Complexation behaviour of *C*- and *N*-functionalized tetradentate ligands based on 1,5,9-triazacyclododecane

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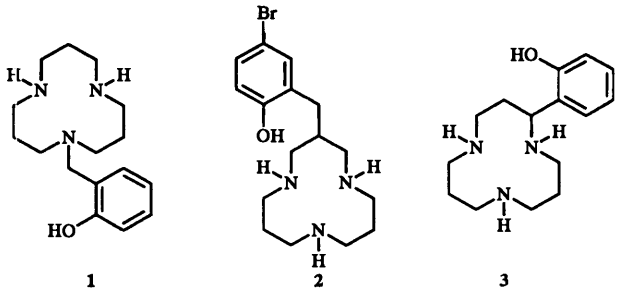
The synthesis and aqueous complexation behaviour of *C*- and *N*-linked *o*-hydroxyaryl substituted derivatives of 1,5,9-triazacyclododecane is reported. The *N*-linked ligand forms strong 1:1 complexes with copper and zinc (log K_{ML} = 18.7 and 14.1, respectively) in which the phenolate acts as an effective donor ligand in the putative tetrahedral complex. The ligand substituted at carbon at the 3-position is less basic and forms much weaker complexes with Cu^{2+}, Ni^{2+} and Zn^{2+} (log K_{CuL} 10.2, log K_{ZnL} 7.32 and log K_{NiL} 6.11) in which phenolate participation is absent.

Ligands which engender a well defined tetrahedral metal-binding site are of considerable interest because of the consequences that then emerge in their affinity and selectivity for particular metal ions. The destabilization of copper(II) complexes is one example of this: the d^9 Cu^{II} ion prefers a square planar coordination environment, whereas the d^{10} ions Cu^{I} and Zn^{II} prefer a tetrahedral geometry. With an appropriate choice of donor atoms in the ligand, it is possible to devise ligands which exhibit a greater affinity for Zn^{II} over copper(II), which is in contradiction to the usual sequence of complex stability Ni < Cu > Zn (Irving–Williams series).[1]

There is a variety of ligand structural types which can be identified, in each of which a well defined binding site imposing tetrahedral coordination can occur, Fig. 1. The possibilities include sterically encumbered bidentate ligands, which, in their ML_2 [2 + 2] complexes, prefer tetrahedral coordination,[2–4] conformationally restricted tetradentate ligands[5] wherein ML [2 − 2] complex formation is favoured, and the more unusual dimeric system wherein M_2L_2 $[2 - 2]_2$ complex formation is imposed by two tetrahedral binding sites created by the cooperative ligation of two orthogonally disposed ligands.[6,7] Monosubstituted tridentate [3 + 1] and trisubstituted monodentate ligands [1 + 3] (Fig. 1), constitute two further ligand structural types that may, in principle, impose tetrahedral coordination on a bound metal ion. In the former case, there have been some reports involving monosubstituted derivatives of 1,5,9-triazacyclododecane ([12]-N_3).[8–11] These have been stimulated not only by the quest for tetrahedral coordination,[8,10] but also because of their similarity to the zinc(II) coordination site in the enzymes carbonic anhydrase and carboxypeptidase-A.[9,11]

In extending this study of [3 + 1] tetrahedrally coordinating ligands, a key aspect was the nature and relative disposition of the pendant donor group. The ligands **1** and **2** were chosen for examination as they allow a direct comparison to be made with the *C*-linked derivative **3**,[9] for which there is detailed complex characterization. At the outset it was noted that in the zinc complex of **3**, the phenolate donor was unable to bind directly over the top of the [12]-N_3 basal plane and the zinc ion was penta-coordinate with a water molecule as the fifth donor. The situation with ligands **1** and **2** is different: in both cases inspection of molecular models suggested that the phenolate donor could occupy a site in a tetrahedral array of donors, notwithstanding the formation of an eight-membered chelate ring in the case of **2**.



1 **2** **3**

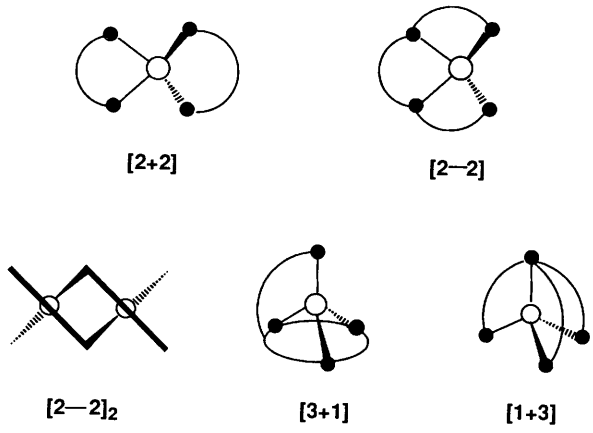
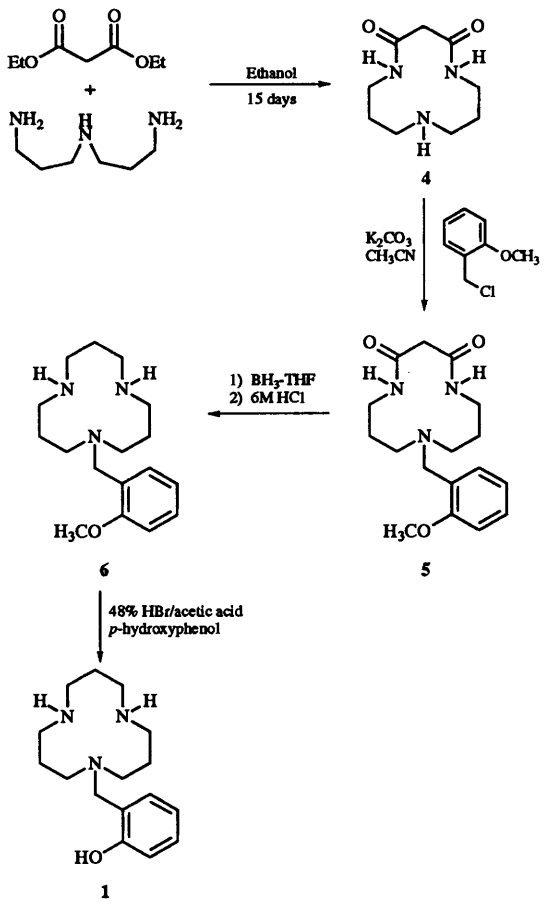


Fig. 1 Variety of ligand structural types imposing tetrahedral coordination

Ligand synthesis

The synthesis of various 12-N_3 ring derivatives has been reported previously involving selective *N*-protection of an acyclic precursor[12] prior to Richman–Atkins cyclization,[13] the condensation of a linear triamine with an appropriate malonate or coumarin derivative,[9,14] or the intermediacy of tricyclic orthoamides.[15] Such 12-N_3 rings are therefore usually fairly straightforward to prepare and functionalize.[16]

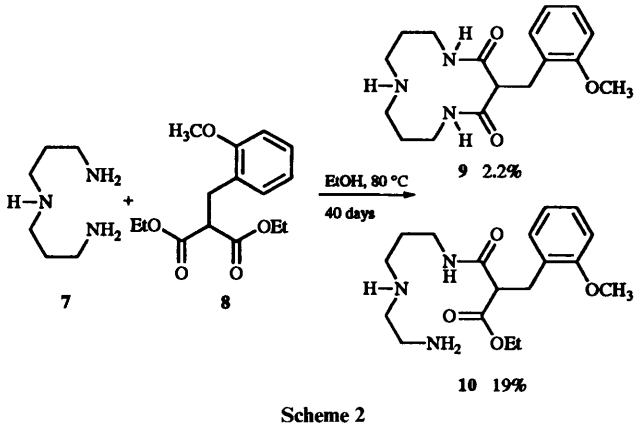
For the synthesis of **1**, differentiation of one nitrogen was required to allow selective *N*-alkylation. Co-condensation of 1,5,9-trizanonane with diethyl malonate under medium dilution[14] yielded the cyclic diamide **4** in modest yield (Scheme 1). Selective mono-alkylation of the amino-nitrogen with *o*-methoxybenzyl chloride (K_2CO_3, MeCN) yielded the *N*-alkyl derivative **5** in 85% yield, and subsequent reduction of the lactam with borane in tetrahydrofuran afforded the triamine **6**. Demethylation proved to be more difficult than expected. Neither nucleophilic cleavage using NaSEt in DMF, nor acid cleavage with BBr_3 or CF_3CO_2H in CH_2Cl_2 resulted in any product formation. However, treatment with HBr in acetic acid (110 °C, 15 h) did allow the demethylation reaction to proceed,



Scheme 1

although it was necessary to add a little *p*-hydroxyphenol in order to inhibit radical bromination of the phenol ring.

The first attempted route to the *C*-functionalized ligand **2**, relied upon a similar strategy. In this case, reaction of the acyclic triamine **7** with the mono-(*o*-methoxybenzyl) malonate derivative, **8**, proceeded very slowly (Scheme 2), and the 12-



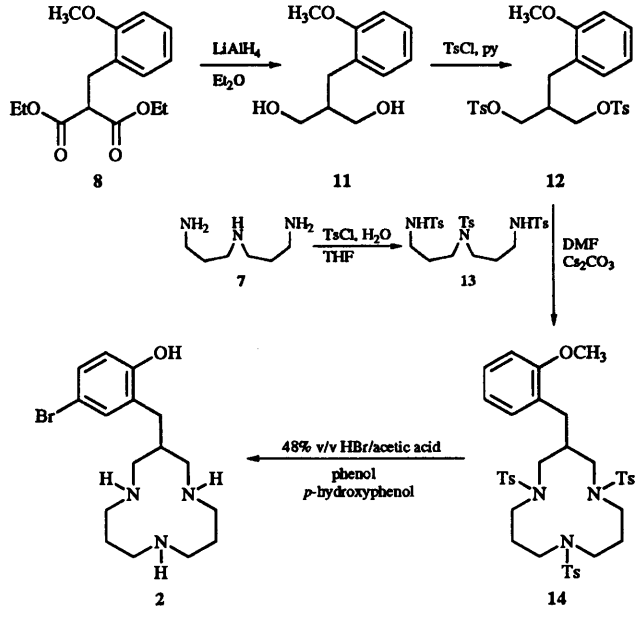
Scheme 2

ring diamide was isolated in 2% yield only. Given that the half-reacted material **10** was the major product isolated, attempts were made to cyclize this material, *e.g.*, boiling in MeCN, but to no avail. An alternative route was studied relying upon a tosylamide/tosylate co-cyclization reaction,[13] Scheme 3. Reduction of the diester **8** followed by tosylation yielded the ditosylate **12**. Reaction of this ditosylate with the tritosylamide **13** (DMF, CS_2CO_3) afforded the cyclized product **14** in a moderate yield (27%). Despite the presence of added *p*-hydroxyphenol, detosylation (HBr–AzOH–PhOH) of **14** gave a product with a *p*-bromo substituent introduced into the

Table 1 Protonation constants for macrocyclic ligands **1**, **2** and **3** (298 K, H_2O, I = 0.1 [NMe_4NO_3])

Ligand	pK_1	pK_2 (phenol)	pK_3	pK_4
1	> 12	9.87	6.64	< 2
2	10.1	8.72	6.92	2.55
3[a]	12.7	9.67	7.09	< 2
(12-N_3), **15**[b]	12.6		7.57	2.41
(13-N_3), **16**[c]	9.79		8.13	4.18
17[c]	12.3		7.34	2.51

[a] Data from ref. 9. [b] Data from ref. 17. [c] Data from ref. 18.



Scheme 3

phenolic ring, irrespective of the amount of phenol and/or *p*-quinol added. The isolated product, **2** possessing the *p*-bromo substituent was entirely suitable for the study: the presence of the bromine atom was expected to reduce slightly the pK_a of the phenol moiety and imposes no steric effect.

Solution complexation equilibria

Protonation constants for ligands **1** and **2** were measured by standard pH-metric methods in a background of 0.1 mol dm^{-3} NMe_4NO_3. Comparison of the measured pK_a values in relation to **3**,[9] and the related 12-N_3 compounds **15**, **16** and **17** has been made (Table 1). The *N*-linked macrocycle **1** behaved in a similar manner to **3**: the first pK_a was beyond the range of accurate measurement (> 12) and is consistent with a structure for the monoprotonated species in which there is a favourable bifurcated hydrogen bond with the proton residing in the plane of the three ring nitrogens. The second protonation constant relates to the phenolic hydrogen and its similarity to the values for simple alkyl phenols is consistent with little or no direct interaction between the monoprotonated cyclic triamine and the phenolate anion.

The situation with the *C*-linked phenolic ligand **2** was rather different. In this case, as was observed with **15**, **16** and **17**, a value for the third ring protonation constant was able to be

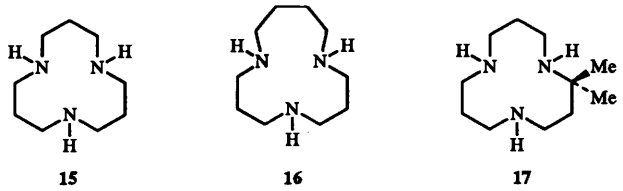


Table 2 Measured formation constants (log K_{ML} and log K_{MLH}) for complexes of ligands **1**, **2** and **3** (298 K, H_2O, I = 0.1 [NMe_4NO_3])

	Ni^{II}		Cu^{II}		Zu^{II}	
Ligand	log K_{ML}	log K_{MLH}	log K_{ML}	log K_{MLH}	log K_{ML}	log K_{MLH}
1	*a*		18.7	*b*	14.1	*b*
2	6.11	8.14	10.2	8.00	7.32	7.50
3[c]	14.0	*b*	18.4	*b*	12.6	*b*
15 (12-N_3)	10.9	*b*	12.6	*b*	8.8	*b*
17[d]	9.8	*b*	11.6	*b*	7.7	*b*

[a] Kinetics of complexation were too slow to be accurately measured. [b] Not determined. [c] Data from ref. 9. [d] Data from ref. 17.

Table 3 Spectrophotometric analysis of metal complexation (293 K, H_2O, pH 7 — unless otherwise stated)

	[NiL]		[CuL]	
Ligand[a]	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}
1[c]	389	14	272	8600
			418	1080
			660	158
2		Very weak[b]	690	110
3	363	180	279	7000
	590	25	392	120
			690	110

[a] At pH 7 the free ligands **1** and **2** each gave rise to two major bands at 226 and 272 nm. At pH 10, the bands were observed at 224 and 293 nm. [b] The (π–π^*) transition, was observed at 294 nm (ε = 3 × 10^3 dm^3 mol^{-1} cm^{-1}), *cf.*, 290 (3 × 10^3) for [Ni**3**] and 292 (3.4 × 10^3) for **3**. [c] The band at 389 nm is likely to be due to a weak ligand to metal charge-transfer interaction.

Table 4 pH dependence of [Cu **1**] (293 K, H_2O)

	Charge-transfer band		d–d transition	
pH	λ/nm	ε/dm^3 mol^{-1} cm^{-1}	λ/nm	ε/dm^3 mol^{-1} cm^{-1}
4	426	32	654	42
5	428	540	658	82
7.2	418	1080	658	158
8.5	416	1050	660	155
9.5	410	1000	660	146
10.5	406	950	666	137
11.5	396	870	672	120

determined. The pK_a for deprotonation of the phenol was 8.72 which is somewhat lower than that measured for *p*-bromophenol itself (9.35) suggesting that there was possibly a weak stabilising interaction between the mono-protonated ring and the phenolate anion. More obvious was the diminution of the first pK_a: the measured value of 10.1 is at least two pK_a units lower than that of **1**, **3**, **15**[17] and **17** and is not dissimilar to the value measured for 1,5,10-triazacyclotridecane ([13]-N_3: pK_a = 9.79, Table 1).[18]

Stability constants for the formation of metal–ligand species were also determined for **1** and **2**, and are compared with those reported for **3**, **15** and **17** (Table 2). With the *N*-linked ligand **1**, the values for [ML] complex formation with copper and nickel were much higher than those observed with [12]-N_3 **15**, itself, reflecting the strong ligation of the phenolate donor. This binding interaction seems to be occurring more strongly than with **3**, as the respective formation constants were 0.3 and 1.5 log units higher for copper and zinc, respectively. This may reflect the better tetrahedral arrangement of the donor atoms in the complex with **1**, which will manifest itself more clearly in the stability of the zinc complex. The value for nickel complexation could not be determined under the experimental conditions used: even using delays of 1 h between base addition led to titration curves that were obviously derived from a system that had not equilibrated. With the *C*-linked ligand **2**, the order of stability of the 1:1 [ML] complexes followed the sequence Cu > Zn > Ni (Table 2). In each case a value for the formation of [MLH] species could also be determined, corresponding to protonation of the relatively innocent phenolate group. That the phenol group in **2** does not bind significantly to the metal in the [ML] complexes is also evident from the correspondence of the values with those measured with the parent ligand **15** ([12]-N_3), itself.

Solution speciation may also be probed using electrospray mass spectrometry. With the *N*-linked ligand **1**, both [CuL] and [ZnL] complexes were observed in the positive ion mode following admixture of wet methanolic solutions of the ligand and a stoichiometric amount of the appropriate metal triflate salt. The protonated ligand gave rise to the most intense peak in each case and with nickel no [NiL] species was discerned—even after 8 h or in the presence of 5 equivs. of nickel, in accord with its apparent slow formation kinetics. For the *C*-linked ligand, the most intense peaks were observed for the [Cu·**2**] complex, with the nickel and zinc species observable but of lower intensity. Reasonable agreement (0.4 mass units) was obtained between the observed and calculated masses for the appropriate isotope pattern, in each case.

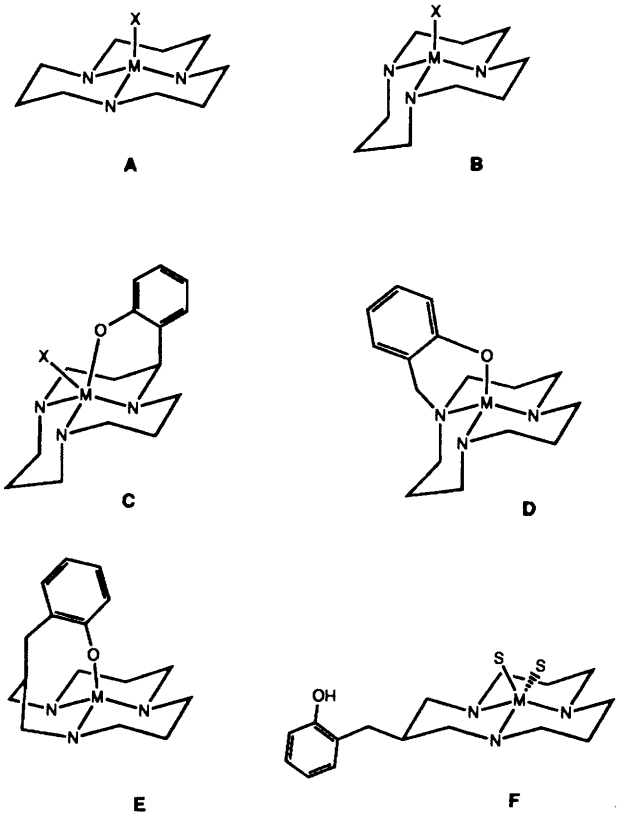
Aqueous solutions of the copper complex of **1** were light yellow in colour, while the corresponding complex of **2** was blue. This behaviour (Table 3) was studied by spectrophotometry and it was apparent that in [Cu·**1**] the charge-transfer band at 418 nm (ε = 1.08 × 10^3 dm^3 mol^{-1} cm^{-1}) was caused by a strong charge interaction between the N_3-bound copper ion and the phenolate. Such behaviour had been noted with [Cu·**3**], but to a much lesser extent [λ = 392 nm (ε = 1.2 × 10^2 dm^3 mol^{-1} cm^{-1})].[9] At higher pH (Table 4), the hydroxide ion competes with the phenolate and the intensity of the charge transfer band (and the position of the d–d band) changed.

Conclusions

This comparative study highlights the similarities between the *N*-linked ligand **1** and the *C*-linked macrocycle **3**. Both form well defined 1:1 complexes with copper, nickel and zinc

involving phenolate binding and this interaction is most pronounced with **1**. Intramolecular phenolate binding gives rises to six-membered ring chelate formation. The *C*-linked ligand **2** is quite different. Formation of 1:1 complexes occurs *via* N_3 binding only, with no phenolate participation evident as revealed by the absence of the charge-transfer band in [Cu·**3**], and the observation of [MLH] species wherein the deprotonation equilibrium was similar to that of the ligand **3** itself.

The different complexation behaviour of the three ligands may be related to the nature of the preferred conformer in solution. In general (Scheme 4), 12-N_3 complexes are likely to



Scheme 4

adopt one of the two all-chair conformations, **A** and **B**. The *C*-linked ligand **3**, explored by Kimura, takes up a conformation of type **B** that allows phenolate participation (shown as **C**), albeit with sufficient space for an additional interaction with an anionic donor. The *N*-substituted ligand **1**, is unable to bind cooperatively in an **A**-type conformation, but phenolate binding is favoured in a **B**-type conformation, as shown in **D**. The *C*-linked ligand **3** is unable to bind the metal in a tetradentate manner in either conformation **A** or **B**. Phenolate participation may occur, however, when one of the six-membered rings adopts a higher energy boat conformation, as in **E**. It is evident that this conformation is relatively unfavourable and in solution the ligand will presumably take up a conformer such as that shown as **F** wherein solvent molecules complete the metal coordination sphere.

In terms of the quest for effective tetrahedral coordination, ligand **1** may represent the best example of an N_3O donor set that favours such a geometry in aqueous solution, although the nature of the donor set does not allow any zinc selectivity to be obtained.

Experimental

All reactions were carried out in apparatus that had been oven-dried and cooled under argon. All solvents were dried from an appropriate drying agent and water was purified from the 'Purite' system.

Alumina refers to Merck Alumina activity II–III that had been soaked in ethyl acetate for at least 24 h prior to use. Silica refers to Merck silica gel F60 (230–400 mesh).

Analytical and preparative HPLC were performed on a Varian Vista 5500 or Star 5065 instrument fitted with a C_{18} reversed-phase column ('Dynamax').

^1H and ^{13}C NMR spectra were obtained with a Bruker AC 250 operating at 250.13 and 62.90 MHz respectively, Varian Gemini 200 operating at 200 and 50.1 MHz, respectively, Varian XL 200 operating at 200.1 MHz and a Varian VXR 400S operating at 400.1 MHz. All chemical shifts are given in ppm relative to the residual solvent resonance and coupling constants are in Hz.

Mass spectra were recorded on a VG 7070E, operating in FAB, EI^+ or DCI ionization modes as stated. Electrospray mass specta were recorded using a VG Platform (Fisons instruments) operating in ES^+ mode or were performed by the EPSRC Mass Spectroscopy service at Swansea. Accurate mass spectroscopy was performed by the EPSRC Mass Spectroscopy service.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as a thin film or KBr disc as stated. Ultraviolet spectra were recorded on a UVIKON 930 spectrometer. Combustion analysis was performed using an Exeter Analytical Inc CE440 elemental analyser. Metal concentrations were determined by atomic absorption spectroscopy using a Perkin-Elmer 5000 atomic absorption spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Potentiometric titrations were performed on a Molspin 1 cm^3 auto titrator using a Corning semi-micro electrode to measure the pH.

Electrospray mass spectrometry complexation analysis

Stocks solutions of the ligand (10 cm^3, 0.3 mmol dm^{-3}) in wet methanol containing about 1–5% water and the appropriate metal triflate (10 cm^3, 1.5 mmol dm^{-3}) in methanol were made up. To a sample of the ligand solution (1 cm^3) the appropriate amount of metal triflate solution (of the order of 0.2 cm^3) was added to make a 1:1 metal/ligand ratio. Using 10 μl of the test solution, mass spectra were obtained on a VG Platform (II) electrospray mass spectrometer (cone voltage 30 V; sample temperature 60 °C) with positive ionization. The following data were obtained for the complexes of **1** and **2** (calculated values in parentheses): [Cu·**1**] 339.3 (339.1), 340.5 (340.1), 341.2 (341.1); [Zn·**1**] 340.2 (340.1), 341.8 (342.1), 343.8 (344.1); [Ni·**2**-H] 412.0 (412.1), 414.2 (414.1), 415.9 (416.1); [Cu·**2**-H] 417.3 (417.0), 418.9 (419.0), 420.6 (421.0).

Ultraviolet and visible spectroscopic analysis

Stock solutions of the ligand (0.001 mol dm^{-3}) to be tested and the metal triflates (0.01 mol dm^{-3}) were dissolved in the stated solvent (water or methanol). The samples to be tested were added to a quartz cuvette (1 cm in width, 4 cm^3 in volume) and the spectra obtained on a UVIKON 930 spectrometer. For metal/ligand complexes, the appropriate amount of metal triflate solution (0.3 cm^3) was added to the ligand solution (3 cm^3) to obtain a 1:1 ratio and tested as before. For aqueous samples the acidity was measured after metal addition.

For the 1-(2-hydroxybenzyl)-1,5,9-triazacyclododecane copper complex, spectra were recorded as a function of pH (range 2–11.5) by adding aqueous hydrochloric acid (0.1 mol dm^{-3}) or aqueous sodium hydroxide (0.1 mol dm^{-3}) as required.

Potentiometric titrations

The titration cell was a double-walled glass vessel of approximate 5 cm^3 capacity (internal dimensions of 1.2 cm in diameter by 5 cm in depth). The contents were kept at a

constant temperature by passing water between the glass walls using a Grant thermostatically controlled water bath and pump. The solutions in the vessel were mixed with a cross-shaped magnetic stirrer bar using an IKA-mini-MR magnetic stirrer. An IBMpc program (Molspin version 1.44 by Academic software) was used to collect and store the measured pH readings during the titration (using a Corning semi-micro pH combination electrode) and operated the 1 cm^3 capacity autotitrator (Molspin, Newcastle upon Tyne, UK). The titrant was delivered to the titration cell through a rigid plastic tube (internal bore size of 0.05 mm). The end of the tube was held in place so that it would always be above the surface of the solution in the titration cell and so it met the glass wall at an angle of 30°. The volume increments, the time between additions (governed by the pH stability over the 'time delay') and final volume added were all controlled by the program and were set before each titration. The pH electrode was calibrated using two NBS buffer solutions (Unicam) of pH 4.008 and 6.865 at 25 °C. The collected data (volume of titrant added and pH) were transferred to a UNIX mainframe and analysed by two non-linear least-squares programs SCOGS2 and Superquad.

All solutions were prepared from 'Purite' water that had been boiled for 30 mins with nitrogen gas bubbling through it to remove carbon dioxide. Ligand solutions (25 cm^3 or 10 cm^3, 0.001 mol dm^{-3}) were prepared in a constant ionic strength background solution of tetramethylammonium nitrate (0.1 mol dm^{-3}). Two or three equivs. of inorganic acid (HCl) were added to obtain an initial pH of between 2 and 2.5. Metal nitrate solutions (10 cm^3, 0.01 mol dm^{-3}) in a background of 0.1 mol dm^{-3} NMe_4NO_3, were prepared and the exact metal concentration determined by atomic absorption spectroscopy prior to use.

The exact molarity of the titrant base solution, tetramethylammonium hydroxide (about 0.05 mol dm^{-3}) in a background of 0.1 mol dm^{-3} NMe_4NO_3 was determined by titration against a standard hydrochloric acid solution (3 cm^3, 0.01 mol dm^{-3}) at 25 °C. From the titration curve a GRAMS plot was obtained (using Molspin program) which allowed the end point to be determined and hence the exact concentration. This was repeated three times until consistent results were obtained.

Measurement of pK_a and metal stability constants

The ligand solution (3 cm^3, 0.001 mol dm^{-3}) was added to the titration cell and the calibrated pH electrode placed into the solution so that its frit was below the liquid surface. With the solution temperature maintained at 25 °C and with efficient stirring the base solution (TMA OH, 0.05 mol dm^{-3}) was titrated (in increments of 0.002 cm^3, time delay of 5 s). The pH curve was analysed as mentioned above to determine the pK_as of the ligand.

For metal stability constants the appropriate volume of metal nitrate solution (about 0.3 cm^3, 0.01 mol dm^{-3}) was added to the ligand solution (3 cm^3, 0.001 mol dm^{-3}) to obtain a metal/ligand ratio of one. The titration was performed as above (increments of 0.0025 cm^3, time delay 10–1800 s depending on the kinetics of complexation).

Synthesis of 1-(2-hydroxybenzyl)-1,5,9-triazacyclododecane (1)

9-(2-Methoxylbenzyl)-1,5,9-triazacyclododecane-2,4-dione (5). To a stirred slurry of 1,5,9-triazacyclododecane-2,4-dione[14] (2.06 g, 10.35 mmol) and fine-mesh potassium carbonate (1.57 g, 11.38 mmol) in anhydrous acetonitrile (40 cm^3), 2-methoxybenzyl chloride (2.13 g, 13.6 mmol) in anhydrous acetonitrile (10 cm^3) was added. The mixture was boiled under nitrogen and then subjected to TLC on silica [1% NH_3OH–59% MeOH–40% CH_2Cl_2, R_f(1,5,9-triazacyclododecane-2,4-dione) = 0.37]. After 48 h the mixture was concentrated to give a crude product. The residue was washed with water (15 cm^3), dissolved in chloroform (20 cm^3) and dried (K_2CO_3) and the solvent was evaporated off under reduced pressure to yield an off-white solid. Recrystallization from methanol gave rectangular colourless crystals (3.14 g, 85%) mp 180–181 °C, $\delta_H(CDCl_3)$ 1.74 (4 H, quintet, $CH_2CH_2CH_2$), 2.54 (4 H, t, CH_2NHCO), 3.07 (2 H, s, CH_2CO), 3.22 (4 H, q, CH_2NH), 3.47 (2 H, s, $ArCH_2$), 3.90 (3 H, s, OMe), 6.98 (2 H, m, Ar), 7.21–7.35 (2 H, m, Ar), 7.41 (2 H, br t, NH); $\delta_C(CDCl_3)$ 24.6 ($CH_2CH_2CH_2$), 40.6 (CH_2NHCO), 46.3 ($ArCH_2$), 53.6 (CH_3), 55.0 (CH_2N), 55.8 (CH_2CO), 111.5 (Ar C3), 121.0 (Ar C5), 126.3 (Ar C1), 129.1 (Ar C4), 132.0 (Ar C6), 157.7 (Ar C2), 166.8 (CO); *m/z* (DCI, NH_3) 320 ($M^+ + 1$); ν_{max}(KBr)/cm^{-1} 3309 (NH), 3067, 3007 (Ar CH), 1683, 1643 (CO), 1242 (COC) (Found: C, 63.93; H, 7.89; N, 13.06. $C_{17}H_{25}N_3O_3$ requires C, 63.93; H, 7.89; N, 13.16%).

1-(2-Methoxybenzyl)-1,5,9-triazacyclododecane (6). To a cold slurry of 9-(2-methoxybenzyl)-1,5,9-triazacyclododecane-2,4-dione (0.5 g, 1.57 mmol) in anhydrous THF (15 cm^3) a solution of borane in THF (1 mol dm^{-3}; 40 cm^3) was added slowly under an argon atmosphere. The reaction was boiled and followed by IR spectroscopy for the disappearance of the carbonyl (1643 cm^{-1}). After 48 h the mixture was cooled and methanol (20 cm^3) was carefully added followed by concentration. Two further additions of methanol (20 cm^3) were made followed by evaporation under reduced pressure.

The resultant solid was boiled with hydrochloric acid (6 mol dm^{-3}; 20 cm^3) for 3 h. Following the removal of the acid, the solid was washed with methanol (3 × 25 cm^3). The white solid was taken up into aqueous sodium hydroxide solution (pH 13, 50 cm^3). Extraction with chloroform (4 × 50 cm^3), drying (K_2CO_3), filtration and concentration gave a clear oil in quantitative yield. Slow recrystallization from toluene gave white crystals mp 118–119 °C, $\delta_H(CDCl_3)$ 1.83 (4 H, quintet, NCH_2CH_2), 1.95 (2 H, quintet, $NHCH_2CH_2CH_2NH$), 2.53 (4 H, t, $HNCH_2CH_2CH_2NH$), 2.78 (4 H, t, $HNCH_2CH_2CH_2N$), 2.97 (4 H, t, NCH_2), 3.55 (2 H, s, $ArCH_2$), 3.80 (3 H, s, CH_3), 6.90 (2 H, t, Ar), 7.23 (2 H, s, Ar); $\delta_C(CDCl_3)$ 23.56 ($NHCH_2CH_2CH_2NH$), 23.93 (NCH_2CH_2), 46.70 ($HNCH_2CH_2CH_2NH$), 49.36 ($HNCH_2CH_2CH_2N$), 52.55 (CH_2N), 55.19 (CH_3), 110.7 (Ar C3), 120.0 (Ar C5), 125.4 (Ar C1), 128.5 (Ar C4), 130.8 (Ar C6), 157.9 (Ar C2); *m/z* (DCI, NH_3) 292 ($M^+ + 1$), 170 ($M^+ - CH_2C_6H_4OCH_3$) (Found: 292.2389 ($M^+ + 1$). $C_{17}H_{30}N_3O$ requires 292.2389); ν_{max}(KBr)/cm^{-1} 1597, 1584 (Ar CC), 1242 (COC).

1-(2-Hydroxybenzyl)-1,5,9-triazacyclododecane (1). A solution of HBr in acetic acid (48% v/v; 6 cm^3) was added to 1-(2-methoxybenzyl)-1,5,9-triazacyclododecane (0.98 g, 3.18 mmol) and *p*-hydroxyphenol (18.6 mg, 0.17 mmol) and the mixture was heated to 110 °C with stirring for 15 h. After evaporation of the solvent the residue was taken up in aqueous sodium hydroxide solution (30 cm^3) and adjusted to pH 12. Extraction with chloroform (3 × 30 cm^3), drying (K_2CO_3), filtration and evaporation gave a dark glass 0.72 g, (82%) which was further purified by HPLC: t_R = 9.8 min observed at λ = 254 nm (Dynamax, reversed-phase) with gradient elution 10 cm^3 min^{-1}; A = H_2O–0.1% TFA, B = CH_3CN–0.1% TFA from t = 0 min; A = 90%, B = 10% to t = 20 min; A = 75%, B = 25% and finally to t = 25 min; A = 100%, B = 0%; $\delta_H(CDCl_3)$ 1.71 (6 H, m, $CH_2CH_2CH_2$), 2.54 (4 H, t, $HNCH_2CH_2CH_2NH$), 2.64 (4 H, t, $HNCH_2CH_2CH_2N$), 2.80 (4 H, t, CH_2N), 3.51 (2 H, s, $ArCH_2$), 6.35 (3 H, br s, NH and OH), 6.66 (1 H, td, Ar H5), 6.79 (1 H, dd, Ar H3), 6.94 (1 H, dd, Ar H6), 7.08 (1 H, td, Ar H4); $\delta_C(CDCl_3)$ 24.82 ($HNCH_2CH_2CH_2N$), 25.13 ($HNCH_2CH_2CH_2NH$), 46.18 ($HNCH_2CH_2CH_2NH$), 48.94 ($HNCH_2CH_2CHN$), 52.79 (CH_2N), 56.50 ($ArCH_2$), 116.7 (Ar C3), 117.4 (Ar C5), 123.9 (Ar C1), 128.3 (Ar C6), 129.8 (Ar C4), 158.6 (Ar C2); *m/z* (DCI, NH_3) 278 ($M^+ + 1$), 172 ($M^+ - CH_2ArOH$), 124 ($M^+ - H_2ArOH + NH_3$), 107 ($M^+ - CH_2ArOH$); ν_{max}(KBr)/cm^{-1} 3401 (OH), 1585 [Found: 278.2232 ($M^+ + 1$). Calc. for $C_{16}H_{29}N_3O + H^+$: 278.2232].

Synthesis of 3-(2-hydroxy-5-bromobenzyl)-1,5,9-triazacyclododecane (2)

Diethyl-(2-methoxylbenzyl)malonate (8). A solution of diethyl malonate (8.37 g, 52.3 mmol) in dry ethanol (20 cm^3) was added dropwise to a solution of sodium ethoxide (27 mmol) in dry ethanol (50 cm^3). After stirring for 30 min under a nitrogen atmosphere a solution of 2-methoxybenzyl chloride (4.02 g, 25.7 mmol) in dry DMF (25 cm^3) was added dropwise over 30 min. The mixture was brought to reflux for 24 h. Water (70 cm^3) was added to the cooled reaction and the solution filtered to remove any precipitated diethyl bis(2-methoxybenzyl)malonate. Reduction in the solvent volume, extraction with diethyl ether (5 × 50 cm^3), drying the extract (K_2CO_3) and concentration gave a light yellow liquid. Purification by vacuum distillation (0.05 mmHg, 125–127 °C) gave the product as a colourless oil, 5.19 g (72%); $\delta_H(CDCl_3)$ 1.19 (6 H, t, CH_3), 3.20 (2 H, d, $ArCH_2$), 3.82 (3 H, s, OCH_3), 3.82 (1 H, t, CH), 4.13 (4 H, q, CO_2CH_2), 6.85 (2 H, m, Ar), 7.20 (2 H, m, Ar); $\delta_C(CDCl_3)$ 14.50 (CH_3), 30.76 ($ArCH_2$), 51.95 (CH), 55.66 (OCH_3), 61.68 (OCH_2), 110.6 (Ar C3), 120.8 (Ar C5), 126.4 (Ar C1), 128.6 (Ar C4), 131.4 (Ar C6), 159.1 (Ar C1), 169.7 (C=O); m/z (EI^+) 280 (M^+), 206, 133, 115; ν_{max}(neat)/cm^{-1} 1730 (C=O) (Found C, 63.78; H, 7.20. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%).

3-(2-Methoxybenzyl)-1,5,9-triazacyclododecane-2,4-dione (9). 1,5,9-Triazanonane (4.67 g, 35.6 mmol) was added to a stirred solution of diethyl (2-methoxybenzyl)malonate (10 g, 35.7 mmol) in ethanol (1.2 dm^3). The mixture was boiled under reflux for 40 days and then evaporated under reduced pressure to give a clear yellow oil. Purification by column chromatography on silica (eluent 0–10% NH_4OH–60–50% MeOH–40% CH_2Cl_2) gave a white solid, 250 mg (2.2%) as the minor product and a viscous oil, 2.53 g (19%) as the major half-cyclized intermediate (**10**). Attempted further cyclization of this material in dry acetonitrile (100 cm^3) did not give any more product. For 3-(2-methoxybenzyl)-1,5,9-triazacyclododecane-2,4-dione, $\delta_H(CD_3OD)$ 1.56 (2 H, m, $CH_2CH_2CH_2$), 1.69 (2 H, m, $CH_2CH_2CH_2$), 2.12 (1 H, t, CH), 2.53 (2 H, td, CH_2N), 2.84 (2 H, td, CH_2N), 3.07 (2 H, m, CH_2N), 3.10 (2 H, d, $ArCH_2$), 3.51 (2 H, td, CH_2N), 3.81 (3 H, s, OCH_3), 6.79 (1 H, t, Ar H5), 6.88 (1 H, d, Ar H3), 7.08 (1 H, d, Ar H6), 7.17 (1 H, t, Ar H4); $\delta_C(CD_3OD)$ 28.02 ($CH_2CH_2CH_2$), 29.18 ($ArCH_2$), 41.56 (CH_2NHCO), 49.88 (CH_2NH), 54.68 (CH), 55.6 (OCH_3), 111.3 (Ar C3), 121.3 (Ar C5), 128.5 (Ar C1), 128.8 (Ar C4), 131.8 (Ar C6), 158.9 (Ar C2), 171.9 (CO); m/z (DCI, NH_3) 320 (M^+ + 1); ν_{max}(KBr)/cm^{-1} 3309 (NH), 1669 (CO).

For **10**, $\delta_H(CDCl_3)$ 1.08 (2 H, t, CH_2CH_3), 1.54 (4 H, quintet, $CH_2CH_2CH_2$) 2.51 (2 H, m, CH_2NHCO), 2.70 (2 H, t, CH_2NH_2), 3.13 (4 H, m, CH_2NH), 3.51 (2 H, t, $ArCH_2$), 3.67 (1 H, d, CH), 3.74 (3 H, s, OCH_3), 4.01 (2 H, q, OCH_2), 6.73 (2 H, m, Ar), 7.07 (2 H, m, Ar), 7.71 (1 H, br s, NHCO); $\delta_C(CDCl_3)$ 13.78, 28.58, 30.83, 32.51, 38.11, 40.01, 47.44, 51.96, 52.59, 55.01, 60.89, 109.9, 120.1, 126.0, 127.8, 130.7, 157.2, 168.0, 170.7; m/z (DCI, NH_3,) 366 (M^+ + 1), 352 (M^+ − CH_3), 294; ν_{max}(neat)/cm^{-1} 1730 (COO), 1650 (HNCO).

2-(2-Methoxybenzyl)propane-1,3-diol (11). Lithium aluminium hydride (5 g, 131.6 mmol) was carefully added to cooled dry ether (300 cm^3) with stirring. The ester diethyl (2-methoxybenzyl)malonate **8** (12.3 g, 43.9 mmol) dissolved in dry ether (50 cm^3) was added dropwise to the cold (0 °C) solution under nitrogen. The mixture was brought to reflux and stirred for 18 h. After cooling to 5 °C, excess $LiAlH_4$ was quenched with water (5 cm^3), followed by sodium hydroxide solution (15%, 10 cm^3) and finally with water (5 cm^3). Filtration through Celite, washing the residue with chloroform (50 cm^3) and evaporation under reduced pressure gave a clear viscous oil, 7.47 g (87%), $\delta_H(CDCl_3)$ 1.99 (1 H, m, CH), 2.66 (2 H, d, $ArCH_2$), 3.02 (2 H, br s, OH), 3.68 (4 H, dd, CH_2O), 3.83 (3 H, s, CH_3), 6.78 (1 H, d, Ar H3), 6.90 (1 H, td, Ar H5), 7.51 (1 H, d, Ar H6), 7.20 (1 H, td, Ar H4); $\delta_C(CDCl_3)$ 27.82 (CH), 43.28 ($ArCH_2$), 55.43 (OCH_3), 64.80 (CH_2OH), 110.4 (Ar C5), 120.8 (Ar C3), 127.4 (Ar C4), 128.1 (Ar C1), 131.0 (Ar C6), 157.3 (Ar C2); m/z (DCI, NH_3) 214 (M^+ + 18), 197 (M^+ + 1), 179 (M^+ − OH); ν_{max}(neat)/cm^{-1} 3906 (OH), 3068, 3009 (Ar CH), 1601, 1588 (Ar) [Found: C, 65.95; H, 8.50; N, 0.0. $C_{11}H_{16}O_3 \cdot \frac{1}{4}(H_2O)$ requires C, 65.81; H, 8.28; N, 0.0%].

2-(2-Methoxybenzyl)propan-1,3-diyl di(toluenesulfonate) (12). The alcohol 2-(2-methoxybenzyl)propane-1,3-diol **11** (1.50 g, 7.65 mmol) was dissolved in dry pyridine (10 cm^3) and stirred at −20 °C. A solution of recrystallized tosyl chloride (4.39 g, 23 mmol) in dry pyridine (10 cm^3) was slowly dripped into the solution under nitrogen and maintaining the temperature at −20 °C. After the addition the flask was sealed and placed in a freezer (−18 °C) for 3 days. The mixture was poured onto crushed ice (25 cm^3) with stirring, which caused a white precipitate to form. Filtration, washing with dilute hydrochloric acid (2 × 10 cm^3, 0.01 mol dm^{-3}) and vacuum drying gave a white solid. Recrystallization from toluene gave needle-shaped crystals (3.38 g, 87%) mp 87–88 °C; $\delta_H(CDCl_3)$ 2.35 (1 H, septet, CH), 2.46 (6 H, s, $ArCH_3$), 2.55 (2 H, d, $ArCH_2$), 3.74 (3 H, s, OCH_3), 3.94 (4 H, dd, CH_2O), 6.70–6.85 (3 H, m, Ar), 7.18 (1 H, td, Ar), 7.33 (4 H, d, tosyl Ar H3), 7.72 (4 H, d, tosyl Ar H2); $\delta_C(CDCl_3)$ 21.60 ($ArCH_3$), 28.34 (CH), 38.00 ($ArCH_2$), 55.01 (OCH_3), 68.56 (CH_2O), 110.2 (Ar C3), 120.3 (Ar C2), 125.6 (Ar C1), 127.8 (TsAr C3), 128.0 (Ar C4), 129.9 (TsAr C2), 130.8 (Ar C6), 132.4 (TsAr C4), 144.9 (TsAr C1), 157.3 (Ar C2); m/z (DCI, NH_3) 522 (M^+ + 18), 504 (M^+), 333 (M^+ − OTs); ν_{max}(KBr)/cm^{-1} 3025, 2978 (Ar CH), 1359, 1178 [$S(=O)_2$] (Found: C, 59.64; H, 5.56. $C_{25}H_{28}O_7S_2$ requires: C, 59.51; H, 5.59%).

1,5,9-Tris(*p*-tolylsulfonyl)-1,5,9-triazanonane (13). 1,5,9-Triazanonane (13.1 g, 0.1 mol) was added to a stirred solution of potassium carbonate (55.2 g, 0.4 mol) in water (150 cm^3). A solution of tosyl chloride (76.4 g, 0.4 mol) in THF (350 cm^3) was slowly added over 1 h. The two-phase system was vigorously stirred and heated to 50 °C for 12 h. On cooling, the upper THF layer was poured onto crushed ice. After evaporation of the THF, the aqueous solution was extracted with dichloromethane (5 × 75 cm^3), and the organic phase dried (K_2CO_3) filtered and concentrated to yield a yellow oil. Trituration of the oil with hot ethanol (100 cm^3), resulted in crystallization after cooling. The crystals were collected by filtration and dried under vacuum to give colourless crystals, 40.68 g (68%), mp 112 °C; $\delta_H(CDCl_3)$ 1.70 (4 H, quintet, $CH_2CH_2CH_2$), 2.41 (9 H, s, CH_3), 2.94 (4 H, q, $NHCH_2$), 3.09 (4 H, t, NCH_2), 5.32 (2 H, t, NH), 7.29 (6 H, d, Ar H2), 7.62 (2 H, d, Ar H3), 7.73 (2 H, d, Ar H3); $\delta_C(CDCl_3)$ 21.40 (CH_3), 28.97 ($CH_2CH_2CH_2$), 40.03 (CH_2NH), 46.57 (CH_2N), 126.9 (C4), 127.0 (C10), 129.6 (C3), 129.8 (C11), 135.3 (C12), 136.6 (C2), 143.3 (C5), 143.6 (C9); m/z (DCI, NH_3) 594 $(M)^+$, 440 (M^+ − Ts); ν_{max}(KBr)/cm^{-1} 1337, 1161 [$S(=O)_2$] (Found: C, 54.69; H, 6.10; N, 6.76. $C_{27}H_{35}N_3O_6S_3$ requires: C, 54.62; H, 5.94; N, 7.08%).

1,5,9-Tri(*p*-toylsulfonyl)-3-(2-methoxybenzyl)-1,5,9-triazacyclododecane (14). 1,5,9-Tri(*p*-tolylsulfonyl)-1,5,9-triazanonane **13** (11.8 g, 19.8 mmol) was dissolved in dry DMF (250 cm^3) with fine-mesh potassium carbonate (5.7 g, 41.2 mmol). 2-(2-Methoxybenzyl)propane-1,3-diyl di(tosylate) **12** (9.98 g, 19.8 mmol) was dissolved in dry DMF (50 cm^3) and the solution was added dropwise over 2.5 h at room temperature with stirring. The temperature was raised to 50 °C for 18 h and then to 70 °C for 4 days. The reaction was followed by TLC on silica [2% MeOH–98% CH_2Cl_2, R_f(product) = 0.69]. DMF was distilled off under reduced pressure and the solids were taken up into water (80 cm^3) and dichloromethane (80 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 30 cm^3). The organic layers were combined, dried (K_2CO_3), filtered and concentrated to give a viscous oil. Crystallization of the residue from toluene gave colourless crystals, 4.03 g (27%) mp 238–239 °C; $\delta_H(CDCl_3)$ 1.64 (2 H, br m, $CH_2CH_2CH_2$), 1.94 (2 H, br m, $CH_2CH_2CH_2$), 2.41 (9 H, s, CH_3), 2.54 (1 H, m, CH), 2.65 (4 H, m, CH_2N), 2.90

(1 H, d, $ArCH_2$), 2.94 (1 H, d, $ArCH_2$), 3.09 (4 H, m, CH_2N), 3.42 (4 H, m, CH_2N), 6.81 (2 H, t, H3 and H4), 7.02 (1 H, dd, H6), 7.69 (1 H, td, H4), 7.28 (4 H, d, H12), 7.29 (2 H, d, H20), 8.09 (2 H, d, H19) and 7.65 (2 H, d, H11); $\delta_C(CDCl_3)$ 21.45 ($CH_2CH_2CH_2$), 25.53 ($ArCH_3$), 32.59 (CH), 33.88 ($ArCH_2$), 44.13, 46.58, 49.84 (ring CH_2N), 55.53 (OCH_3), 110.2 (C3), 120.1 (C5), 126.9 (C1), 127.1 (C11), 127.5 (C19), 127.7 (C4), 129.7 (C12 and C20), 131.0 (C6), 135.9 (C13), 143.3 (C18), 143.7 (C10), 157.4 (C2); *m/z* (DCI, NH_3) 754 (M^+), 598 (M^+ − Ts), 444 (M^+ − 2 × Ts), 288 (M^+ − 3 × Ts); ν_{max}(KBr)/cm^{-1} 1335, 1159 [$S(=O)_2$] (Found: C, 60.86; H, 6.34; N, 5.40. $C_{38}H_{47}O_7S_3$ requires: C, 60.54; H, 6.28; N, 5.57%).

3-(2-Hydroxy-5-bromobenzyl)-1,5,9-triazacyclododecane (2). A solution of HBr in acetic acid (48% v/v; 80 cm^3) was added to a mixture of 1,5,9-tri(*p*-toylsulfonyl)-3-(2-methoxybenzyl)-1,5,9-triazacyclododecane (4.03 g, 5.34 mmol) and phenol (3 g, 31.9 mmol). The mixture was heated at 110 °C for 5 h. More HBr–acetic acid solution (48% v/v; 15 cm^3) was added and the mixture boiled for a further 12 h. On cooling, a pink precipitate of the hydrobromide salt of **2** formed which was collected by filtration and dried, 1.48 g (53%). Initial purification of the free amine by column chromatography on silica (eluent 0.5% NH_3OH–15% MeOH–84.5% CH_2Cl_2) and further purification by HPLC: t_R = 11.8 min observed at λ = 254 nm (Dynamax, reversed-phase) with gradient elution 10 cm^3 min^{-1}; A = H_2O–0.1% TFA, B = CH_3CN–0.1% TFA from t = 0 min; A = 90%, B = 10% to t = 20 min; A = 75%, B = 25% and finally to t = 25 min; A = 100%, B = 0% gave the product as a colourless solid. $\delta_H(CD_3OD)$ 1.68 (4 H, quintet, $CH_2CH_2CH_2$), 2.05 (1 H, m, CH), 2.59 (2 H, d, $ArCH_2$), 2.74–2.92 (12 H, m, CH_2N), 6.66 (1 H, d, Ar H3), 7.10 (2 H, m, Ar H6 and H4); $\delta_C(CDCl_3)$ 26.37 ($HNCH_2CH_2CH_2NH$), 31.02 (CH), 38.23 (Ar CH_2), 48.80 ($HNCH_2CH$), 49.15 (CH_2NHCH_2CH), 52.34 (CH_2CH_2-CH_2NHCH_2CH), 107.8 (Ar C5), 118.9 (Ar C3), 129 (Ar C1), 130 (Ar C4), 132.6 (Ar C6), 159.5 (Ar C2); *m/z* (DCI, NH_3) 356, 358 (M^+ + 1); ν_{max}(KBr)/cm^{-1} 3422 (OH), 1590, 755 (CBr) (Found: 356.1337 (M^+ + 1). Calc. for $C_{16}H_{26}BrN_3O$ + H^+: 356.1337).

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