Synthesis of 1,10-Dithia-4,7,13,16-tetra-azacyclo-octadecane, 1-aza-4,7-dithiacyclononane, and N,N'-1,2-Bis(1-aza-4,7- dithia-cyclononyl)ethane. Structural and Solution Studies of their Silver Complexes

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The synthesis of the ligands 1-aza-4,7-dithiacyclononane, N,N'-1,2-bis(1-aza-4,7-dithiacyclononyl)ethane, and 1,10-dithia-4,7,13,16-tetra-azacyclo-octadecane and their silver(I) complexes are reported. Stability constants in water and methanol have been determined using pH-metric methods, and enthalpies of complexation measured calorimetrically in methanol. The N-alkyl derivatives show enhanced enthalpies of complexation, but exhibit unfavourable entropies of complexation. Crystal structures of the [18]-N₄S₂ and bis[9]-NS₂ silver complexes reveal distorted octahedral co-ordination geometry, although in aqueous solution the bis[9]-NS₂ silver complex does not adopt the sandwich structure revealed in the crystallographic analysis.

Most of the [18]-X_6 (X = O,N,S) and [9]-X_3 coronands have now been described, and all of the mixed oxa–aza macrocyclic ligands in these series have been reported.[1,2] Less work has been carried out on the aza–thia macrocycles partly because—with some obvious exceptions, e.g. [18]-N_2S_4[3] and [9]-N_2S—they are less accessible by standard macrocyclisation methods involving either tosylamide–thiol[4] or amine–acid chloride[5] precursors. In particular the [9]-NS_2, (12), and [18]-N_4S_2, (7), ligands have not previously been studied, although they may be expected to give a rich co-ordination chemistry with 'soft' transition metal ions such as Co^{2+}, Cu^{2+}/Cu^+, Ni^{2+} and with lower oxidation states of the second- and third-row elements.[6]

A stimulus to the study of the complexes of these compounds was given by a developing interest in [111]Ag-based radioimmunotherapy. Silver-111 is an attractive radioisotope with a convenient half-life ($t_{\frac{1}{2}}$ = 179 h) and energy (1.04 MeV, mean range in tissue 1.1 mm) for antibody based therapy. Previous studies with other metallic radioisotopes for this purpose, e.g. ^{67}Cu,[7] ^{90}Y,[8] have defined the properties required for this work. A ligand is required (for [111]Ag in this case) that will bind the isotope quickly in aqueous solution (radiolabelling yield > 70% within 1 h) and selectively (minimal binding to the protein) under ambient conditions (4 °C < temperature < 37 °C; pH 4 to 8), yet yield a complex which is kinetically inert in vivo with respect to acid-catalysed or cation-promoted exchange. At present there appear to be no complexes of silver(I) which satisfy these exacting criteria.
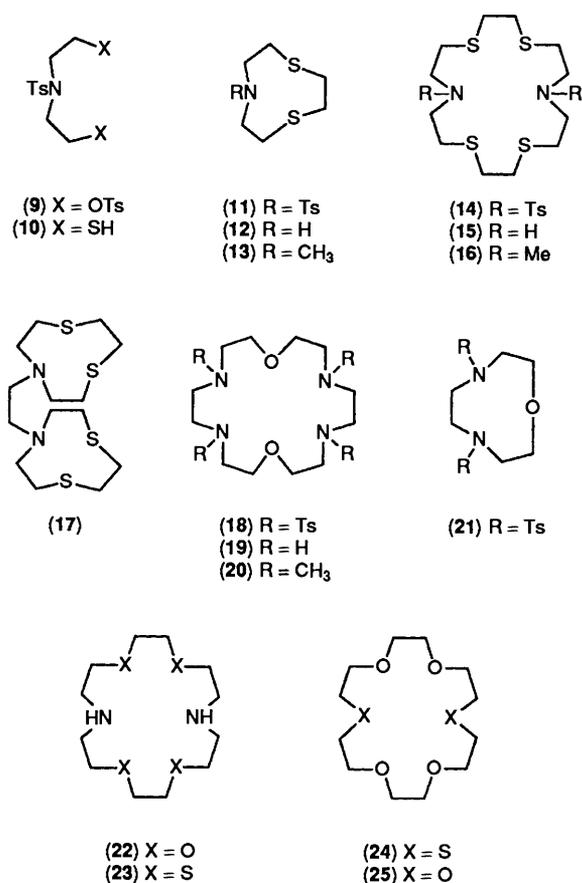
Results and Discussion
The primary synthetic targets for this work were the [18]-N_4S_2 compound (7), and the N,N-bis([9]-NS_2) coronand, (17). It was postulated that the enthalpic donor-atom preference of silver(I)[9] for NR > S > NH > O, tempered by the unfavourable entropies of complexation induced by incorporating bulky nitrogen or sulphur atoms[10] into a macrocycle, should favour complexation of silver(I) by (7) or the tetramethyl analogue

(1) R = OH
(2) R = OEt
(3) R = NH₂

(4) R = H
(5) R = Ts

(6) R = Ts
(7) R = H
(8) R = Me
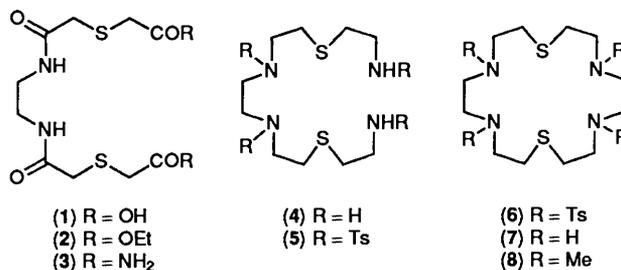
(8). Complexation of silver(I) by (17) was envisaged as a sandwich complex with a direct analogy to the apparently robust complex of 1,4,7-trithiacyclononane.[11] Furthermore, protonation of one of the nitrogen donors (likely at lower pH) in (7), (8) [or even (17)] should not lead to a dramatic loss in binding energy as had been observed with various silver cryptate complexes.[12] Some of this work has been reported in preliminary communications.[13,14]

Ligand Synthesis.—The synthesis of (7) was accomplished in a seven-step route. Addition of ethylenediamine to thiodiglycollic anhydride gave the diacid, (1) which was immediately esterified in moderate yield (27% overall from ethylenediamine) to form the ester (2). This reaction was amenable to scale-up to the 20 g level, but no attempt was made to optimise the yield. Condensation of (3) with ammonia in ethanol yielded the tetra-amide, (3) (75%) which was reduced with borane–tetrahydrofuran to give the tetra-amine, (4) (71%). Tosylation of (4) gave the tetratosylamide (5) and co-cyclisation of (5) with 1,2-bis(toluene-p-sulphanato)ethane in DMF in the presence of Cs_2CO_3[4] gave the desired cycle, (6) in 62% yield. Detosylation was attempted by two methods. Reaction of (6) with hydrogen bromide in acetic acid in the presence of phenol was slow (10 days, 80 °C) and gave the tetra-amine in poor yield, 32%. The preferred method involved reductive cleavage with lithium in liquid ammonia (3 h, 67%). Conversion of (7) to the

(9) X = OTs
(10) X = SH

(11) R = Ts
(12) R = H
(13) R = CH₃

(14) R = Ts
(15) R = H
(16) R = Me

(17)

(18) R = Ts
(19) R = H
(20) R = CH₃

(21) R = Ts

(22) X = O
(23) X = S

(24) X = S
(25) X = O

Figure 1. The structure of [(7)-Ag]⁺ in the crystal.

tetramethylated compound was also performed using standard Eschweiler–Clarke conditions.

The synthesis of the [9]-NS₂ macrocycle, (12), completes the series of [9]-X₃ coronands[1] and opens up a short synthetic route to a series of N,N-linked aza-coronands.[15] Condensation of N-(toluene-p-sulphonyl)-3-azapentan-1,5-dithiol, (10) [prepared from the ditosylate, (9) using thiourea] with dibromoethane in DMF in the presence of caesium carbonate[16] afforded the monotosylamide, (11) (43%) and the [18]-N₂S₄ ditosylamide, (14) (10%). The products were separated by fractional crystallisation and improved yields of (14) could be obtained by working at lower dilution (up to 35%). Thus, an alternative direct synthesis of this [18]-N₂S₄ monocyclic system, which avoids the use of the toxic precursors required for previous syntheses may be effected.[3,5] Detosylation of (11) with hydrogen bromide in acetic acid gave the monoamine, (12), and alkylation of (12) with 1,2-bis(toluene-p-sulphonato)ethane gave the N,N'-linked bis-coronand (17).

In order to compare the binding properties of (7) and (8) with their dioxa analogues (19) and (20), the synthesis of the [18]-N₄O₂ ring was undertaken.[17,18] Co-condensation of 1,2-bis(toluene-p-sulphonyl)diaminoethane with 3-oxa-1,5-bis-(toluene-p-sulphanato)pentane gave a mixture of [9]-N₂O, (21), and [18]-N₄O₂, (18), tosylamides. Separation by fractional crystallisation and subsequent detosylation (HBr–AcOH–PhOH) gave the desired tetra-amine (19), which was also converted into the tertiary tetra-amine (20).

Complexation Studies: ¹H *NMR and Crystallographic Analyses.*—A mixture of equimolar quantities of silver nitrate and (7) in an acetonitrile–dichloromethane solvent mixture gave a solution from which a crystalline complex could not be
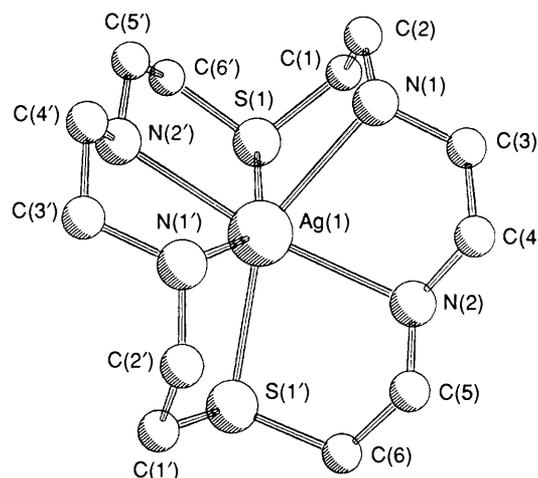
obtained. Anion exchange with hexafluorophosphate in methanol permitted the isolation of the colourless complex, [(7)-Ag]⁺PF₆⁻. The ¹H NMR spectrum of this complex (CD₃OD, 298 K, 250 MHz) was deceptively simple with the N–CH₂–CH₂N protons resonating as a singlet at 2.79 ppm, and the CH₂S and CH₂N resonances occurring together at 2.99 ppm, *i.e.* coincidentally isochronous. A similar spectrum was recorded in D₂O. Complexation was monitored at pD 5 (acetate buffer at 296 K) following addition of silver nitrate (one equivalent) to the ligand solution (10⁻² mol dm⁻³), but was >95% complete within the 100 s it took to acquire the spectrum following silver salt addition. Similar behaviour was observed for silver complexation with (8) (pD 5) and (17) (pD 4); in the former case, the CH₂S protons shifted by 0.29 ppm on complexation and resonated as a triplet while in the latter case the spectrum due to the complex appeared as a rather broad multiplet (250 MHz, 296 K). The 2:1 complex of (12) with silver was also prepared and in deuteriomethanol, small co-ordination shifts were recorded [0.08 ppm for the SCH₂CH₂S singlet and for the CH₂N and CH₂S multiplet (AA'BB')].

The crystal structure of [(7) Ag]⁺ PF₆⁻ revealed that all of the ligand heteroatoms were binding to silver and the cation possessed crystallographically imposed C₂-symmetry (Figure 1), with only the silver ion lying on the symmetry axis. The symmetry-related nitrogen atoms N(2) and N(2') were most nearly '*trans*' related with an N(2)–Ag–N(2') angle of 164.3(5)°. Assuming that these atoms occupy the axial sites of a distorted octahedron, then S(1) and N(1') are displaced by 0.684 and 0.823 Å below the equatorial plane with the O₂ related atoms S(1') and N(1) equally displaced above this plane. An alternative interpretation views the macrocycle as providing two tridentate meridianal fragments, one of which, comprising atoms N(1'), N(2'), and S(1), is inclined at 70° to its symmetry related equivalent. Positional and geometric parameters are given in Tables 1 and 2. The silver–sulphur bond length, 2.658(5) Å, is similar to those found in related silver complexes of aza–thia macrocyclic ligands. Bond lengths ranging from 2.65 to 2.95 Å have been observed in an irregular [18]-py-NN₂S₃ complex,[19] 2.70–2.75 Å in a bis[9]-S₃ complex,[11,20] 2.67–3.00 Å in the [15]-N₂S₂O and [15]-S₂N₂O complexes[21] and 2.50 to 2.61 Å in an unusual [18]-py-NS₂O₃ dimeric structure.[22] Both of the independent silver–nitrogen bond distances are similar [2.553(11) and 2.589(10) Å] and are typical values for the silver complexes described above.

In the structure of the complex [(17)-Ag]⁺PF₆⁻ all of the heteroatoms were bound to silver with the cation (and the PF₆ anion) possessing twofold crystallographic symmetry

Table 1. Atomic co-ordinates ($\times 10^4$).

Atom	x	y	z
Ag(1)	0	953(1)	2 500
S(1)	-1 502(3)	341(1)	760(4)
N(1)	-107(12)	1 738(4)	405(10)
N(2)	2 162(9)	1 125(5)	1 535(12)
C(1)	-1 331(12)	859(6)	-736(13)
C(2)	-1 128(13)	1 602(7)	-492(14)
C(3)	1 119(15)	1 739(7)	-258(15)
C(4)	2 141(13)	1 746(7)	749(15)
C(5)	3 087(13)	1 136(8)	2 624(15)
C(6)	3 000(11)	569(7)	3 544(16)
P(1)	5 000	1 395(2)	7 500
F(1)	6 068(15)	989(7)	7 225(21)
F(2)	4 687(11)	1 420(10)	5 988(13)
F(3)	4 058(12)	1 969(6)	7 717(12)

Table 2. Bond lengths and bond angles.

Bond angles/Å

Ag(1)-S(1)	2.658(1)	Ag(1)-N(1)	2.589(10)
Ag(1)-N(2)	2.553(11)	S(1)-C(1)	1.805(13)
S(1)-C(6a)	1.822(13)	N(1)-C(2)	1.438(18)
N(1)-C(3)	1.480(20)	N(2)-C(4)	1.472(18)
N(2)-C(5)	1.461(18)	C(1)-C(2)	1.540(18)
C(3)-C(5)	1.481(21)	C(5)-C(6)	1.459(21)
P(1)-F(1)	1.447(16)	P(1)-F(2)	1.513(13)
P(1)-F(3)	1.561(14)		

Bond angles/°

S(1)-Ag(1)-N(1)	75.9(3)	S(1)-Ag(1)-N(2)	113.2(3)
N(1)-Ag(1)-N(2)	70.6(4)	S(1)-Ag(1)-S(1a)	124.5(2)
S(1)-Ag(1)-N(1a)	144.7(3)	N(1)-Ag(1)-N(1a)	104.3(4)
S(1)-Ag(1)-N(2a)	74.6(3)	N(1)-Ag(1)-N(2a)	99.5(4)
N(2)-Ag(1)-N(2a)	164.3(5)	Ag(1)-S(1)-C(1)	100.4(4)
Ag(1)-S(1)-C(6a)	101.1(5)	C(1)-S(1)-C(6a)	104.2(7)
Ag(1)-N(1)-C(2)	113.4(8)	Ag(1)-N(1)-C(3)	107.7(8)
C(2)-N(1)-C(3)	115.4(10)	Ag(1)-N(2)-C(4)	107.1(8)
Ag(1)-N(2)-C(5)	111.5(8)	C(4)-N(2)-C(5)	112.0(11)
S(1)-C(1)-C(2)	117.2(9)	N(1)-C(2)-C(1)	113.0(11)
N(1)-C(3)-C(4)	112.6(11)	N(2)-C(4)-C(3)	110.4(11)
N(2)-C(5)-C(6)	112.9(12)	C(5)-C(6)-S(1a)	119.0(9)
F(1)-P(1)-F(2)	91.1(10)	F(1)-P(1)-F(3)	166.6(8)
F(2)-P(1)-F(3)	87.7(8)	F(1)-P(1)-F(1a)	110.7(12)
F(1)-P(1)-F(2a)	91.1(10)	F(2)-P(1)-F(2a)	176.2(16)
F(1)-P(1)-F(3a)	82.7(8)	F(2)-P(1)-F(3a)	89.4(8)
F(3)-P(1)-F(3a)	84.0(10)		

(Figure 2). Positional and geometric parameters are given in the supplementary data.* Both of the nine-membered rings adopt the expected [3.3.3] conformation allowing facial co-ordination to the silver ion. There is a relatively short silver–nitrogen bond 2.586(3) Å, and one short [Ag–S(7) = 2.611(2) Å] and one longer [Ag–S(4) = 2.802(2) Å] silver–sulphur bond. The planes which pass through S(4), S(7), and N(1) in the two rings are not parallel but are inclined at an angle of 17°. The resultant co-ordination at silver is distorted octahedral, in which the trigonal donor sets N(1), S(4), and S(7) are twisted by 15° relative to one another, *i.e.* half-way towards trigonal-prismatic geometry. It is probable that the bridging ethylene group is too short to allow the two nine-membered rings to adopt optimal 'chelating' positions. Moreover the [9]-NS₂ ligand perhaps has too small a 'bite' for effective

* For further information see Instructions for Authors, January Issue.
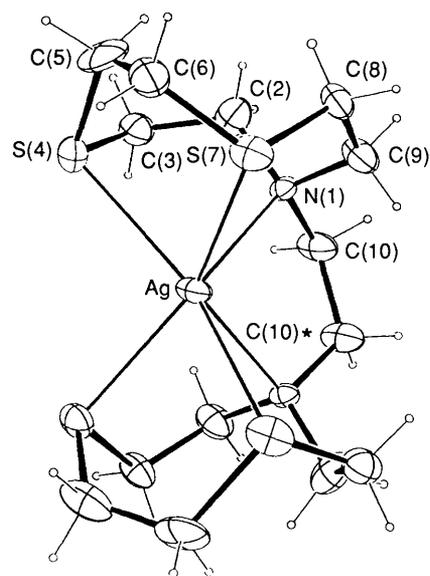
Figure 2. The structure of [(17)]-Ag]⁺ in the crystal. Three of the ring carbon atoms were disordered over two sites (0.84:0.16 occupancies), only the positions of the atoms of the major component are shown.

complexation with the silver(I) ion, and is more appropriate to bind smaller cations.

Complex Stability in Methanolic and Aqueous Solution.—The stability constants for silver complex formation in anhydrous methanol were measured (298 K, 0.05 mol dm⁻³ $NMe_4NO_3^-$) for (7), (8), (19), and (20), using silver ion selective electrodes and methods established by Schneider *et al.*[23] following the original work of Frensdorff.[24] Varying the initial silver ion concentration from 5×10^{-4} to 5×10^{-3} mol dm⁻³ did not affect the calculated log K_s values, precluding significant 2:1 complexation. Enthalpies of complexation were measured calorimetrically under similar conditions, permitting the calculation of the entropies of complexation (Table 3). Comparison has been made with the related [18]-membered ring coronands [18]-N₂O₄, -S₂O₄, -N₂S₄, and -O₆ and cryptand [221] for which equivalent data have been reported.[2,9] The silver binding constant for (8) is the highest yet reported for a 1:1 complex of a monocyclic ligand in methanol. Alkylation of nitrogen leads to complexes of higher stability [*cf.* (7) *vs.* (8), (19) *vs.* (20)] and this effect is directly related to the enhanced enthalpy of complexation; *i.e.* tertiary amine donors are better for silver(I) than secondary amine donors. This large effect is diminished, in terms of the overall free energy of complexation, by the large negative entropies of complexation calculated for the tetra-alkylated ligands. In particular the entropy of complexation for the [18]-N₄S₂Me₄ ligand, (8), $(T\Delta S = -18.7 \text{ kJ mol}^{-1})$ is most unfavourable and contrasts with the favourable entropy change with the parent [18]-N₄S₂, (7), $(T\Delta S = +3.3 \text{ kJ mol}^{-1})$. Clearly there are unfavourable steric interactions between neighbouring groups in the transition state structure leading to complex formation, and the ligand, therefore, must undergo an unfavourable conformational change. In addition, desolvation of the ligand is a major contributor to the overall ΔS term. Ligand (7) is more strongly solvated than (8) because of additional hydrogen-bonding interactions and lesser steric inhibition of solvation. This may well enhance the difference in the entropies of complexation for these two ligands. Further evidence for this solvation effect comes from studies in aqueous solution (*vide infra*) where ligand (7) now forms the more stable complex in accord with enhanced differential ligand solvation. Examin-

Table 3. [18]-Monocycles (298 K, MeOH).

Ligand	$\log K_s^c$ / $dm^3\ mol^{-1}$	$-\Delta H$ / $kJ\ mol^{-1}$	$T\Delta S$ / $kJ\ mol^{-1}$
(7) N_4S_2	14.1	77.0	+3.3
(8) $N_4S_2Me_4$	14.6	102.1	−18.7
(19) N_4O_2	11.2	59.5	+4.4
(20) $N_4O_2Me_4$	13.4	84.3	−7.8
(22) $N_2O_4^a$	10.0	51.4	+5.7
(23) $N_2S_4^a$	13.7	83.2	−5.0
(24) $S_2O_4^a$	10.3	64.0	−5.3
(25) O_6^b	4.6	38.3	−12.1
[2.2.1] Cryptand	14.4	81.9	+0.1

^{a} Data from reference 9. ^{b} Data from reference 2. ^{c} Errors on log K are typically (± 0.1) or less, and for ΔH ± 0.3 kJ mol^{-1} or less.

(a)

Species distribution for [18] − N_4S_2 silver complexes

(b)

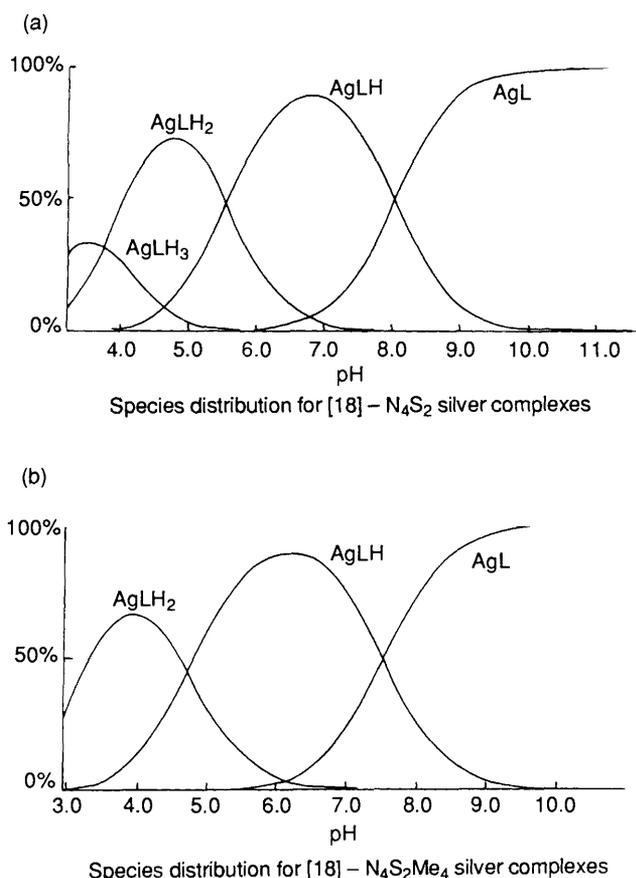Species distribution for [18] − $N_4S_2Me_4$ silver complexes

Figure 3. Species distribution curves for silver(ı) complexes of (7) (*a*) and (8) (*b*). The fraction of Ag$^+$ is omitted for clarity.

ation of the solid-state structure of $[(7)$-$Ag]^+$, (Figure 1), shows clearly that the macrocycle is wrapped around the silver in such a way that tetra-N-alkylation will destabilise this conformation and another one will need to be adopted. Such an effect is not uncommon in macrocyclic polyamine co-ordination chemistry and has been noted, for example, with dinuclear rhodium tricarbonyl complexes of $[24]$-N_6O_2,[25] ruthenium dioxo complexes of $[14]$-N_4 (cyclam),[26] and copper complexes of $[18]$-$N_2S_4Me_2$, (24).[27]

A further feature of the data in Table 3 is that increasing the number of sulphur donors in the ring enhances the enthalpy of complexation, $[(22)$ *vs.* (23), (7) *vs.* (19)] but this is generally offset by an unfavourable entropy change. This effect, which has been well documented previously,[10] may be related to the tendency of sulphur atoms in macrocyclic ligands to adopt exodentate

conformations, *i.e.* the lone pairs are directed away from the cavity, leading to an unfavourable (ΔS and ΔH) conformational change associated with complexation.

The protonation constants (pK_n) and silver ion formation constants in aqueous solution (298 K, I = 0.1 NMe$_4$NO$_3$) have been determined by pH-metric titration for (7), (8), (17), (12), and (13). The pK_a values obtained (Table 4) for (7) and (8) are comparable with those obtained for (19) (successive pK_a 9.67, 8.85, 6.61, and 3.21).[17] The binding constants for the 1:1 silver complexes in water are about 10^4-times lower than those recorded in methanol due to the greater solvation of both the cation and the ligand in water. The silver complex of the tetra-N-methylated ligand, (8) is less stable than that of (7), the reverse of the order obtained in methanol. This is consistent with an enhanced negative entropy of complexation associated primarily with ligand desolvation and in accord with pK_a measurements. The binding constants with (8) and (7) for the successively protonated complexes show clearly that loss of one nitrogen donor does not markedly diminish silver binding. Species distribution plots (Figure 3) show that the mono-protonated complex is the major species about ambient pH, and that relatively stable AgLH$_2^{3+}$ and AgLH$_3^{4+}$ complexes are even present at pH 4. Such behaviour may be contrasted with silver complexes of poly-aza cryptands with which only mono-protonated silver complexes were observed.[12]

With the [9]-ring monocyclic ligands, (12) and (13), both 1:1 and 2:1 complexes were observed, but no protonated complexes could be detected in the analysis of the titration curves.[29] The relatively high overall stability of, *e.g.* $[(12)_2$-$Ag]^+$, with β_{AgL_2} = 12.03, suggests that with sterically constrained ligands, moderately stable complexes of silver may be obtained in aqueous solution. It is clear from the constants measured with the bis[9]-NS$_2$ ligand, (17), compared with those obtained with (12) and (13), that only one of the [9] rings is participating significantly in binding in aqueous solution. Indeed the other nitrogen site is quite readily protonated, log K_{AgLH} = 4.97, with a pK_a of 4.50 for the complex (Table 4). There is no strong evidence for the formation of the sandwich structure in solution that was revealed by the crystallographic analysis of the complex in the solid-state.

Although the silver complexes of (7) and (8) show reasonable stability even at lower pH, it is highly doubtful that they are sufficiently kinetically stable over the physiological pH range (2 to 8) required for *in vivo* application. Incorporation of one basic donor may be required, possibly with a modified [12]-ring aza–thia coronand, in order to gain sufficient binding of silver at low pH, while retaining fast kinetics of complexation.

Experimental

Proton and ^{13}C NMR spectra were recorded on a Bruker AC250 (250.13 and 62.1 MHz) spectrometer. Chemical shifts are quoted to higher frequency of SiMe$_4$ and are given in ppm with coupling constants in Hz. IR spectra were recorded on a Perkin-Elmer 580A IR spectrophotometer and mass spectra were recorded either in the EI, CI, DCI, or FAB modes and column chromatography on silica was effected using Merck 60 7354 or 9385 for flash chromatography and on alumina using Merck neutral alumina, previously treated with ethyl acetate. HPLC analyses were carried out with a Varian 5500 instrument using both ion exchange (TSK–DEAE) or reverse-phase (Hypersil 5005) columns for analytical or semi-preparative work typically with aqueous NH$_4$OAc/MeCN gradient elution. Compounds that did not give correct microanalyses or high resolution spectra were checked for their purity by HPLC and were >97% pure.

Diethyl 3,8-*dioxo*-1,10-*dithia*-4,7-*diazadecane*-1,10-*diyldiace*-

Table 4. Protonation constants for the ligands and binding constants for silver complexes. (298 K, H_2O, I = 0.1 NMe_4NO_3).[a,b]

Ligand[d]	pK_1	pK_2	pK_3	pK_4	log K_{AgL}	log K_{AgL_2}	log K_{AgLH}	log K_{AgLH_2}	log K_{AgLH_3}	log K_{AgLOH}
(7)	9.26	8.45	5.81	4.88	10.4	—	9.05	6.00	4.13	—
					(7.91)	—	(5.40)	(3.94)		
(8)	8.82	8.35	4.13	3.71	9.47		8.06	4.31	—	—
					(7.41)		(4.60)			
(17)[c]	6.53	6.00	—		7.03		4.97	—	—	—
					(4.50)					
(12)	7.56	—	—		6.43	5.60	—	—	—	−2.80
(13)	8.32	—	—		7.66	6.06	—	—	—	−2.08

[a] Values in parentheses refer to protonation constants of the complexes ($\pm$0.10). [b] pH-Metric data was analysed by SCOGS and SUPERQUAD and typically gave φ^2 and σ values of 1.5 to 6 and 1.3 to 3 respectively. [c] The accuracy of these values is no better than ($\pm$0.3) because above pH 7, solutions become cloudy due to the insolubility of the free ligand. Analysis was restricted therefore to the lower pH range. [d] Protonation constants were obtained using SCOGS and formation constant SUPERQUAD[28] analysis.

tate, **(2)**.—Ethane-1,2-diamine (6.14 g, 0.123 moles) in dichloromethane (90 cm^3) was added dropwise to a solution of thiodiglycollic anhydride (25.0 g, 0.189 mmol) in dichloromethane (250 cm^3) with vigorous stirring to give a white resinous solid. After heating under reflux for 2 h, the solid was collected by filtration and dried *in vacuo* (10^{-2} mmHg). The crude di-acid, **(1)**, was heated under reflux in a solution of ethanol (1.5 dm^3) and concentrated sulphuric acid (15 cm^3) for 60 h to give a clear solution. The volume of the reaction mixture was reduced to approximately 60 cm^3 and a white solid removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in distilled water (50 cm^3) and basified with saturated sodium carbonate solution. The aqueous layer was extracted with chloroform (4 × 100 cm^3), dried (MgSO$_4$), filtered and the solvent removed by evaporation under reduced pressure to give a brown solid. Recrystallisation from toluene gave a white crystalline solid (9.6 g, 27%); m.p. 93–94 °C; (Found: C, 41.7; H, 5.92; N, 6.89. C$_{14}$H$_{24}$N$_2$O$_6$S$_2$·H$_2$O requires C, 42.2; H, 6.5; N, 7.0); IR (Nujol) 3 295 cm^{-1} (NH), 1 715 cm^{-1} (C=O ester), 1 640 cm^{-1} (amide I), and 1 535 cm^{-1} (amide II); *m/z* (CI-NH$_3$) 381 (*M*$^+$ + 1) 367, 363, and 335; δ_H(CDCl$_3$) 7.36 (2 H, br s, N*H*CO), 4.19 (4 H, q, *J* 7.2 Hz, CH$_2$-O), 3.46 (4 H, m, CH$_2$-N), 3.34 (8 H, s, CH$_2$-S), and 1.29 (6 H, t, CH$_3$); δ_C(CDCl$_3$) 14.1 (CH$_3$), 34.6, 36.4 (CH$_2$-S), 39.8 (CH$_2$N), 62.0 (CH$_2$O), 170.2 (C=O, amide), and 174.4 (C=O, ester).

3,8-Dioxo-1,10-dithia-4,7-diazadecane-1,10-diyldiacetamide, **(3)**.—The diester, **(2)**, (8.92 g, 23.5 mmol) was dissolved in ethanol (350 cm^3) saturated with ammonia and allowed to stand at room temperature in a tightly stoppered vessel for 60 h. The solution was re-saturated with ammonia by bubbling ammonia gas through it every 12 h. The white solid was collected by filtration and dried *in vacuo* (10^{-2} mmHg) (5.67 g, 75%); m.p. 185–187 °C; (Found: C, 36.0; H, 5.28; N, 16.6. C$_{10}$H$_{18}$N$_4$O$_4$S$_2$·½H$_2$O requires C, 36.2; H, 5.74; N, 16.9); *m/z* (CI, NH$_3$) 279 (*M*$^+$ – CONH$_2$); IR (Nujol) 3 360, 3 295, 3 180 (NH str), 1 640 (Amide I), and 1 540 (Amide II); δ_H(D$_2$O) 3.36 (8 H, s, CH$_2$S) and 3.32 (4 H, s, CH$_2$N); δ_C 34.8, 35.3 (CH$_2$S), 38.7 (CH$_2$N), 170.8 (CONH), and 174.3 (CONH$_2$).

1,14-(3,12-Dithia-6,9-diaza)tetradecanediamine, **(4)**.—A solution of BH$_3$·THF (250 cm^3, 0.250 mol) was added by syringe to compound **(3)**, (4.73 g, 14.6 mol) under nitrogen and the mixture heated under reflux for 60 h. After cooling, the reaction mixture was quenched cautiously with methanol (20 cm^3) and the solvent evaporated under reduced pressure.

The residue was dissolved in methanol (3 × 40 cm^3) and the solvent removed under reduced pressure. After reflux in hydrochloric acid solution (6 mol dm^{-3}, 100 cm^3) for 3 h the

solvent was evaporated under reduced pressure and the residue dissolved in potassium hydroxide solution (50 cm^3, 6 mol dm^{-3}). The aqueous layer was extracted with chloroform (4 × 50 cm^3) dried (MgSO$_4$), filtered and solvent evaporated under reduced pressure to give a pale brown oil (2.76 g, 71%); [Found: (*M*$^+$ + 1), 267.1295; C$_{10}$H$_{26}$N$_4$S$_2$ requires 267.1295); IR (thin film), 3 350 cm^{-1} br (NH str), 1 575 cm^{-1} (NH bend), and 1 120 cm^{-1} (C–N str), *m/z* (DCI, NH$_3$) 269 (*M*$^+$ + 2), 268 (*M*$^+$ + 1), and 267; δ_H(CDCl$_3$), 2.78 (16 H, d of pentets, *J* 6.4 Hz, N–CH$_2$CH$_2$-S), 2.74 (4 H, s, N–CH$_2$CH$_2$-N), and 1.80 (6 H, s, NH); δ_C(CDCl$_3$) 31.7, 35.6 (CH$_2$S) and 41.0, 48.5, 48.71 (CH$_2$N).

N,N′,N″,N‴-Tetrakis(tolyl-p-sulphonyl)-1,14-(3,12-dithia-6,9-diaza)tetradecanediamine, **(5)**.—A solution of toluene-*p*-sulphonyl chloride (9.31 g, 48.9 mmol) in pyridine (40 cm^3) was added to a solution of **(4)** in pyridine (100 cm^3) under nitrogen over a period of 30 min. After heating at 60 °C for 2 h the cooled reaction mixture was poured onto ice (200 g) with stirring, using a glass rod, until the ice melted. After stirring the mixture at room temperature for 1 h the aqueous layer was extracted with dichloromethane (3 × 200 cm^3) and washed with hydrochloric acid (2 × 300 cm^3, 1.0 mol dm^{-3}) and then with distilled water (2 × 300 cm^3). The organic layer was dried (MgSO$_4$), filtered and solvent removed under reduced pressure to give a brown oil. Two recrystallisations from chloroform–methanol (60 cm^3, 1:10) with cooling to −5 °C gave a pale brown solid (4.82 g, 56%). R_F 0.8 [silica gel; CH$_2$Cl$_2$–MeOH (9:1)]; m.p. 131–133 °C; (Found: C, 51.0; H, 5.7; N, 6.0; C$_{38}$H$_{59}$N$_4$O$_8$S$_6$·½H$_2$O requires C, 51.2; H, 5.7; N, 6.3%); *m/z* (DCI, NH$_3$), 901 (*M*$^+$ + 17), 884 (*M*$^+$ + 2), 883 (*M*$^+$ + 1), and 730; δ_H(CDCl$_3$), 7.73 (4 H, d, *J* 8.1 Hz, half of AA″XX″ system, aromatic H), 7.68 (4 H, d, *J* 8.1 Hz, half of AA″XX″ system, aromatic H), 7.35 (4 H, d, *J* 8.1 Hz, half of AA″XX″ system, aromatic H), 7.27 (4 H, d, *J* 8.1 Hz, half of AA′XX′ system, aromatic H), 5.24 (2 H, t, *J* 6.0 Hz, NH), 3.32 (4 H, s, N–CH$_2$CH$_2$-N), 3.28 (4 H, t, *J* 8.3 Hz, TsN–CH$_2$), 3.18 (4 H, m, CH$_2$NHTs), 2.67 (8 H, m, CH$_2$S), 2.45 (6 H, s, CH$_3$), and 2.40 (6 H, s, CH$_3$); δ_C(CDCl$_3$), 21.3 (CH$_3$), 30.5, 32.0 (CH$_2$S), 42.4 (CH$_2$N), 49.4, 50.2 (CH$_2$NTs), 126.7, 127.0, 129.5, 129.6, 134.9, 136.7, and 143.7 (toluene-*p*-sulphonyl aromatic).

N,N′,N″,N‴-Tetrakis(tolyl-p-sulphonyl)-1,10-dithia-4,7,13, 16-tetra-azacyclo-octadecane, **(6)**.—Caesium carbonate (3.13 g, 9.62 mmol) and compound **(5)**, (4.04 g, 4.58 mmol) were stirred vigorously in dry DMF (300 cm^3) under nitrogen. A solution of 1,2-di(tolyl-*p*-sulphonyloxy)ethane (1.69 g, 4.58 mmol) in DMF (120 cm^3) was added dropwise over a period of 3 h using a pressure equalised addition funnel. The mixture was stirred at room temperature for 18 h then heated to 60 °C for 4 h. Solvent was removed under reduced pressure and the brown residue

dried *in vacuo* (10^{-2} mmHg, 60 °C). Dichloromethane (50 cm^3) was added to the residue and the resulting suspension was filtered. After washing with distilled water (3 × 20 cm^3) the collected solid was dried *in vacuo* (10^{-2} mmHg, 40 °C). After treatment with hot toluene (50 cm^3) the resulting suspension was filtered and the collected pale brown solid dried *in vacuo* (10^{-2} mmHg) (2.59 g, 62%); R_F 0.7 [silica gel: CH$_2$Cl$_2$:MeOH (97:3)]; m.p. 254–256 °C; (Found: C, 52.0; H, 5.80; N, 6.21. C$_{40}$H$_{52}$N$_4$O$_8$S$_6$·$\frac{1}{2}$H$_2$O, requires C, 52.3; H, 5.8; N, 6.1); *m/z* (DCI, NH$_3$) 909 (M^+ + 1) and 753 (M^+ − Ts); δ_H(CDCl$_3$) 7.68 (8 H, d, *J* 8.1 Hz, part of AA″XX″ system, aromatic H), 7.33 (8 H, d, *J* 8.1 Hz, part of AA″XX″ system, aromatic H), 3.34 (8 H, s, N–CH$_2$CH$_2$–N), 3.29 (8 H, t, *J* 7.4 Hz, CH$_2$N), 2.80 (8 H, m t, *J* 7.4 Hz, CH$_2$S), and 2.43 (12 H, s, CH$_3$).

1,10-Dithia-4,7,13,16-tetra-azacyclo-octadecane, **(7)**.—Compound **(6)**, (1.80 g, 1.98 mmol) was dissolved in dry THF (50.0 cm^3) and dry ethanol (5.0 cm^3), stirred vigorously in a reaction vessel fitted with an ammonia condenser and an anhydrous calcium carbonate guard tube. After cooling the mixture to −77 °C (solid CO$_2$–acetone bath), ammonia (250 cm^3) was condensed into the reaction mixture and lithium (0.75 g, 108 mmol) was added in several portions with vigorous stirring. A deep blue solution resulted, which endured for 5–6 min before changing to yellow. After stirring at −77 C for 2 h the solution was allowed to return to room temperature and the ammonia evaporated. Distilled water (20 cm^3) was added to the remaining solution and solvent removed under reduced pressure to give a white residue which was dissolved in hydrochloric acid (40 cm^3, 6 mol dm^{-3}) and washed with diethyl ether (2 × 40 cm^3). The aqueous layer was evaporated to dryness and the residue dissolved in KOH solution (40 cm^3, 6 mol dm^{-3}) and extracted with dichloromethane (5 × 50 cm^3). The organic layer was dried (anhydrous MgSO$_4$), filtered and the solvent removed under reduced pressure to give a pale brown oil which solidified over 5 min. The crude product was recrystallised twice from toluene (20 cm^3) to give a white solid (0.37 g, 64%); m.p. 88–89 °C; (Found: C, 49.5; H, 10.0; N, 18.8. C$_{12}$H$_{28}$N$_4$S$_2$ requires C, 49.3; H, 10.0; N, 19.1); *m/z* (DCI, NH$_3$) 293 (M^+ + 1), 294 (M^+ + 2), 295 (M^+ + 3), 190, 116; δ_H(CDCl$_3$) 2.85 (8 H, m, CH$_2$N, CH$_2$S), 2.78 (8 H, m, CH$_2$N, CH$_2$S), 2.76 (8 H, s, N–CH$_2$CH$_2$–N), and 2.05 (4 H, br s, NH); δ_C(CDCl$_3$) 32.93 (CH$_2$S), 48.0 (CH$_2$N), and 48.3 (CH$_2$N).

N,N′,N″,N‴-Tetramethyl-1,10-dithia-4,7,13,16-tetra-azacyclo-octadecane, **(8)**.—1,10-Dithia-4,7,13,16-tetra-azacyclooctadecane (80.0 mg, 0.274 mmol) was heated at 95 °C with formaldehyde (0.24 cm^3; 37% solution) and formic acid (0.32 cm^3) for 20 h. To the cooled solution was added hydrochloric acid (1.0 mol dm^{-3}; 5.0 cm^3) and the solution evaporated under reduced pressure to give a pale brown residue. After dissolving in water (3 cm^3) the pH was adjusted to 14 with KOH solution and the solution extracted with dichloromethane (5 × 5 cm^3), dried (anhydrous K$_2$CO$_3$) and solvent removed under reduced pressure to give a colourless residue. Recrystallisation from hexane gave a white solid (52.0 mg, 55%); m.p. 43–44 °C; (Found: C, 54.8; H, 10.8; N, 15.5. C$_{16}$N$_{36}$N$_4$S$_2$·$\frac{1}{2}$H$_2$O requires C, 54.6; H, 10.4; N, 15.9); *m/z* (DCI, NH$_3$) 350 (M^+ + 2), 351 (M^+ + 3), 335, 323, 262, and 161; δ_H(CDCl$_3$) 2.64 (16 H, s, CH$_2$N, CH$_2$S), 2.51 (8 H, s, CH$_2$N), and 2.27 (12 H, s, CH$_3$); δ_C(CDCl$_3$) 29.2 (CH$_3$), 43.1 (CH$_2$S), and 55.2, 57.7 (CH$_2$N).

N-(Tolyl-p-sulphonyl)-3-aza-1,5-bis(tolyl-p-sulphonyloxy)pentane, **(9)**.—To a solution of toluene-*p*-sulphonyl chloride (107.8 g, 0.565 mol) in pyridine (100 cm^3) was added a solution of di-(2-hydroxymethyl)amine (16.5 g, 0.157 mol) in pyridine (90 cm^3) dropwise over a period of 30 min, under nitrogen. The mixture was left at −18 °C for 48 h. After pouring the mixture

onto ice (400 g) with stirring until the ice melted, the mixture was left at room temperature for 2 h to give a yellow–brown solid which was collected by filtration and twice recrystallised from ethanol–toluene (5:1) to give a yellow solid (75.0 g, 84%); m.p. 96–97 °C; (Found: C, 525.5; H, 4.92; N, 1.81. C$_{25}$H$_{29}$NO$_8$S$_3$ requires C, 52.9; H, 5.11; N, 2.11); *m/z* (DCI, NH$_3$) 585 (M^+ + 18), 568 (M^+ + 1); δ_H(CDCl$_3$) 7.75 (2 H, d, *J* 8.1 Hz, part of AA′XX′ system, aromatic H), 7.35 (2 H, d, *J* 8.1 Hz, part of aromatic AA′XX′ system, aromatic H), 7.60 (4 H, d, *J* 8.1 Hz, part of AA′XX′ system, aromatic H), 7.28 (4 H, d, *J* 8.1 Hz, part of AA′XX′ system, aromatic H), 4.11 (4 H, t, *J* 5.9 Hz, CH$_2$O), 3.37 (4 H, t, *J* 5.9 Hz, CH$_2$N), 2.43 (3 H, s, CH$_3$), and 2.35 (6 H, s, CH$_3$).

N-(Tolyl-p-sulphonyl)-3-azapentane-1,5-dithiol, **(10)**.—Thiourea (22.8 g, 0.299 mol) was added to a solution of compound, **(9)**, (75.0 g, 0.136 mol) in dry ethanol (500 cm^3) and the solution was heated under reflux, under a nitrogen atmosphere for 30 h. The solvent was evaporated under reduced pressure and the residue taken up in saturated sodium bicarbonate solution (250 cm^3) and heated under reflux for 3 h. The cooled solution was adjusted to pH 7 with hydrochloric acid (6 mol dm^{-3}). The aqueous layer was extracted with dichloromethane (3 × 250 cm^3), dried (anhydrous MgSO$_4$), filtered and the solvent removed under reduced pressure. The colourless residue was chromatographed on 'flash' silica gel eluting with dichloromethane:methanol, (199:1). Evaporation of the eluates gave a clear oil which crystallised over a period of 24 h (32.7 g, 83%); R_F 0.5 [silica gel:CH$_2$Cl$_2$–MeOH (99:1)]; (Found: M^+ + 1) 292.0490. C$_{11}$H$_{17}$NO$_2$S$_3$ requires 292.0496); *m/z* (DCI, NH$_3$) 292 (M^+ + 1); δ_H(CDCl$_3$) 7.70 (2 H, d, *J* 8.1 Hz, part of AA′XX′ system, aromatic H), 7.33 (2 H, d, *J* 8.1 Hz, part of AA′XX′ system, aromatic H), 3.28 (4 H, t, *J* 7.5 Hz, N–CH$_2$), 2.74 (4 H, m, S–CH$_2$), 2.43 (3 H, s, CH$_3$), and 1.44 (2 H, t, *J* 8.5 Hz, SH); δ_C(CDCl$_3$) 21.4 (CH$_3$), 23.8 (CH$_2$S), 52.6 (CH$_2$N), and 126.7, 126.9, 129.7, 135.9, 143.6 (aromatic C).

N-(Tolyl-p-sulphonyl)-1,4-dithia-7-azacyclononane, **(11)**, *and N,N″-bis(tolyl-p-sulphonyl)-1,4,10,13-tetrathia-7,16-diazacyclo-octadecane*, **(14)**.—Caesium carbonate (3.60 g, 11.0 mmol) was added to dry DMF (500 cm^3) under a nitrogen atmosphere in a reaction vessel fitted with two pressure equalised addition funnels and the suspension heated to 55 °C. A solution of *N*-(tolyl-*p*-sulphonyl)-3-azapentane-1,5-dithiol (2.91 g, 10.0 mmol) in DMF (200 cm^3) and a solution of 1,2-dibromoethane (1.88 g, 10.0 mmol) in DMF (200 cm^3) were added synchronously over a period of 12 h with vigorous stirring. After stirring for a further 6 h at 55 °C the solvent was removed under reduced pressure and the residue dried *in vacuo* (10^{-2} mmHg, 50 °C). The residue was taken up in dichloromethane (100 cm^3) and washed with distilled water (2 × 100 cm^3). The organic layer was dried (anhydrous MgSO$_4$), filtered and the solvent removed under reduced pressure to give a pale brown oil. Two products were isolated as white crystalline solids by fractional crystallisation from toluene–hexane; [(4:1), 25 cm^3] gave the 18-membered ring product (0.31 g, 10%); [(2:1), 10 cm^3] gave the 9-membered ring product (1.38 g, 43%).

Compound **(14)**; R_F = 0.4 [silica gel:methanol–dichloromethane (1.99)]; m.p. 206 °C; (Found: C, 49.2; H, 5.97; N, 4.20. C$_{26}$H$_{38}$N$_2$O$_4$S$_6$ requires C, 49.1; H, 5.83; N, 4.27); *m/z* (DC, NH$_3$) 636 (M^+ + 2) and 576, 480; δ_H(CDCl$_3$) 7.72 (4 H, d *J* 8.2 Hz, part of AA′XX′ system, aromatic H), 7.32 (4 H, d, *J* 8.2 Hz, part of AA′XX′ system, aromatic H), 3.32 (8 H, t, *J* 7.2 Hz, CH$_2$N), 2.86 (8 H, t *J* 7.2 Hz, CH$_2$S), 2.79 (8 H, s, S–CH$_2$CH$_2$–S), and 2.42 (6 H, s, CH$_3$).

Compound **(11)**; R_F = 0.5 [silica gel:MeOH–CH$_2$Cl$_2$ (1.99)]; m.p. 122–124 °C; (Found: C, 49.2; H, 5.99; N, 4.42. C$_{13}$H$_{19}$NO$_3$S$_3$ requires C, 49.1; H, 5.83; N, 4.27); *m/z* 318 (M^+

+ 1) and 244, 162; δ_H(CDCl$_3$) 7.70 (2 H, d, J 8.1 Hz, part of AA'XX' system, aromatic H), 7.34 (2 H, d J 8.1 Hz, part of AA'XX' system, aromatic H), 3.40 (4 H, m, CH$_2$N), 3.15 (4 H, s, S–CH$_2$CH$_2$–S), 3.14 (4 H, m, CH$_2$), and 2.43 (3 H, s, CH$_3$); δ_C(CDCl$_3$) 21.3 (CH$_3$), 32.2, 34.0 (CH$_2$S), 53.3 (CH$_3$N), and 127.3, 129.6, 134.0, 143.6 (aromatic C).

1,4-*Dithia*-7-*azacyclononane*, (12).—A solution of hydrogen bromide in acetic acid (45%, 15.0 cm^3) and phenol (1.40 g, 14.9 mmol) were added to *N*-(tolyl-p-sulphonyl)-1,4-dithia-7-azacyclonane (1.17 g, 3.69 mmol) and the solution was stirred at 80 °C for 48 h. [A further addition of hydrogen bromide in acetic acid (45%, 5.0 cm^3) was made after 12 h.] Toluene was added to the cooled reaction mixture and solvent removed under reduced pressure (azeotrope: 72% toluene, 28% acetic acid). The residue was taken up in dichloromethane (15 cm^3) and water (15 cm^3) and the aqueous layer separated and washed with dichloromethane (3 × 15 cm^3). The solution was adjusted to pH 14 with sodium hydroxide solution (5 mol dm^{-3}) and extracted with chloroform (4 × 20 cm^3). The combined organic extracts were dried (anhydrous MgSO$_4$) and the solvent removed under reduced pressure to give a pale-brown solid. Recrystallisation from toluene–hexane gave a pale yellow solid (0.43 g, 73%); m.p. 71–72 °C; (Found: C, 43.2; H, 7.83; N, 7.61. C$_6$H$_{13}$NS$_2$·$\frac{1}{2}$H$_2$O requires C, 43.2; H, 8.04; N, 8.40); m/z (DCI, MeOH) 164 (M^+ + 1) and 116, 89; δ_H(CDCl$_3$) 3.00 (4 H, s, S–CH$_2$CH$_2$–S), 2.95 (8 H, d of m, CH$_2$N, CH$_2$S), and 2.36 (1 H, br s, NH); δ_C(CDCl$_3$) 33.1, 33.2 (CH$_2$S) and 48.1 (CH$_2$N).

1,2-*Bis*-(1-*aza*-4,7-*dithia*-1-*cyclononyl*)*ethane*, (17).—A mixture of 1,4-dithia-7-azacyclononane (0.200 g, 1.23 mmol), 1,2-bis(tolyl-p-sulphonyloxy)ethane (0.227 g, 6.15 × 10^{-4} mol) and sodium carbonate (0.130 g, 1.23 mmol) in acetonitrile (30 cm^3) was heated under reflux for 36 h. The cooled reaction mixture was filtered and solvent evaporated under reduced pressure. The brown residue was dissolved in hydrochloric acid (0.3 mol dm^{-3}, 15 cm^3) and washed with dichloromethane (3 × 15 cm^3). The aqueous layer was adjusted to pH 14 with KOH solution (6.0 mol dm^{-3}) and extracted with dichloromethane (4 × 20 cm^3). The organic layer was dried (anhydrous MgSO$_4$), filtered and solvent removed under reduced pressure to give a pale-brown solid. Recrystallisation from toluene gave a pale-yellow solid (0.114 g, 53%); R_F 0.9 [silica gel:MeOH–CH$_2$Cl$_2$ (1.99)]; m.p. 104–106 °C; (Found: C, 47.3; H, 7.75; N, 7.31. C$_{14}$H$_{18}$N$_2$S$_4$·0.3H$_2$O requires C, 47.2; H, 8.04; N, 7.87); m/z (DCI, NH$_3$) 353 (M^+ + 1) and 259, 232, 176; δ_H(CDCl$_3$) 3.09 (8 H s, S–CH$_2$CH$_2$–S), 2.87, 2.72 (4 H, d of m, CH$_2$N, CH$_2$S), and 2.62 (4 H, s, N–CH$_2$CH$_2$–N); δ_C(CDCl$_3$) 58.7, 55.6 (CH$_2$N) and 34.8, 33.1 (CH$_2$S).

N,N',N'',N'''-Tetrakis(tolyl-p-*sulphonyl*)-1,10-*dioxa*-4,7,13,-16-*tetra-azacyclo-octadecane*, (18), *and* N,N'-*bis*(*tolyl*-p-*sulphonyl*)-1-*oxa*-4,7-*diazacyclononane*, (21).—Caesium carbonate (8.26 g, 25.4 mmol) was added to a solution of 3-oxa-1,5-bis(tolyl-p-sulphonyloxy)pentane (5.00 g, 12.1 mmol) in anhydrous DMF (50 cm^3) under a nitrogen atmosphere. A solution of *N,N''*-bis(tolyl-p-sulphonyl)ethane-1,2-diamine (4.44 g, 12.1 mmol) in anhydrous DMF (50 cm^3) was added dropwise over a period of 4 h with vigorous stirring. The reaction mixture was stirred at room temperature for 12 h and heated to 60 °C for 4 h. The solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3) and washed with distilled water (2 × 100 cm^3). The organic layer was dried (anhydrous MgSO$_4$), filtered and the solvent removed under reduced pressure to give a pale-yellow solid. The mixture was taken up in hot toluene (40 cm^3) and the 18-membered ring compound was collected as a white solid by filtration (warmed filtration apparatus) (1.06 g, 20%). The nine-membered ring

compound was obtained from the cooled filtrate as a crystalline solid and collected by filtration and dried *in vacuo* (10^{-2} mmHg) (2.17 g, 41%).

Compound (21).—M.p. 160–161 °C [lit.[29] 160 °C]; (Found: C, 54.8; H, 6.02; N, 6.34. C$_{20}$H$_{26}$N$_2$O$_5$S$_2$ requires C, 54.8; H, 5.94; N, 6.39); m/z (CI, NH$_3$) 440 (M^+ + 2), 439 (M^+ + 1) and 283; δ_H(CDCl$_3$) 7.70 (4 H, d, J, 8.1 Hz, part of AA'XX' system, aromatic H), 7.32 (4 H, d, J 8.2 Hz, part of AA'XX' system, aromatic H), 3.90 (4 H, t, J 4.3 Hz, CH$_2$O), 3.47 (4 H, s, N–CH$_2$CH$_2$–N), 3.26 (4 H, t, J 4.3 Hz, CH$_2$N), and 2.43 (6 H, s, CH$_3$).

Compound (18).—M.p. 242–244 °C [lit.[30] 245 °C]; (Found: C, 55.0; H, 6.13; N, 6.12. C$_{40}$H$_{52}$N$_4$O$_{10}$S$_4$ requires C, 54.8; H, 5.94; N, 6.39); m/z (CI, NH$_3$) 880 (M^+ + 2) and 722; δ_H(CDCl$_3$) 7.71 (8 H, d, J, 8.1 Hz, part of AA'XX' system, aromatic H), 7.32 (8 H, d, J 8.1 Hz, part of AA'XX' system, aromatic H), 3.54 (8 H, t, J 4.9 Hz, CH$_2$O), 3.32 (8 H, s, N–CH$_2$CH$_2$–N), 3.22 (8 H, t, J 4.8 Hz, CH$_2$N), and 2.44 (12 H, s, CH$_3$).

1,10-*Dioxa*-4,7,13,16-*tetra-azacyclo-octadecane*, (19).—A solution of hydrogen bromide in acetic acid (45%, 100 cm^3) and phenol (5.0 g, 53 mmol) were added to compound (18) (1.25 g, 1.43 mmol) and the solution heated under reflux for six days. Diethyl ether (40 cm^3) was added to the cooled reaction mixture and a fine white precipitate collected by filtration. This was taken up in distilled water (40 cm^3) basified with aqueous KOH (30%) and extracted with dichloromethane (4 × 40 cm^3). The organic layer was dried (anhydrous K$_2$CO$_3$), filtered and the solvent removed under reduced pressure. The residue was recrystallised from dichloromethane–hexane to give a colourless crystalline solid (90 mg, 25%); m.p. 58–60 °C (lit.[6] 58–60 °C); m/z (DCI, NH$_3$) 262 (M^+ + 1) and 204, 131; δ_H(CDCl$_3$) 3.59 (8 H, t, J 4.9 Hz, CH$_2$O), 2.80 (8 H, t, J 4.0 Hz, CH$_2$N), 2.78 (8 H, s, N–CH$_2$CH$_2$–N), and 2.07 (4 H, br s, NH); δ_C(CDCl$_3$) 70.0 (CH$_2$O) and 49.2 (CH$_2$N).

N,N',N'',N'''-Tetramethyl-1,10-*dioxa*-4,7,13,16-*tetra-aza-cyclo-octadecane*, (20).—1,10-Dioxa-4,7,13,16-tetra-azacyclo-octadecane (60 mg, 23 mmol) was heated at 95 °C with formaldehyde (37%, 0.20 cm^3) and formic acid (0.27 cm^3) for 20 h. Hydrochloric acid (1.0 mol dm^{-3}, 5.0 cm^3) was added to the cooled solution and the solvent removed under reduced pressure. The residue was redissolved in water (3.0 cm^3) and adjusted to pH 14 with potassium hydroxide. After extraction with dichloromethane (5 × 5 cm^3) the organic layer was dried (anhydrous K$_2$CO$_3$), filtered and the solvent removed under reduced pressure. The residue was treated with hexane (3 × 5 cm^3), the extracts combined and the solvent removed under reduced pressure to give a clear oil which crystallised on cooling (5 °C) (59 mg, 80%); m.p. = 23–25 °C; δ_H(CDCl$_3$) 3.55 (8 H, t, J 5.5 Hz, CH$_2$O), 2.63 (8 H, t, J 5.5 Hz, CH$_2$N), 2.59 (8 H, s, NCH$_2$CH$_2$N), and 2.28 (12 H, s, CH$_3$).

Silver(I) *Complexes.*—*Silver*(I) *complex of* 1,10-*dithia*-4,7,13,16-*tetra-azacyclo-octadecane*, (7), [Ag-L][PF$_6$]. Silver nitrate (8.4 mg, 4.9 × 10^{-5} mol) in dry acetonitrile (1.0 cm^3) was added to 1,10-dithia-4,7,13,16-tetra-azacyclo-octadecane (14.4 mg, 4.9 × 10^{-5} mol) in dry dichloromethane (1.0 cm^3). The solution was filtered to remove a small amount of dark precipitate. Solvent was removed from the filtrate under reduced pressure and the residue dissolved in dry methanol (1 cm^3). To this was added ammonium hexafluorophosphate (8.0 mg, 4.9 × 10^{-5} mol) in methanol (1.0 cm^3). After rapid filtration the solution was left at −20 °C in the dark for 3 h. Colourless crystals were collected by filtration, washed with cold methanol (2 × 0.5 cm^3) and dried *in vacuo* (10^{-2} mmHg) (19.5 mg, 73%); (Found: C, 25.3; H, 4.96; N, 9.84.

$C_{12}H_{28}N_4S_2PF_6Ag\cdot H_2O$ requires C, 25.6; H, 5.33; N, 9.95); m/z (FAB, glycerol) 401, 399 (M^+) [$^{109}Ag^+$-L and $^{107}Ag^+$-L); $\delta_H(CD_3OD)$ 2.99 (16 H, s, CH_2N, CH_2S) and 2.79 (8 H, s, CH_2N).

Silver(I) *complex of* 4,7,13,16-*tetramethyl*-1,10-*dithia*-4,7,13,16-*tetra-azacyclo-octadecane*, (8), [Ag-L][PF_6]. Silver nitrate (13.2 mg, 7.76 × 10^{-5} mol) in acetonitrile (1.0 cm^3) was added to the ligand, (8), (27.0 mg, 7.76 × 10^{-5}) in dichloromethane (1.0 cm^3). After leaving the solution to stand for 30 min, the solution was filtered and the solvent evaporated from the filtrate under reduced pressure. The brown residue was dissolved in methanol (1.0 cm^3) and to this was added ammonium hexafluorophosphate (12.5 mg, 7.7 × 10^{-5} mol). After filtration the volume of solvent was reduced to 0.75 cm^3 and the solution left in the dark at −20 °C for 24 h. Brown crystals were isolated and redissolved in hot methanol (0.5 cm^3) and kept at −20 °C for 12 h. Colourless crystals were collected by filtration, washed with cold methanol (2 × 0.5 cm^3) and dried *in vacuo* (10^{-2} mmHg) (28.4 mg, 61%); (Found: C, 31.4; H, 5.91; N, 8.89. $C_{16}H_{36}N_4S_2PF_6Ag$ requires C, 31.9; H, 5.99; N, 9.31); m/z (FAB, glycerol) 457, 455 (M^+) [$^{109}Ag^+$-L and $^{107}Ag^+$-L]; $\delta_H(CD_3OD)$ 3.05 (8 H, t, J 5.8 Hz, CH_2S), 2.72 (8 H, t, J 5.6 Hz, CH_2N), 2.60 (8 H, br s, N–CH_2CH_2–N), and 2.41 (12 H, s, CH_3); $\delta_C(CD_3OD)$ 59.0 (CH_2N), 55.8 (CH_2N), 44.3 (CH_3–N), and 33.4 (CH_2–S).

Silver(I) *complex of* 1,2-*bis*(1-*aza*-4,7-*dithia*-1-*cyclononyl*)-*ethane*, (17), [Ag-L][PF_6]. Silver nitrate (9.4 mg, 5.5 × 10^{-5} mol) in acetonitrile (1.0 cm^3) was added to the ligand, (7), (19.4 mg, 5.5 × 10^{-5} mol) in dichloromethane (1.0 cm^3) and the mixture filtered and solvent evaporated from the filtrate under reduced pressure. The colourless residue was dissolved in methanol (1.0 cm^3) and to this was added ammonium hexafluorophosphate (9.0 mg, 5.5 × 10^{-5} mol) in methanol (1.0 cm^3) and the solution filtered. The volume of the filtrate was reduced to 0.5 cm^3 and the solution kept at −20 °C for 36 h. Needleshaped colourless crystals were collected by filtration and washed with cold methanol (2 × 0.5 cm^3) and dried *in vacuo* (10^{-2} mmHg) (17 mg, 55%). Crystals suitable for *X*-ray diffraction studies were grown from a solution of the complex in MeOH:MeCN (10:1); (Found: C, 27.6; H, 4.61; N, 4.39. $C_{14}H_{28}N_2S_4PF_6Ag$ requires C, 27.8; N, 4.62; N, 4.62); m/z (FAB, glycerol) 461, 459 (M^+), [$^{109}Ag^+$-L and $^{107}Ag^+$-L]; $\delta_H(D_2O)$ 2.6–2.9 (28 H, m).

Silver(I) *complex of* 1,4-*dithia*-7-*azacyclononane*, (12), [Ag-(L)$_2$][PF_6]. Synthesis as for [Ag-(17)]$^+$ using a 2:1 ratio of ligand to silver nitrate. Colourless crystals were obtained after recrystallisation from methanol (10 mg, 28%); m/z (FAB, glycerol) 435, 433 [^{109}Ag-(L)$_2^+$ and ^{107}Ag-(L)$_2^+$]; $\delta_H(D_2O)$ 2.93 (8 H, s, S–CH_3CH_2–S), 2.86 (8 H, m, CH_2S), and 2.78 (8 H, m, CH_2N).

pH-Metric Titrations.—Water. (*i*) *Apparatus.* The titration cell was a double-walled glass vessel (capacity 5 cm^3) which was maintained at 25 °C, using a Techne Tempette Junior TE-8J. Titration solutions were stirred using a magnetic stirrer and kept under an atmosphere of nitrogen. Titrations were performed using an automatic titrator (Mettler DL20, 1 cm^3 capacity) and burette functions (volume increments and equilibration time) were controlled by a BBC microprocessor. The pH was measured using a Corning 001854 combination microelectrode which was calibrated using buffer solutions at pH 4.008 ($CO_2H\cdot C_6H_4CO_2K$, 0.05 mol dm^{-3}) and pH 6.865 (KH_2PO_4, 0.025 mol dm^{-3}–Na_2HPO_4, 0.025 mol dm^{-3}). Data was stored on the BBC microprocessor and transferred to the MTS mainframe using KERMIT and subsequently analysed by two non-linear least-squares programs SCOGS and SUPERQUAD.

(*ii*) *Acid-dissociation constants.* Stock solutions of the

ligand (0.002 mol dm^{-3}) in Milli-Q water (25.0 cm^3) with nitric acid (1 mol equiv. per amine nitrogen of the ligand) and tetramethylammonium nitrate (I = 0.10 mol dm^{-3}) were prepared. In each titration 3.5 cm^3 of the stock ligand solution was titrated with tetramethylammonium hydroxide (0.109 mol dm^3), the exact molarity of which was determined by titration against hydrochloric acid, 0.100 mol dm^3.

Methanol. Metal binding constants. Stock solutions were prepared as above with the addition of one equivalent of silver nitrate. Titrations were performed as before.

Using the assumption that only 1:1 complex formation was occurring we have equations (1) and (2).

$$C_{Ag}^{\circ} = [Ag^+] + [AgL^+] \tag{1}$$

$$C_L^{\circ} = [L] + [AgL^+] \tag{2}$$

Here C_{Ag}° was the initial concentration of silver ion and C_L° was the overall concentration of ligand in solution (free or complexed). Thus

$$K_s = \frac{C_{Ag}^{\circ}\text{-}[Ag^+]}{[Ag^+](C_L^{\circ}\text{-}[AgL^+])} = \frac{C_{Ag}^{\circ}\text{-}[Ag^+]}{[Ag^+](C_L^{\circ}\text{-}C_L^{\circ} + [Ag^+])} \tag{3}$$

Varying the initial silver ion concentration from 5 × 10^{-4} to 5 × 10^{-3} mol dm^3 did not affect the calculated K_s values. The enthalpies of complexation (ΔH) were measured by standard calorimetric methods using a Tronac 450 microcalorimeter.

A solution of silver nitrate (1.0 mmol, 20 cm^3) in methanol was titrated with a solution of the ligand in methanol (0.02 mol dm^3). The ionic strength was kept constant at I = 0.05 mol dm^3 by addition of tetramethyl ammonium perchlorate. The concentration of free silver ion was measured using a silver ion selective electrode (Metrohm EA282) with a second silver electrode as a reference electrode. The emf observed could be used directly to determine the free silver ion concentration, according to the Nernst equation, which simplifies to equation (4),

$$E = E_0 + A\ln[Ag^+] \tag{4}$$

where [Ag$^+$] is the concentration of free silver ion and A is a constant which may be determined using appropriate calibration solutions.

The stability constant K_s which refers to the reaction, equation (5)
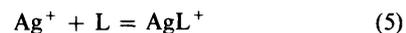
$$Ag^+ + L = AgL^+ \tag{5}$$

is defined by equation (6).

$$K_s = \frac{[AgL^+]}{[Ag^+][L]} \tag{6}$$

K_s is the concentration stability constant, assuming that the activity coefficients of the three species are equal to unity.

Crystal Data for [Ag(7)]$^+$PF$_6$.—$C_{12}H_{28}AgN_4F_4PS_2$, M = 545.34, orthorhombic, a = 10.859(22), b = 20.247(26), c = 9.742(10) Å, U = 2 142(6) Å^3, Z = 4, D_c = 1.691 g cm^{-3}, $F(000)$ = 1 103.84, $\mu(Mo\text{-}K_\alpha)$ = 12.46 cm^{-1}. Space group P_{bcn}. Crystal dimensions 0.45 × 0.25 × 0.225 mm.

Data collection and processing. Nicolet R-3 diffractometer, ω-2θ mode with ω scan width = 0.6 + 0.35 tan θ, ω scan speed = 1.0° min^{-1}, graphite monochromated Mo-K_α radiation; 2 951 reflections measured of which 2 376 were unique. Data were collected to a maximum 2θ of 50°. The 1 205 independent

reflections for which $|F|/\sigma(|F|) > 3.0$ were corrected for Lorentz and polarisation effects and for absoprtion, by analysis of seven azimuthal scans.

Structure analysis and refinement. The structure was solved by Patterson and Fourier techniques and refined by blocked cascade least-squares methods. Hydrogen atoms were included in calculated positions with isotropic thermal parameters related to those of the supporting atom. Refinement converged at a final $R = 0.0718$ with allowance for the thermal anisotropy of all non-hydrogen atoms. All calculations were performed on a Data General Nova 3 computer using the SHELXTL program package (revision 4).

Crystal Data for [Ag-(17)]$^+$PF$_6^-$.—C$_{14}$H$_{28}$F$_6$N$_2$PS$_4$; $M = 605.48$, tetragonal, $a = 10.128(3)$, $c = 21.711(4)$ Å, $U = 2\,227(2)$ Å^3, $Z = 4$, $D_c = 1.81$ g m^{-3}, $F(000) = 1\,224$, $\mu(Mo\text{-}K_\alpha) = 13.9$ cm^{-1}. Space group is either P4(1), 2(1), 2 or P4(3), 2(1), 2 from the systematic absences; P4(1), 2(1), 2 was established for the crystal used for the analysis by anomalous dispersion calculations. Crystal dimensions $0.07 \times 0.18 \times 0.20$ mm.

Data collection and processing. CAD-4 diffractometer, $\omega\,2\theta$ mode with ω scan width $= 0.6 + 0.350 \tan \theta$, ω scan speed 1 to 7° min^{-1}, graphite monochromated Mo-K_α radiation; 4 341 reflections were measured of which 1 946 were unique. Data were collected in the range $2 < 2\theta < 50°$. The range of indices was h, -12 to 12; l, 0 to 27; k, 0 to 12. After correction for Lorentz, polarisation and absorption effects 1 050 were used with $I > 3\sigma(I)$.

Structure analysis and refinement. The co-ordinates of the silver atom were located from a three-dimensional Patterson synthesis and the remaining non-hydrogen atoms were located by the heavy-atom method. Refinement was by full-matrix, least-squares calculations with all non-hydrogen atoms allowed anisotropic motion, and with hydrogen atoms 'riding' at calculated positions from the relevant atoms. The final cycle of refinement had 141 variable parameters and converged with $R = 0.030$, $R' = 0.035$. Electron density difference maps at $R = 0.030$ showed that three of the carbon atoms in each nine-membered ring were disordered over two sites $(0.84:0.16)$ occupancies. All calculations were prepared on a PDP 11/73 computer using the SDP-PLUS suite of programs.

Acknowledgements

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