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Metal ion recognition. Selective interaction of silver(I) with tri-linked N_2S_2-donor macrocycles and their single-ring analogues

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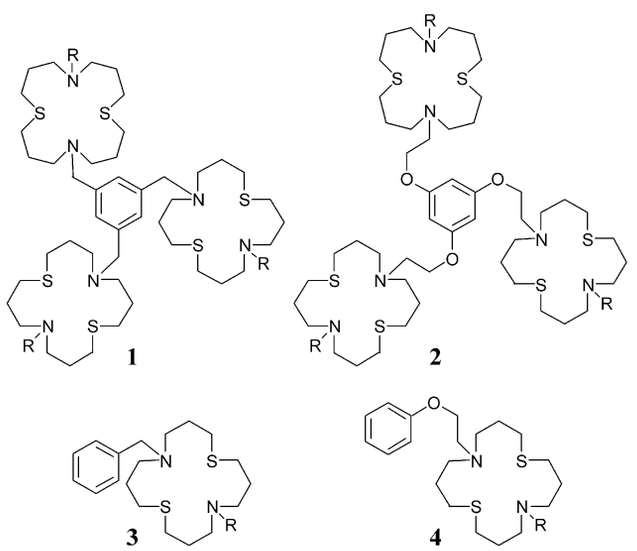
The interaction of four tri-linked N_2S_2-donor macrocyclic ligands and their single ring analogues with silver(I) has been investigated. The 3 : 1 (metal : ligand) stoichiometries of the silver(I) complexes of the tri-linked species in dimethyl sulfoxide-d^6/$CDCl_3$ were confirmed by means of NMR titrations involving the incremental addition of silver(I) nitrate to the respective ligands in the above solvent mixture and following the corresponding induced shifts in the ^1H NMR spectrum. Solid 3 : 1 (metal : ligand) complexes were isolated for each of the parent (unsubstituted) tri-linked ligands. Competitive solvent extraction experiments (water/chloroform) and related bulk membrane transport (water/chloroform/water) experiments have been performed in which each of the four tri-linked ligands as well as their single ring analogues were employed as the extractant/ionophore in the chloroform phase. In both sets of experiments the respective aqueous source phases (buffered at pH 4.9) contained an equimolar mixture of cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), silver(I) and lead(II) nitrates. For membrane transport the aqueous receiving phase was buffered at pH 3. Under the conditions employed, both the solvent extraction and the bulk membrane transport experiments resulted in high extraction/transport selectivity for silver(I) relative to the other six metal ions present.

Introduction

Arising from their often unique properties, such as their tendency to yield both very kinetically and thermodynamically stable metal complexes,[1] macrocyclic rings have frequently proved to be desirable building blocks for incorporation into new supermolecular and supramolecular systems.[2] Initially, such studies have mainly involved crown or azacrown rings[3]– largely due to the ready synthesis of suitably functionalised derivatives from these macrocyclic categories.[4] However, more recently, porphyrin ring and other amine-containing systems have also been increasingly employed in this context.[5]

In a recent study by our group, the application of a protecting group strategy involving introduction of complementary protecting groups into the precursors of the parent, 16-membered, S_2N_2-heteroatom macrocycle has enabled a clean and efficient synthesis of the new tri-linked macrocycles **1** (R = H or CH_2Ph) and **2** (R = H or CH_2Ph).[6] We report here the results of an investigation of the interaction of silver(I), with all four of these tri-linked species as well as with their corresponding single ring analogues **3** (R = H or CH_2Ph) and **4** (R = H or CH_2Ph). The study includes the use of these systems as ionophores in competitive extraction and membrane transport experiments involving cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), silver(I) and lead(II).

The behaviour of **1** (R = H or CH_2Ph) – **4** (R = H or CH_2Ph) towards silver(I) was of particular interest since these ring systems incorporate structural features that might be expected to enhance their relative affinity for this ion. Thus, when considering the coordination chemistry of silver(I), two features appear amenable for exploitation in ligand design. The first is silver's preference for linear diammine coordination, as exemplified by the structure of $[Ag(NH_3)_2]^+$, while the second is its well documented affinity for soft donors[7] such as thioether sulfur. Both these aspects are capable of being accommodated by the present ring systems of type **1** (R = H or CH_2Ph) – **4** (R = H or CH_2Ph).



Surprisingly, there have been relatively few prior reports of the interaction of silver(I) with fully saturated N_2S_2-donor macrocycles related to present systems. In one previous investigation, Kaden *et al.*[8] have probed the solution complexation behaviour of silver(I) with *N*-substituted, *cis*-S_2N_2 macrocycles related to the present monomeric (*trans*-donor) rings. The isolation and X-ray structure determinations of solid silver(I) complexes of the type AgLX (X = NO_3, OAc), incorporating a related octamethylated *trans*-N_2S_2-donor macrocycle, have also been reported.[9,10]

In keeping with the expectation that ligands of the present type will show enhanced binding towards 'softer' metals, an

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initial study by our group has recently demonstrated that the 'unsubstituted' derivatives, **1** (R = H)–**4** (R = H), yield stable complexes with both palladium(II) and platinum(II).[11]

Experimental

Where available, all reagents and solvents were A.R. grade. High resolution mass spectra were obtained on a Kraytos M25RFA spectrometer or a Bruker APEX 47e spectrometer (ESI). NMR spectra were recorded on a Bruker AM-300 spectrometer; δ_H values are relative to Me_4Si and δ_C values are relative to $CDCl_3$ at 77.0 ppm, J are in Hz.

NMR titrations

NMR titrations were employed to investigate silver complexation by the tri-linked ring derivatives **1** (R = H or CH_2Ph) and **2** (R = H or CH_2Ph). Titrations were performed by sequential 15 μL additions of silver(I) nitrate solution (≈0.5 mol dm^{-3}) in $CDCl_3$/DMSO-d^6 (1 : 1) to a solution of the ligand (≈0.02 mol dm^{-3}) in the same solvent mixture contained in the NMR tube. This procedure was carried out in the dark to minimise light catalysed decomposition of the corresponding silver complex. For each system, the change in the chemical shift of the methylene protons adjacent to the thioether sulfur atoms in the macrocyclic ring was monitored throughout the titration. The induced chemical shift corresponding to each addition of silver ion was then plotted against the ratio of metal ion concentration to ligand concentration present in the NMR tube. The NMR titration data were analysed using a local version of the program, EQNMR.[12] EQNMR is used to evaluate stability constants in systems where the species are in rapid equilibrium and where the NMR chemical shift data reflect the degree of complex formation. The program fits a titration curve to the measured data using an iterative process that starts with initial estimates of the stepwise stability constants.

Extraction experiments

The procedure employed involved 'competitive' metal extractions from an aqueous phase into a chloroform phase. The aqueous phase was buffered at pH 4.9 ± 0.1 with sodium acetate/acetic acid buffer and contained equal concentrations (10^{-2} mol dm^{-3}) of cobalt(II), copper(II), lead(II), silver(I), cadmium(II), zinc(II) and nickel(II) as their respective nitrate salts. The extractions were carried out in small sealed flasks in the absence of light to minimise the possibility of light-induced silver(I) decomposition. The flasks were agitated for one hour on a mechanical shaker after which time an aliquot of the organic phase was removed and evaporated to dryness. The residue was then taken up in nitric acid and, after appropriate dilution, was analysed by atomic absorption spectrophotometry. Each experiment was performed in quadruplicate and the quoted values are the average from individual experiments.

Membrane transport

The transport experiments employed a 'concentric cell' in which the aqueous source phase (10 cm^3) and receiving phase (30 cm^3) are separated by a chloroform phase (50 cm^3). Details of the cell design have been reported elsewhere[13] and the conditions employed were generally similar to those used for a recent study.[14] For each experiment (which was carried out in subdued light), both aqueous phases and the chloroform phase were stirred separately at 10 revolutions min^{-1}; the cell was enclosed by a water jacket and thermostatted at 25 °C. The aqueous source phase was buffered (acetic acid/sodium acetate) at pH 4.9 ± 0.1 and contained 10^{-2} mol dm^{-3} of each of the following nitrate salts: cobalt(II), nickel(II), copper(II), zinc(II), silver(I), cadmium(II) and lead(II). The chloroform phase contained the required macrocyclic ligand (1.00×10^{-3} mol dm^{-3} for the single ring ligands and 3.33×10^{-4} mol dm^{-3} for the tri-linked ligands). The receiving phase was buffered (formic acid/sodium formate) at pH 3.0 ± 0.1. All transport runs were terminated after 24 h and were performed in duplicate. A control experiment in which the chloroform phase did not contain ionophore, as expected, yielded no evidence of metal ion transport, indicating that entrainment of the aqueous phase in the organic phase was not a problem. Atomic absorption spectrometry was used for metal ion analysis of the receiving phase. Transport fluxes are expressed as J values in mol h^{-1} and represent mean values from duplicate runs measured over 24 h.

Ligand synthesis

1,3,5-Tris[(1,9-dithia-5,13-diazacyclohexadec-5-yl)methyl]-benzene **1** (R = H),[6] 1,3,5-tris[(2-(1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxy]benzene **2** (R = H),[6] 1,3,5-tris[(*N*-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)methyl]benzene **1** (R = CH_2PH),[6] 1,3,5-tris[2-(*N*-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxy]benzene **2** (R = CH_2PH),[6] 5-benzyl-1,9-dithia-5,13-diazacyclohexadecane **3** (R = H),[6] 2-(1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxybenzene **4** (R = H)[6] and 5-benzyl-1,9-dithia-13-chloroacetyl-5,13-diazacyclohexadecane[6] were synthesised as described elsewhere. The syntheses of **3** (R = CH_2Ph) and **4** (R = CH_2Ph), which were performed under an atmosphere of dry nitrogen, are given below.

5,13-Dibenzyl-1,9-dithia-5,13-diazacyclohexadecane 3 (R = CH_2Ph). 5-Benzyl-1,9-dithia-5,13-diazacyclohexadecane **3** (R = H) (1.33 g, 3.7 mmol) was dissolved in dry tetrahydrofuran (40 cm^3). Triethylamine (0.43 g, 4.2 mmol) and then benzoyl chloride (0.58 g, 4.15 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h after which the tetrahydrofuran was removed under reduced pressure. The residue was partitioned between dichloromethane (100 cm^3) and water (50 cm^3). The organic phase was washed with a further 50 cm^3 of water and then dried (sodium sulfate). The solvent was evaporated and the crude product chromatographed on silica gel (eluting with methanol–dichloromethane, 1 : 99) to give *5-benzoyl-13-benzyl-1,9-dithia-5,13-diazacyclohexadecane* as a yellow oil [Found: M + H^+, 457.2374 (LSIMS). $C_{27}H_{37}N_2OS_2$ requires M + H^+, 457.2347]; R_f (MeOH–dichloromethane, 1 : 19) 0.61; δ_H ($CDCl_3$, 300 MHz) ≈7.3 (10 H, m, OCPh, CH_2*Ph*), 3.66, 3.38 (4 H, br m, CH_2NCOPh), 3.51 (2 H, s, CH_2Ph), 2.59 (4 H, t, J 7.4, $CH_2CH_2CH_2NCH_2Ph$), 2.48 (4 H, t, J 6.0, $PhCH_2NCH_2$), 2.60, 2.36 (4 H, br m, $PhCONCH_2CH_2CH_2$), 2.06, 1.92 (4 H, br m, $PhCONCH_2CH_2$), 1.74 (4 H, br m, CH_2CH_2-NCH_2Ph); δ_C ($CDCl_3$, 75 MHz) 171.4, 167.4, 139.1, 136.5, 129.2, 128.9, 128.5, 128.1, 127.7, 126.5, 126.2, 126.0, 121.1, 114.1, 58.7, 52.5, 48.7, 47.0, 46.9, 44.5, 29.5, 29.3, 28.7, 28.5, 27.3, 26.8.

5-Benzoyl-13-benzyl-1,9-dithia-5,13-diazacyclohexadecane (1.09 g, 2.4 mmol) was dissolved in dichloromethane (50 cm^3) at 0 °C and a 1.0 mol dm^{-3} solution of diisobutylaluminium hydride (11.1 cm^3, 11.1 mmol) was then added. The reaction mixture was stirred for 2 h after which the excess diisobutylaluminium hydride was destroyed by careful addition of methanol. The residue was then partitioned between 10% aqueous sodium hydroxide (100 cm^3) and diethyl ether (100 cm^3). The aqueous layer was extracted with ether (100 cm^3 × 2) and the combined organic layers dried (sodium sulfate) and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with ethyl acetate–hexane, 1 : 9) to give *5,13-dibenzyl-1,9-dithia-5,13-diazacyclohexadecane* **3** (R = CH_2Ph) as a yellow oil (0.57 g, 55%) [Found: M + H^+, 443.2560 (LSIMS). $C_{26}H_{38}N_2S_2$ requires M + H^+, 443.2555); R_f (ethyl acetate–hexane, 1 : 3) 0.26;

δ_H ($CDCl_3$, 300 MHz) ≈7.3 (10 H, m, Ph), 3.54 (4 H, s, CH_2Ph), 2.57 (8 H, t, *J* 7.7, CH_2S), 2.49 (8 H, t, *J* 6.3, CH_2N), 1.77 (8 H, quin, *J* 7.0, $NCH_2CH_2CH_2S$); δ_C ($CDCl_3$, 75 MHz) 139.7, 128.8, 128.1, 126.8, 59.4, 52.6, 30.0, 27.7.

2-(*N*-Benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxybenzene 4 (R = CH_2Ph). Caesium carbonate (0.923 g, 2.83 mmol) was suspended in a solution of 5-benzyl-1,9-dithia-13-chloroacetyl-5,13-diazacyclohexadecane[6] (1.10 g, 2.6 mmol) in dry dimethylformamide (25 cm^3). Solid phenol (0.267 g, 2.83 mmol) was added and the mixture stirred at 70 °C for 48 h. The dimethylformamide was removed *in vacuo* and the residue suspended in dichloromethane (100 cm^3). The solid was removed by filtration through Celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with ether–hexanes, 1 : 1) to give *5-benzyl-13-(2-phenoxyacetyl)-1,9-dithia-5,13-diazacyclohexadecane* (0.80 g, 64%) as a viscous oil [Found: M + H^+, 487.2468 (LSIMS). $C_{27}H_{38}N_2O_2S_2$ requires M + H^+, 487.2453]. δ_H ($CDCl_3$, 300 MHz) 7.3–7.0 (10 H, m, CH_2*Ph*, OPh), 4.70 (2 H, s, PhOCH_2), 3.55–3.52 (4 H, overlapping t, CH_2NCO), 2.54 (8 H, m, CH_2S), 2.46 (4 H, t, *J* 6.0, C$H_2$$NCH_2$Ph), 1.95 (4 H, overlapping quin, CH_2CH_2NCO), 1.73 (4 H, quin, *J* 6.0, C$H_2CH_2NCH_2$Ph); δ_C ($CDCl_3$, 75 MHz) 167.9, 157.8, 139.4, 129.6, 128.8, 128.1, 126.9, 121.6, 114.4, 67.7, 59.1, 52.8, 52.7, 47.6, 45.8, 29.9, 29.8, 29.5, 29.2, 28.9, 27.7, 27.4, 27.2.

5-Benzyl-13-(2-phenoxyacetyl)-1,9-dithia-5,13-diazacyclohexadecane (1.59 g, 3.3 mmol) was dissolved in dry tetrahydrofuran (50 cm^3). A 2.0 mol dm^{-3} solution of borane–dimethyl sulfide complex in tetrahydrofuran (8.2 cm^3, 16.4 mmol) was added slowly and the mixture heated to reflux for 12 h. The solution was allowed to cool to room temperature and the excess borane destroyed by careful addition of methanol. The solvent was removed under reduced pressure and the residue was hydrolysed in refluxing methanol–water–concentrated hydrochloric acid (40 : 10 : 4; 55 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution was partitioned between 10% aqueous sodium hydroxide (100 cm^3) and dichloromethane (100 cm^3). The aqueous layer was extracted twice further with dichloromethane (100 cm^3) and the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure. Purification by chromatography on silica gel (eluting with ethyl acetate–hexanes, 1 : 3) gave *2-(N-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxybenzene* **4** (R = CH_2Ph) as a colourless oil (1.01 g, 66%) [Found: M + H^+, 473.2662 (LSIMS). $C_{27}H_{40}N_2OS_2$ requires M + H^+, 473.2660]. δ_H ($CDCl_3$, 300 MHz) ≈7.3 (5 H, m, CH_2*Ph*), ≈6.9 (5 H, m, OPh), 4.04 (2 H, t, *J* 6.0, CH_2O), 3.51 (2 H, s, CH_2Ph), 2.86 (2 H, t, *J* 6.0, OCH_2CH_2N), 2.63 (4 H, t, *J* 7.2, CH_2S), 2.62 (4 H, t, *J* 6.3, CH_2NCH_2-CH_2OPh), 2.55 (4 H, t, *J* 7.4, CH_2S), 2.46 (4 H, t, *J* 6.3, CH_2NCH_2Ph), 1.76 (8 H, quin, *J* 7.4, $PhCH_2NCH_2CH_2$), 1.74 (8 H, quin, *J* 7.8, C$H_2CH_2NCH_2CH_2O$); δ_C ($CDCl_3$, 75 MHz) 158.7,139.6, 129.3, 128.7, 128.0, 126.7, 120.5, 114.3, 66.3, 59.4, 53.5, 53.4, 52.5, 30.0, 29.8, 27.7, 27.5.

Metal complex synthesis

1,3,5-Tris[(1,9-dithia-5,13-diazacyclohexadec-5-yl)methyl]benzenetrisilver(I) nitrate pentahydrate $[Ag_3L](NO_3)_3\cdot5H_2O$ (L = 1, R = H). Silver(I) nitrate (0.017 g, 0.01 mmol) in absolute ethanol (2 cm^3) was added dropwise to a solution of **1** (R = H) (0.030 g, 0.03 mmol) in dry 4 : 1 ethanol/dichloromethane (1 cm^3) in the dark. The reaction was stirred for 30 min during which a white solid precipitated from solution which was filtered off, washed with dry ethanol and ether, then dried over P_2O_5 under vacuum to give $[Ag_3L](NO_3)_3\cdot5H_2O$ (L = **1**, R = H) (0.044 g, 88%) as an off-white microcrystalline product [Found $(M - 2NO_3)^{2+}$, 641.6080 (ESI). $C_{45}H_{84}Ag_3N_9O_9S_6$ requires $(M - 2NO_3)^{2+}$, 641.6051. Found: C, 35.79; H, 5.92; N 8.45. $C_{45}H_{84}Ag_3N_9O_9S_6\cdot5H_2O$ requires C, 36.00; H, 6.31; N, 8.40%].

1,3,5-Tris[2-(1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxy]benzenetrisilver(I) nitrate pentahydrate $[Ag_3L](NO_3)_3\cdot5H_2O$ (L = 2, R = H). Using a similar procedure to that described for $[Ag_3L](NO_3)_3\cdot5H_2O$ (L = **1**, R = H), silver nitrate (0.017 g, 0.01 mmol) and **2** (R = H) (0.033 g, 0.03 mmol) yielded $[Ag_3L](NO_3)_3\cdot5H_2O$ (L = **2**, R = H), (0.040 g, 75%) as an off-white microcrystalline product [Found $(M - 2NO_3)^{2+}$, 686.6206 (ESI). $C_{48}H_{90}Ag_3N_9O_{12}S_6$ requires $(M - 2NO_3)^{2+}$, 686.6209. Found: C, 36.10; H, 6.09; N 7.87. $C_{48}H_{90}Ag_3N_9O_{12}S_6\cdot5H_2O$ requires C, 36.23; H, 6.33; N, 7.92%].

Results and discussion

Ligand synthesis

The macrocyclic derivatives **1** (R = H, CH_2Ph), **2** (R = H, CH_2Ph), **3** (R = H) and **4** (R = H) were synthesised using procedures reported previously by our group.[6] It is noted that the parent (unsubstituted) 16-membered S_2N_2 macrocycle has been reported by Kaden *et al.*;[8] however, the synthetic approach employed in this previous study was not suitable for use for the preparation of the present derivatives [with the exception of the symmetrically substituted derivative **3** (R = CH_2Ph)] since it did not allow easy chemical differentiation between the two ring nitrogen sites. For the present syntheses, an alternate disconnection of the parent macrocycle was employed that placed the nitrogens in separate synthons, enabling the former to be differentially protected prior to cyclisation. Namely, the procedure employed bis-alkylation of the terminal dithiolate groups of a *N*-protected bis(thiolopropyl)amine species with a bis(3-halogenopropyl)amine derivative incorporating different nitrogen protection.

The new macrocyclic derivative **3** (R = CH_2Ph) was obtained from **3** (R = H)[6] by initial acylation with benzoyl chloride in dry tetrahydrofuran in the presence of base. The resulting amide derivative was then reduced with diisobutylaluminium hydride to yield crude **3** (R = CH_2Ph) as an oil which was purified by partitioning between aqueous sodium hydroxide and ether, followed by chromatography on silica gel.

The related derivative **4** (R = CH_2Ph) was obtained using a similar strategy to that employed for the tri-linked compound **2** (R = CH_2Ph)[6] in which the required macrocyclic chloroamide derivative was used to alkylate phenol (rather than phloroglucinol (1,3,5–trihydroxybenzene)). The resulting substituted macrocyclic amide was then reduced using borane/dimethyl sulfide to give **4** (R = CH_2Ph).

Metal complex isolation

Initial attempts to isolate solid silver(I) nitrate complexes of the tri-linked ligands of type **1** and **2** resulted in coloured contaminated products. However, in the case of **1** (R = H) and **2** (R = H), when the syntheses were performed in the absence of light in dry dichloromethane/ethanol, analytically pure (off-white) products of type $[Ag_3L](NO_3)_3\cdot5H_2O$ were obtained, confirming the ability of these ligands to bind three silver ions. Unfortunately, we were not able to obtain suitable crystals for X-ray structure determinations in either case.

NMR titrations

The interaction of the tri-linked S_2N_2-donor ligands **1** (R = H or CH_2Ph) and **2** (R = H or CH_2Ph) with silver(I) was investigated by means of ^{1}H NMR titration experiments in $CDCl_3$/DMSO-d_6. Titration curves for incremental addition of silver nitrate to both **1** (R = H) and **2** (R = H) yielded sharp 3 : 1 (metal : ligand) end points (Fig. 1), indicating that binding of silver by these ligands is relatively strong. The thermodynamic formation constants for these two systems are clearly too high

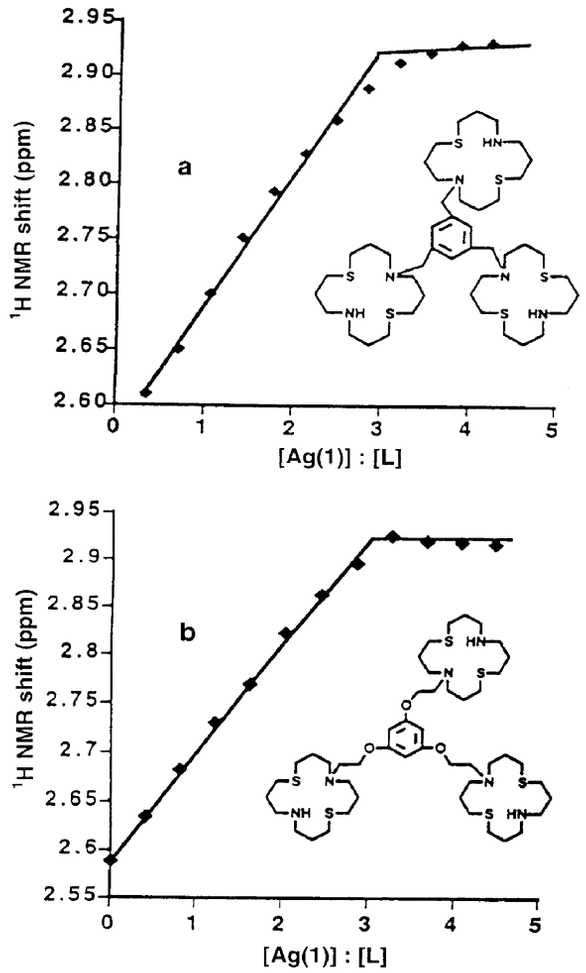

Fig. 1 NMR titration curves for the addition of silver nitrate to the tri-linked macrocyclic species in DMSO-d_6/$CDCl_3$ (1 : 1) (a) **1** (R = H), (b) **2** (R = H).

to be determined under the conditions employed. However, the binding of silver(I) by the tribenzylated derivatives **1** (R = CH_2Ph) and **2** (R = CH_2Ph) under similar conditions is significantly weaker (Fig. 2), as indicated by the absence of a sharp end point in the respective titration curves. Analysis of these latter curves using a local version of EQNMR [12] enabled calculation of the corresponding log β values for Ag(I) complexation; the values obtained for **1** (R = CH_2Ph) are log $\beta_1 = 3.54$, log $\beta_2 = 6.52$ and log $\beta_3 = 8.61$ and, for **2** (R = CH_2Ph), log $\beta_1 = 3.66$, log $\beta_2 = 6.94$ and log $\beta_3 = 9.21$. No satisfactory fit of the experimental data was obtained when other simple models were substituted for the 3 : 1 (metal : ligand) model used for the calculations.

As expected from statistical considerations, the stepwise constants decrease for successive complexation steps. A possible further contribution to the diminishing step-wise stability constants could involve charge repulsion between the positive metal centres. However, this does not appear to make a major contribution in the present cases; the respective log β_n values for the complexes of **1** (R = CH_2Ph) and **2** (R = CH_2Ph) given above differ only slightly even though a different number of linking atoms separate the macrocyclic rings in each system.

Extraction experiments

Metal ion solvent extraction experiments (water/chloroform) have been carried out using each of the tri-linked macrocycles and their single ring macrocyclic analogues as extractants. The procedure employed involved 'competitive' metal extractions from an aqueous phase at pH 4.9 (sodium acetate/acetic acid buffer) containing equal concentrations ($\approx 10^{-2}$ mol dm^{-3}) of

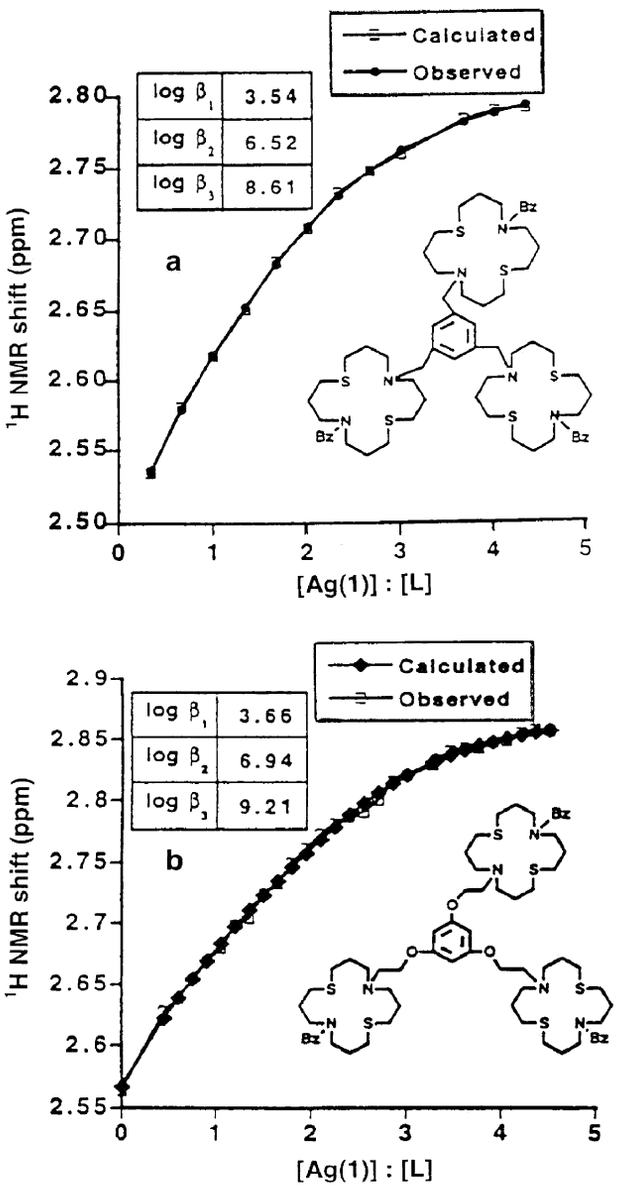

Fig. 2 NMR titration curves for the addition of silver nitrate to the tri-linked macrocyclic species (a) **1** (R = CH_2Ph) and (b) **2** (R = CH_2Ph) in DMSO-d_6/$CDCl_3$ (1 : 1), showing fitted EQNMR plots.

each of cobalt(II), copper(II), lead(II), silver(I), cadmium(II), zinc(II) and nickel(II) as their nitrate salts. In individual experiments, the tri-linked species, **1** (R = H or CH_2Ph), **2** (R = H or CH_2Ph), and corresponding single ring species, **3** (R = H or CH_2Ph) and **4** (R = H or CH_2Ph), were employed as the ionophore in the respective chloroform phases. To enable direct comparison of results, individual experiments were performed under 'equivalent concentrations' with respect to the number of macrocyclic rings present in each ionophore. Hence ionophore concentrations of 3.33×10^{-4} mol dm^{-3} for the tri-linked systems and 1.00×10^{-3} mol dm^{-3} for the single ring systems were employed. The results are presented in Fig. 3; for ready comparison of the 'efficiencies' of the single and three-ring species, the degree of extraction is presented as the percentage of ligand sites occupied in each experiment. Clearly, under the conditions employed, each single ring macrocycle is a more effective extracting agent on a 'per hole' basis than its tri-linked analogue. In all experiments, the respective systems showed sole selectivity for silver(I)–in confirmation of the expected affinity of this ion for a N_2S_2-donor set. Hence, while the macrocyclic ring substitution (and linkage) pattern clearly influences the efficiency of the extraction, silver ion selectivity is maintained in each case.

Both the lipophilicity of a ligand and its binding strength with a particular cation are factors that are well documented to influence overall extraction efficiencies.[15] In the present study the *N*-benzylated single-ring and tri-linked ligands were found to be more efficient extractors of silver(I) relative to their corresponding non-benzylated analogues (Fig. 3). This was so

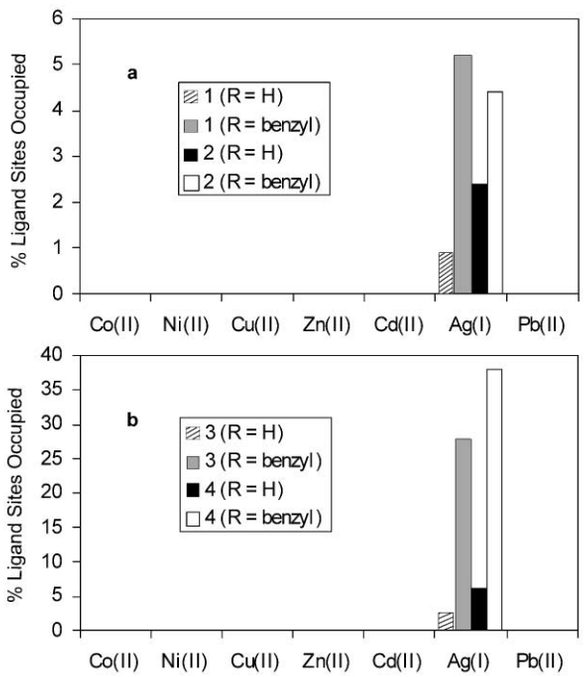

Fig. 3 Mixed metal ion extraction data (a) for the tri-linked ligands ligands **1** (R = H or CH_2Ph) and **2** (R = H or CH_2Ph) and (b) their respective single ring analogues **3** (R = H or CH_2Ph) and **4** (R = H or CH_2Ph). [Source phase contained seven metal nitrates, each at $\approx 10^{-2}$ mol dm^{-3} buffered at pH 4.9; for individual experiments the chloroform phase contained a tri-linked ligand at 3.33×10^{-4} mol dm^{-3} or a single ring ligand at 1.00×10^{-3} mol dm^{-3}; experiments terminated after 1 h; 25 °C.]

even though the NMR titration results (in $CDCl_3$/DMSO-d_6) indicated (see above) that higher complex stabilities occur for the silver complexes of the non-benzylated tri-linked ligands **1** (R = H) and **2** (R = H) under the conditions employed for these latter experiments. Hence, it appears that it is the greater lipophilicity of the benzylated derivatives **1** (R = CH_2Ph), **2** (R = CH_2Ph), **3** (R = CH_2Ph) and **4** (R = CH_2Ph) that favours the observed enhanced extraction efficiencies of these ring systems relative to those of the corresponding systems with R = H.

Transport experiments

The study involved metal ion transport from an aqueous source phase containing the nitrate salts of cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), silver(I) and lead(II), each at $\approx 10^{-2}$ mol dm^{-3}, across a bulk chloroform membrane incorporating an ionophore chosen from **1** (R = H or CH_2Ph), **2** (R = H or CH_2Ph), **3** (R = H or CH_2Ph) or **4** (R = H or CH_2Ph). Transport was performed against a back gradient of protons, maintained by buffering the source and receiving phases at pH 4.9 and 3.0, respectively.

Even though theory does not decree that it need be the case,[16] it was nevertheless of interest to see whether the clear silver(I) selectivity observed in the solvent extraction experiments for each of the present ligands would be maintained in the transport studies. This indeed was found to be the case, with evidence for a minor amount of zinc(II) transport also occurring in individual cases. The 'per macrocyclic hole' results from the above experiments are presented in Fig. 4. Under the conditions employed, the single ring ligands resulted in relatively higher

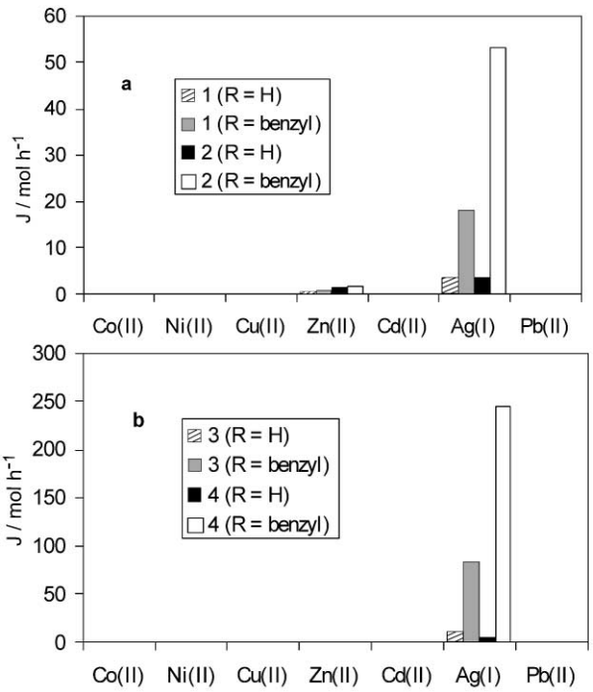

Fig. 4 Comparative transport flux rates (a) for the tri-linked ligands **1** (R = H or CH_2Ph) and **2** (R = H or CH_2Ph) and (b) their respective single ring analogues **3** (R = H or CH_2Ph) and **4** (R = H or CH_2Ph). Flux values J are in mol h^{-1} (all plotted J values are by 10^{-9}). [Source phase contained seven metal nitrates, each at $\approx 10^{-2}$ mol dm^{-3} buffered at pH 4.9; receiving phase buffered at pH 3.0; for individual experiments the chloroform phase contained a tri-linked ligand at $\approx 3.33 \times 10^{-4}$ mol dm^{-3} or a single ring ligand at 1.00×10^{-3} mol dm^{-3}; runs terminated after 24 h; 25 °C.]

transport fluxes than their respective tri-linked analogues – a result that again directly parallels the corresponding solvent extraction results. Also, as before, the benzylated ligands (both tri-linked and mono-ring) are each more efficient ionophores than their NH-containing parents, with the single ring species being better transporters than their tri-linked analogues when compared on a 'per hole' basis.

Clearly, the transport and extraction results closely parallel each other for the present ligand series, a situation also found to occur in our recent studies[14] in which a series of oxygen–nitrogen donor macrocycles were employed as extractants/ionophores in comparative experiments of the above type.

Concluding remarks

The study demonstrates the high selectivity of all the present ligands for silver(I) and confirms that all three macrocyclic sites in the linked ligands readily bind this cation. Overall, the results provide a foundation for a study of the metal binding behaviour of related dendritic systems incorporating the present tri-linked frameworks to which additional N_2S_2-donor macrocyclic units have been appended. An investigation of this type is currently underway and the results will be presented in due course.

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