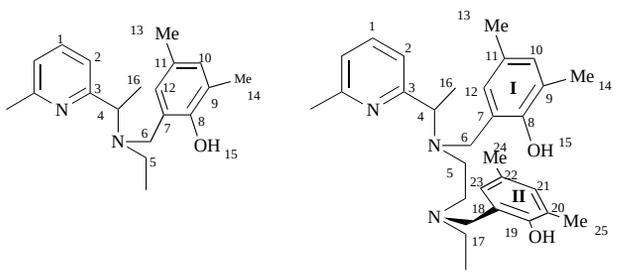
3, **4**, **7** and **8** (Table 1) had base peaks corresponding to the molecular ion $[M + H]^+$, and the second most intense peak corresponded to the backbone of the macrocycle tetraamine core unit in all except that for **8**. One characteristic feature for all the ligands was the successive cleavage of the whole pendant arms ($C_9H_{12}O$, *m*/*z* 136, or $C_9H_{10}O$, *m*/*z* 134) on decomposition, leaving the backbone of the macrocycle.

NMR Spectra

The solution structures of the macrocycles **3**, **4**, **7** and **8** have



been elucidated by ^{1}H NMR spectroscopy and, where necessary, with 2D-COSY spectroscopy at 250 MHz (Table 2). The tetramethyl-substituted compounds **4** and **8** theoretically give rise to multiple diastereoisomers, and for **4** both (*R*,*R*,*S*,*S*) and (*R*,*S*,*S*,*R*) have been characterised in the solid state (*vide infra*). Despite this evidence of diastereoisomers in **4**, all the NMR spectra at room temperature are fully assignable indicating that where isomers exist they interconvert rapidly in solution. The purity and the integral values depicted by the spectra support the tetra-substitution by the 2-hydroxy-3,5-dimethylbenzyl group of the amine precursor in **3** and **4**, and hexa-substitution in **7** and **8**. For example, the integration of each of the protons on the benzylic ring **I** (H^{12} and H^{10}) and on the benzylic ring **II** (H^{23} and H^{21}) of the octaaza macrocycle **7** are four and two respectively.

A broad peak at δ_H 10.38 for **3** and at δ_H 10.15 for **7** collapses on D_2O addition, and this band is assigned to the phenolic protons. Generally, a phenolic proton peak is a sharp singlet (due to rapid exchange) with a chemical shift in the range δ_H 4.0–7.5 depending on the concentration, solvent and temperature of the solution. The shift downfield from this range to *ca.* δ_H 10 is evidence of intramolecular hydrogen bonding[25] to the tertiary amine nitrogen atom. X-Ray structure analysis of **4** confirms strong hydrogen bonding between the four amine nitrogen and the four phenolic groups (*vide infra*).

The off-resonance broad band proton-decoupled ^{13}C NMR spectra of **3**, **4** and **7** were solved with the aid of DEPT-135 and ^{13}C–^{1}H COSY spectra (Table 2). The number of bands observed could be assigned to a quarter of the structure. ^{13}C NMR Spectra of **8** could not be obtained due to its insolubility in most deuteriated solvents.

Crystal structures

The tetracation $[H_4\mathbf{2}]Br_4{\cdot}2H_2O$, illustrated in Fig. 1, is centrosymmetric giving a mesomeric configuration in the solid state;

Table 1 Liquid secondary ion mass spectrometry fragmentation of the macrocycles with phenolic pendant arms

Compound	Fragment	*m*/*z* (relative intensity, %)
3	$[M + H]^+$	864(100)
	$[M + H - 136]^+$	728(11)
	$[M + H - 136 - 134]^+$	594(10)
	$[M + H - 136 - 2(134)]^+$	460(26)
	$[M + H - 136 - 3(134)]^+$	326(96)
4	$[M + H]^+$	920(100)
	$[M + H - 134]^+$	786(8)
	$[M + H - 2(134)]^+$	652(5)
	$[M + H - 136 - 2(134)]^+$	516(12)
	$[M + H - 136 - 3(134)]^+$	382(83)
7	$[M + H]^+$	1218(100)
	$[M + H - 136]^+$	1082(10)
	$[M + H - 136 - 134]^+$	948(7)
	$[M + H - 136 - 2(134)]^+$	814(6)
	$[M + H - 136 - 3(134)]^+$	680(33)
	$[M + H - 136 - 4(134)]^+$	546(39)
	$[M + H - 136 - 5(134)]^+$	412(74)
8	$[M + H]^+$	1273(100)
	$[M + H - 136]^+$	1137(61)
	$[M + H - 136 - 134]^+$	1003(18)
	$[M + H - 136 - 2(134)]^+$	869(20)
	$[M + H - 136 - 3(134)]^+$	735(16)
	$[M + H - 136 - 4(134)]^+$	601(89)
	$[M + H - 136 - 5(134)]^+$	467(43)

Table 2 Proton and carbon-13 NMR data for the macrocycles with pendant arms

	δ_H [a]				δ_C [b]		
Assignment	**3**	**4** [b]	**7**	**8** [b]	**3**	**4** [b]	**7**
1	7.55 (t)	7.55	7.59 (t)	7.64	136.9	136.2	137.2
2	7.06 (d)	6.99	7.09 (d)	7.06	122.1	120.5	122.3
3	—	—	—	—	157.0	160.2	157.1
4	3.74 (s)	4.11	3.75 (s)	4.61	58.9	59.7	58.9
5	2.87 (s)	2.78, 3.31	2.78 (s)	2.66	50.9	49.0	50.2
6	3.66 (s)	3.66	3.57 (s)	3.55	58.2	54.6	57.8
7	—	—	—	—	127.6	127.6	124.5
8	—	—	—	—	153.3	160.2	153.1
9	—	—	—	—	124.7	124.5	120.8
10	6.57 (d)	6.56	6.54 (d)	6.65	127.1	127.2	127.3
11	—	—	—	—	121.0	120.5	127.6
12	6.84 (d)	6.80	6.83 (d)	6.65	130.7	130.3	130.8
13	2.16 (s)	2.15	2.16 (s)	2.45	15.7	15.7	15.9
14	2.20 (s)	2.15	2.18 (s)	2.45	20.4	20.4	20.4
15	10.38 (br)	10.53	10.15 (br)	10.15 (br)	—	—	—
16	—	1.40	—	1.32	—	20.4	15.0
17	—	—	3.54 (s)	3.55	—	—	58.1
18	—	—	—	—	—	—	124.6
19	—	—	—	—	—	—	153.2
20	—	—	—	—	—	—	120.5
21	—	—	6.32 (d)	6.65	—	—	126.7
22	—	—	—	—	—	—	127.5
23	—	—	6.81 (d)	6.65	—	—	130.6
24 and 25	—	—	2.07 (s)	2.45	—	—	15.6, 20.4

[a] Values in ppm relative to $SiMe_4$ in $CDCl_3$ except **8** (run in $[^2H_6]$DMSO). [b] Diastereoisomeric mixture, average values given.

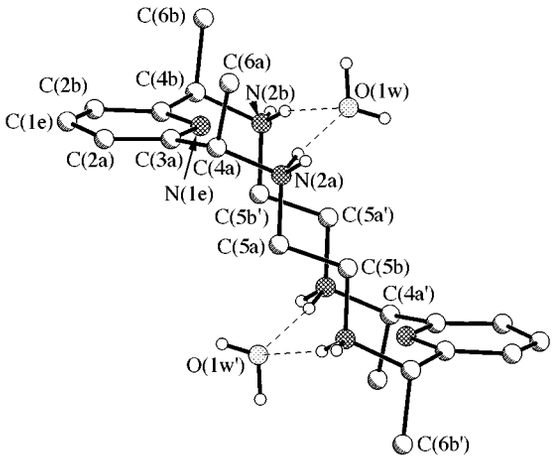


Fig. 1 The structure of the centrosymmetric tetracation of the tetramethyl hexaaza macrocycle $[H_4\mathbf{2}]^{4+}$ showing the hydrogen bonding interaction with two water molecules which determines the conformation of the inner great ring

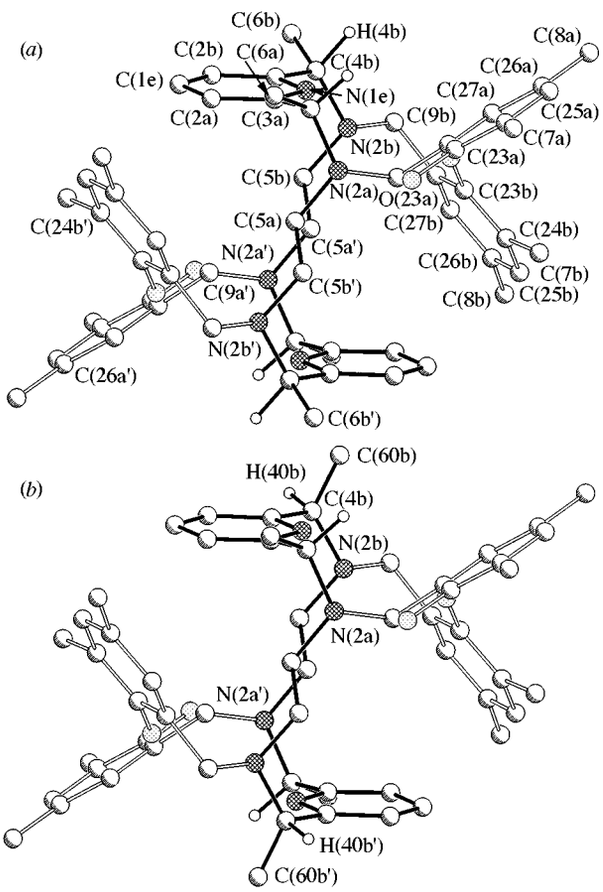


Fig. 2 The structure of the two diastereoisomers that are disordered in the crystal structure of the tetramethyl substituted hexaaza macrocycle with 2-hydroxy-3,5-dimethylbenzyl pendant arms **4**, illustrated with the components of molecular unit **A**: (a) the molecule of 60% occupancy with *R*,*S*,*S*,*R* configuration; (b) the molecule of 40% occupancy with *R*,*R*,*S*,*S* configuration

the two independent chiral carbon atoms C(4a) and C(4b) have configurations *S* and *R* respectively, and the symmetry related atoms C(4a′) and C(4b′) have the corresponding inversion related configurations *R* and *S* respectively.

In the crystal of **4**, two independent centrosymmetric molecular units **A** and **B** were established, each of which is composed of two superimposed diastereoisomers differing only in the orientations of two methyl groups, so that in each constituent molecule the configurations of two of the four chiral

Table 3 Selected bond lengths (Å) for $[H_4\mathbf{2}]^{4+}$ and the two independent molecules of **4**

	Bond length/Å		
	$[H_4\mathbf{2}]^{4+}$	**4(A)**	**4(B)**
C(1e)–C(2a)	1.376(15)	1.430(21)	1.412(22)
C(1e)–C(2b)	1.389(16)	1.350(24)	1.354(21)
C(2a)–C(3a)	1.387(16)	1.381(23)	1.377(23)
C(3a)–C(4a)	1.520(14)	1.473(21)	1.476(21)
N(1e)–C(3a)	1.327(13)	1.347(19)	1.344(14)
N(1e)–C(3b)	1.345(12)	1.365(20)	1.351(18)
C(2b)–C(3b)	1.383(16)	1.402(20)	1.403(21)
N(2a)–C(4a)	1.523(11)	1.482(15)	1.458(20)
N(2b)–C(4b)	1.502(12)	1.461(18)	1.486(18)
N(2a)–C(5a)	1.495(12)	1.494(18)	1.468(19)
N(2b)–C(5b′)[a]	1.494(12)	1.478(17)	1.484(19)
C(5a)–C(5b)[a]	1.516(15)	1.469(18)	1.501(18)
C(3b)–C(4b)	1.538(14)	1.488(24)	1.497(16)
C(4a)–C(6a)	1.536(15)	1.510(24)	1.503(21)
C(4b)–C(6b)	1.533(15)	1.55(3)	1.44(3)
C(4b)–C(60b)	—	1.37(3)	1.44(3)
N(2a)–C(9a)	—	1.486(20)	1.479(17)
N(2b)–C(9b)	—	1.451(19)	1.477(18)
C(23a)–O(23a)	—	1.351(12)	1.347(13)
C(23b)–O(23b)	—	1.340(14)	1.338(12)

[a] C(5b) and C(5b′) are interchanged for **4(A)** and **4(B)**.

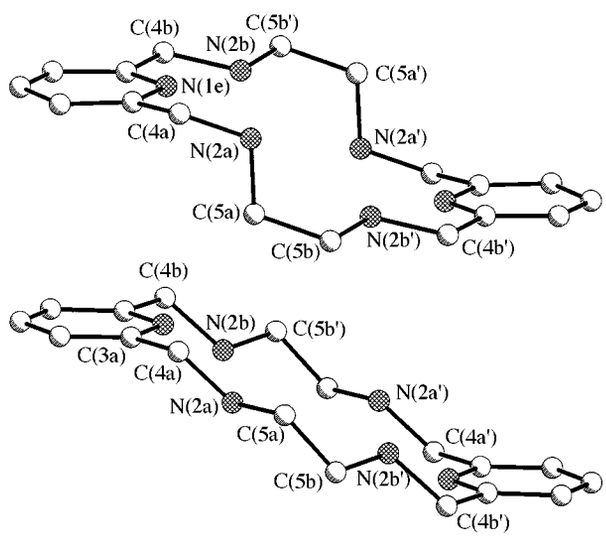


Fig. 3 The two conformations adopted by the unsubstituted hexaaza macrocycle $[H_4\mathbf{1}]^{4+}$ in the crystals of: (a) $[H_4\mathbf{1}]Br_4$[26]; (b) $[H_4\mathbf{1}](NO_3)_4$[27]

carbon atoms are dependent on the disordered methyl groups. In molecular unit **A**, the methyl group attached to chiral carbon atom C(4b), is disordered over two sites [*viz.* C(6b) in Fig. 2(a) and C(60b) in Fig. 2(b)] with the corresponding hydrogen atoms [H(4b) and H(40b)]. The sites are of *unequal* occupancies, 60% for C(6b) and 40% for C(60b), so that it may be concluded that the two inversion related methyl groups of 60% occupancy belong to one mesomeric molecule of configuration *R*,*S*,*S*,*R* and the two inversion related methyl groups of 40% occupancy belong to a second mesomer of *R*,*R*,*S*,*S* configuration. The diastereoisomers which constitute molecular unit **B**, in equal occupancies, may also be assigned *R*,*S*,*S*,*R* and *R*,*R*,*S*,*S* configurations with structures similar to those illustrated in Fig. 2(a) and 2(b). Selected bond lengths for $[H_4\mathbf{2}]^{4+}$ and **4** are listed together for comparison in Table 3.

The macrocycles $[H_4\mathbf{2}]^{4+}$ and **4** both adopt step conformations (Fig. 1 and 2 respectively) with the pyridyl rings lying on opposite sides of the inner great rings. The differences in conformation appear to arise from differences in hydrogen-bonding interactions. In $[H_4\mathbf{2}]^{4+}$ the two backbone chains are 'tied' together by hydrogen-bonding between amino protons and

Table 4 Principal torsion angles (°) in $[H_4\mathbf{2}]^{4+}$ and **4** (mean value). Those for the reported salts of $[H_4\mathbf{1}]^{4+}$ are given for comparison

		4	$[H_4\mathbf{1}]^{4+}$	
Torsion angles[a]	$[H_4\mathbf{2}]^{4+}$	Mean	Bromide[26]	Nitrate[27]
C(3a)–C(4a)–N(2a)–C(5a)	−72.3	−45.7	−74.2	−166.2
C(4a)–N(2a)–C(5a)–C(5b)	−172.4	−140.0	−167.7	−169.6
N(2a)–C(5a)–C(5b)–N(2b′)	175.9	−178.4	−77.6	−72.0
C(5a)–C(5b)–N(2b′)–C(4b′)	−171.9	117.5	171.3	−173.3
C(5b)–N(2b′)–C(4b′)–C(3b′)	−74.0	−59.3	175.5	−175.9

[a] The numbering corresponds to $[H_4\mathbf{2}]^{4+}$; for **4** (molecular unit **A**) the atomic labels are similar except for C(5b) and C(5b′) which are interchanged, and in molecular unit **B** labels a and b are replaced by d and c.

water molecules above and below the macrocycle cavity [O(1w)···H(N2b) 1.93, O(1w)···H(N2d) 2.17 Å] resulting in an elongated framework. In contrast, in **4**, each amino nitrogen atom is involved in strong intramolecular hydrogen bonding with the 3,5-dimethylphenol pendant attached to it [O(23a)···N(2a) 2.68, O(23b)···N(2b) 2.63, O(23c)···N(23c) 2.64 and O(23d)···N(2d) 2.68 Å] consistent with the NMR observation (*vide supra*). These differences cause the 'step' in **4** to be much steeper than in $[H_4\mathbf{2}]^{4+}$, and result in marked differences in the torsion angles of the inner great rings (Table 4). In $[H_4\mathbf{2}]^{4+}$ the substituents around the central three bonds of the macrocycle are in favourable *anti* conformation [middle, N(2a)–C(5a)–C(5b)–N(2b′), 175.9°; outer, C(4a)–N(2a)–C(5a)–C(5b), −172.4° and C(5a)–C(5b)–N(2b′)–C(4b′), −171.9°] but in both molecules of **4** only the middle backbone bond has an *anti* conformation (mean torsion angle −178.4°), the outer two deviating considerably (mean torsions angles 117.5 and −140.0°).

The macrocyclic framework of the unsubstituted hexaazamacrocycle $[H_4\mathbf{1}]^{4+}$ is basically the same as those of $[H_4\mathbf{2}]^{4+}$ and **4**, but a step conformation was not observed in structures reported for the bromide and nitrate salts shown in Fig. 3(a) and 3(b). In $[H_4\mathbf{1}]Br_4$[26] and $[H_4\mathbf{1}]NO_3$[27] gauche conformations occur at the middle of the backbones with torsion angles of −77.6 and −72.0° respectively (Table 4) in contrast to the *anti* conformations in $[H_4\mathbf{2}]^{4+}$ and **4** (*vide supra*). The two outer torsion angles of the five bonds of the reported structures are in *anti* arrangements with angles ranging from −166.2 to −175.9° with the exception of one *gauche* conformation [Fig. 3(a), C(3a)–C(4a)–N(2a)–C(5a) of −74.2°] in the bromide.

Conclusion

This work has demonstrated that the synthesis of macrocyclic ligands with 2-hydroxy-3,5-dimethyl pendant arms can be achieved in moderate yields by a straightforward synthetic method. Theoretically a large number of isomers are expected for compounds **4** and **8** and in the solid state the *R*,*S*,*S*,*R* and *R*,*R*,*S*,*S* isomers have been characterised for **4**. Strong hydrogen bonding between the tertiary amine groups and the attached phenolic hydrogen atoms was observed in the solid state structure of **4** and the NMR spectra indicate that this is a feature of all new pendant arm macrocycles.

Jackels and co-workers have shown earlier that the totally unsubstituted macrocycle $[H_4\mathbf{1}]^{4+}$ acts as a hexadentate ligand for lanthanides and d-block metals.[22] In this work it has been shown that addition of phenolic pendant arms gives a versatile ligand, **3**, for which we have been able to obtain a range of d-block and lanthanide metal complexes.[21,28] We are currently studying the effect of tetramethyl substitution on the coordinating ability of the hexaazamacrocycles.

Experimental

Materials

All reagents and solvents were generally of GPR grade, obtained from Aldrich Chemical Company and used without further purification. 2,6-Diformylpyridine was prepared by following a literature method[29] in 87% yield.

Physical measurements

Microanalyses were performed by the Microanalysis Laboratory and mass spectrometry was carried out by Mass Spectrometry Service of University of North London; liquid secondary ion (LSI) and electron impact (EI) mass spectra were recorded on a Kratos Profile spectrometer with *m*-nitrobenzyl alcohol as matrix. FT-IR Spectra were recorded as potassium bromide discs for solid samples on a Bio-rad FTS-40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 250 MHz spectrometer.

Synthesis of macrocyclic amines

Both amines **1** and **2** were prepared following a literature method.[22] To a refluxing suspension of barium(II) chloride dihydrate (4.52 g, 18.5 mmol) and 2,6-diformylpyridine (5.03 g, 37.3 mmol) in methanol (200 cm^3) was added dropwise a solution of 1,2-diaminoethane (2.4 g, 40.0 mmol) in methanol (40 cm^3). The mixture was refluxed for 3 h and cooled to 0 °C. A first portion of sodium tetrahydroborate (6.08 g, 160 mmol) and a second portion (3.04 g, 80 mmol) 30 min later was added to the stirred mixture slowly and in incremental amounts whilst maintaining the temperature at 0 °C. The reaction mixture was allowed to reach room temperature whilst being stirred overnight and was concentrated to dryness under reduced pressure. Extraction of the white solid with dichloromethane (3 × 100 cm^3) afforded an orange–red oil of **1** on removal of the solvent under reduced pressure. The amine **1** was isolated as the tetrahydrobromide salt (6.63 g, 51%) by adding hydrobromic acid (*ca.* 20 cm^3) dropwise.

The macrocyclic amine **2** was prepared as above but using 2,6-diacetylpyridine instead of 2,6-diformylpyridine. An orange–red oil of **2** was obtained and was isolated as the tetrahydrobromide salt in 68% yield. Analyses were carried out on the tetrahydrobromide salts of **1** and **2**. For $[H_4\mathbf{1}]Br_4$, mp 294 °C (decomp.) (lit.,[22] 291 °C, decomp.) *m*/*z* (EI) 326 (M^+ − 4HBr); $\delta_H(D_2O)$ 3.63 (8H, s, NCH_2CH_2N), 4.50 (8H, s, pyridyl CH_2), 7.53 (4H, d, *J* 7.78, pyridine *CH*), 8.00 (2H, t, 7.78, pyridine *CH*); $\delta_C(D_2O)$ 48.11 (NCH_2CH_2N), 54.43 (pyridyl CH_2), 125.22, 142.01, 154.82 (pyridine) (Found: C, 32.6; H, 4.7; N, 12.7. Calc. for $[H_4\mathbf{1}]Br_4{\cdot}\frac{1}{2}H_2O$ $C_{18}H_{31}N_6Br_4O_{\frac{1}{2}}$: C, 32.8; H, 4.7; N, 12.8%). For $[H_4\mathbf{2}]Br_4$, mp 322 °C (decomp.); *m*/*z* (EI) 706 (M^+), 326 (M^+ − 4HBr); $\delta_H(D_2O)$ 1.5 (12H, m, Me), 3.0 (8H, s, NCH_2CH_2N), 4.3 (4H, m, pyridyl CH_2), 7.4 (4H, m, pyridine *CH*), 7.9 (2H, m, pyridine *CH*) (Found: C, 37.4; H, 5.4; N, 12.1. Calc. for $[H_4\mathbf{2}]Br_4$ $C_{22}H_{38}N_6Br_4$: C, 37.4; H, 5.4; N, 11.9%).

Compounds **5** and **6** were prepared using the metal template method as **1** and **2** except that diethylenetriamine was used instead of 1,2-diaminoethane. Both macrocyclic amines were isolated as the hexahydrochloride salt in *ca.* 60% yield. For $[H_6\mathbf{5}]Cl_6{\cdot}2H_2O$, $C_{22}H_{46}N_8Cl_6O_2$ requires: C, 39.6; H, 6.9; N, 16.8; found C, 39.8; H, 7.3; N, 16.8%. For $[H_6\mathbf{6}]Cl_6{\cdot}4H_2O$, $C_{26}H_{58}N_8Cl_6O_4$ requires: C, 41.1; H, 7.63; N, 14.7; found C, 41.0; H, 7.6; N, 14.8%.

Macrocycles with pendant arms

Compound 3. The hexaazamacrocycle tetraamine was prepared in the same way as described above using barium(II) chloride dihydrate (3.22 g, 13.2 mmol), 2,6-diformylpyridine (3.56 g, 26.4 mmol) in methanol (150 cm^3) and 1,2-diaminoethane (1.6 g, 25.7 mmol) in methanol (10 cm^3). The orange–red oil (**1**) was refluxed in methanol (40 cm^3) for 30 min before 2,4-dimethylphenol (9.8 g, 80.3 mmol) was added neat and the mixture refluxed for 1 h. A solution of aqueous methanal (3.2 g, 106.7 mmol, 37% solution in water) in methanol (20 cm^3) was added dropwise over a period of 1–2 h. The white solid **3** (4.46 g, 39%) precipitated during reflux and was filtered under suction, washed with methanol (3 × 20 cm^3) and dried under vacuum (10^{-2} mmHg) over calcium chloride. Yield 39%, mp 189–191 °C ($C_{54}H_{66}N_6O_4$ requires C, 75.1; H, 7.6; N, 9.7. Found: C, 75.1; H, 7.5; N, 9.4%), ν_{max}/cm^{-1} 3062, 3009, 2966, 2915, 2849, 1614, 1590, 1574, 1485, 1457, 1343, 1376, 1241.

Compound 4. The same procedure was used as in preparing **3**. The quantities used were as follows: barium(II) chloride dihydrate (1.87 g, 7.7 mmol), 2,6-diacetylpyridine (2.51 g, 15.4 mmol) in methanol (150 cm^3), 1,2-diaminoethane (1.0 g, 16.7 mmol) in methanol (10 cm^3), sodium borohydride (2.28 g, 60 mmol followed by 1.14 g, 30 mmol), 2,4-dimethylphenol (7.3 g, 59.8 mmol) and aqueous methanal (1.4 g, 46.7 mmol) in methanol (10 cm^3). Yield 35%, mp 202–205 °C ($C_{58}H_{74}N_6O_4$ requires C, 75.7; H, 8.2; N, 9.2. Found: C, 75.7; H, 8.2; N, 9.1%), ν_{max}/cm^{-1} 3060, 3006, 2972, 2937, 2914, 2855, 1614, 1588, 1574, 1485, 1456, 1377, 1244.

Compound 7. The same procedure was used as in preparing **3**. The quantities used were as follows: barium(II) chloride dihydrate (2.44 g, 10.0 mmol), 2,6-diformylpyridine (3.04 g, 22.5 mmol) in methanol (200 cm^3), diethylenetriamine (2.1 g, 21.0 mmol) in methanol (20 cm^3), sodium borohydride (4.05 g, 106.6 mmol followed by 2.05 g, 54.0 mmol), 2,4-dimethylphenol (11.1 g, 91.0 mmol) and aqueous methanal (3.2 g, 106.7 mmol) in methanol (15 cm^3). Yield 47%, mp 211–212 °C ($C_{76}H_{96}N_8O_6$ requires C, 75.0; H, 7.9; N, 9.2. Found: C, 75.1; H, 8.0; N, 9.3%), ν_{max}/cm^{-1} 3054, 3009, 2954, 2916, 2850, 1612, 1590, 1573, 1485, 1456, 1442, 1378, 1244.

Compound 8. The same procedure was used as in preparing **3**. The quantities used were as follows: barium(II) chloride dihydrate (1.12 g, 4.6 mmol), 2,6-diacetylpyridine (1.52 g, 9.2 mmol) in methanol (100 cm^3), diethylenetriamine (0.95 g, 9.5 mmol) in methanol (10 cm^3), sodium borohydride (2.28 g, 60.0 mmol followed by 1.14 g, 30 mmol), 2,4-dimethylphenol (4.9 g, 40.2 mmol) and aqueous methanal (1.5 g, 50.0 mmol) in methanol (10 cm^3). Yield 32%, mp 232–236 °C ($C_{80}H_{104}N_8O_6$ requires C, 75.5; H, 8.2; N, 8.8. Found: C, 75.5; H, 8.2; N, 9.1%), ν_{max}/cm^{-1} 3057, 2970, 2938, 2906, 2850, 1613, 1587, 1575, 1485, 1454, 1376, 1243.

X-Ray structural analyses of $[H_42]Br_4\cdot 2H_2O$ and 4

Crystal data. $[H_42]Br_4\cdot 2H_2O$. $C_{22}H_{42}Br_4N_6O_2$, $M = 742.23$, triclinic, space group, $P\bar{1}$ (No. 2), $a = 9.655(2)$, $b = 10.391(3)$, $c = 8.059(2)$ Å, $\alpha = 103.71(2)$, $\beta = 98.85(2)$, $\gamma = 74.76(2)°$, $U = 754.24$ Å^3, $Z = 2$, $F(000) = 372$, $D_C = 1.634$ g cm^{-3}, μ(Mo-Kα) = 53.1 cm^{-1}, $\lambda = 0.710\ 69$ Å.

Compound 4. $C_{58}H_{74}N_6O_4$, $M = 919.26$, triclinic, space group, $P\bar{1}$ (No. 2), $a = 12.320(3)$, $b = 22.594(3)$, $c = 10.591(3)$ Å, $\alpha = 98.82(2)$, $\beta = 104.81(2)$, $\gamma = 102.57(2)°$, $U = 2712.77$ Å^3, $Z = 2$, $F(000) = 992$, $D_C = 1.125$ g cm^{-3}, μ(Mo-Kα) = 0.7 cm^{-1}, $\lambda = 0.710\ 69$ Å.

Data collection. Intensity data were collected on a Philips PW1100 four-circle diffractometer using Mo-Kα radiation from a graphite monochromator, in the θ-range of 3–25° with a scan width of 0.90°, using the method described previously.[30] The crystals used were colourless with dimensions 0.35 × 0.40 × 0.30 mm and 0.30 × 0.38 × 0.35 mm for $[H_42]Br_4\cdot 2H_2O$ and **4** respectively. In each case, three reference reflections were measured every 5 h which showed no significant variation in intensities throughout data collection. Lorentz and polarization corrections were applied to the data and equivalent reflections were merged to give 1581 and 2098 unique reflections with $I/\sigma(I) \geqslant 3$ for $[H_42]Br_4\cdot 2H_2O$ and **4** respectively ($R_{int} = 0.021$ for $[H_42]Br_4\cdot 2H_2O$ and 0.027 for **4**).

Structure solution[31] and refinement.[32] Direct methods were used to solve both structures and gave the positions of most non-hydrogen atoms. The remaining non-hydrogen atoms, in each case, were located from subsequent difference-Fourier syntheses. For $[H_42]Br_4\cdot 2H_2O$, the asymmetric unit contains only half of the macrocyclic ligand, the second half being generated by an inversion centre in the middle of the molecule. After all the atoms had been refined with isotropic displacement parameters, absorption corrections[33] were applied to the data (maximum = 1.15 and minimum = 0.86). For **4**, the solution was complicated by the existence of two independent centrosymmetric molecules **A** and **B**. In molecule **A** the methyl group, attached to the chiral carbon atom C(4b), is disordered with the hydrogen atom; refinement of the partial atoms [C(6b) and C(60b)] at two sites with fixed thermal displacement parameter indicated occupancy of *ca.* 0.6 and 0.4 respectively. Similarly, in molecule **B**, disorder was established for the equivalent methyl carbon atom C(6c) for which two sites [C(6c) and C(60c)] of 0.5 occupancy were established. For both molecules, the sites of two hydrogen atoms [H(4b) and H(40b) for **A** and H(4c) and H(40c) for **B**] partial occupancy were calculated and included in structure factor calculation with the appropriate occupancy but were not refined. Due to shortage of data, the phenylene rings were constrained to refine as idealised hexagons with C–C and C–H bond lengths fixed at 1.395 and 1.08 Å respectively. A succession of difference-Fourier syntheses calculated using data with $\sin\theta < 0.35$ revealed the positions of all hydrogen atoms bonded to nitrogen and oxygen for $[H_42]Br_4\cdot 2H_2O$, and these were included at the observed positions but were not refined; for **4**, only some of the carbon bonded hydrogen atoms were found. In each case, for consistency all carbon bonded hydrogen atoms were placed at idealised geometry (C–H 1.08 Å) and their displacement parameters fixed at 0.08 Å^2 for $[H_42]Br_4\cdot 2H_2O$ and 0.1 Å^2 for **4**. Anisotropic displacement parameters were assigned to all non-hydrogen atoms in $[H_42]Br_4\cdot 2H_2O$, and in **4** the nitrogen, oxygen and seven of the methyl carbon atoms of the phenyl groups [except for C(8b) which became non-positive definite during refinement so that an isotropic parameter was used]. The final cycles of full-matrix least-squares refinement converged at $R = 0.0642$ and $R_\omega = 0.0681$ for 154 parameters with weights $1/[\sigma^2(F) + 0.000\ 881\ (F^2)]$ assigned to the individual reflections for $[H_42]Br_4\cdot 2H_2O$, and at $R = 0.0997$ and $R_\omega = 0.1059$ for 313 parameters with weights of $1/[\sigma^2(F) + 0.000\ 093\ (F^2)]$ for **4**. In the final difference-Fourier map a number of residual peaks of *ca.* 0.8 e Å^{-3} were found in the vicinity of the bromine atom Br(2), in $[H_42]Br_4\cdot 2H_2O$, and there were no residual peaks greater than 0.8 e Å^{-3} in **4**.

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., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/150.

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