Rational ligand design for metal ion recognition. Synthesis of a *N*-benzylated N_2S_3-donor macrocycle for enhanced silver(I) discrimination†

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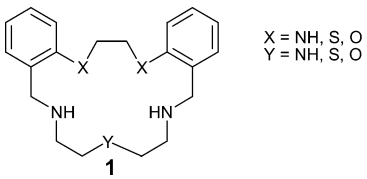
Four previously documented ligand design strategies for achieving Ag(I) discrimination have been applied to the design of a new *N*-benzylated N_2S_3-donor macrocycle; the latter shows high selectivity for Ag(I) over Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Pb(II) in log *K* and bulk membrane transport studies.

We have previously reported the synthesis of an extended series of 16- to 19-membered, dibenzo-substituted macrocycles incorporating oxygen, nitrogen and/or sulfur heteroatoms.[1] These rings were synthesised as part of an investigation of structure–function relationships underlying discrimination behaviour within the above seven metal-ion series. Several examples of such discrimination are documented;[2–4] for example, step-wise 'tuning' of the donor set present within 17-membered rings of type **1** resulted in $>10^9$ discrimination for Ag(I) over Pb(II)[4]—metals that are found together in nature. However discrimination for Ag(I) over Cu(II),[5] while less spectacular, was still $\sim 10^4$.



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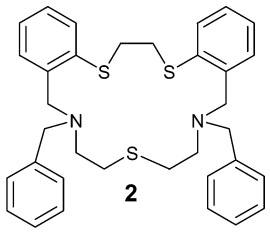
In our previous (wide-ranging) studies involving ligands of type **1** four design elements that influence the discrimination for Ag(I) over the above transition and post-transition ions are documented: (i) the macrocyclic ring size, (ii) the macrocyclic donor set, (iii) macrocyclic donor atom sequence and (iv) the nature of any donor atom substituents present. We have now applied the 'lessons learnt' in the these studies to the design and synthesis of the new macrocyclic ligand **2** which was thus anticipated to yield enhanced discrimination for Ag(I) over the other six transition and post-transition ions mentioned above.

In the previous studies, as expected from a consideration of HSAB theory,[6] it was confirmed that progressive substitution of thioether sulfur atoms for oxygen in an O_3N_2-donor ring of type **1** led to increased silver ion discrimination. A second general observation was that both the strength of binding as well as silver ion discrimination tended to peak for the 17-membered ring



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system (which forms three five-membered and two six-membered chelate rings when all donors bind to a central metal ion). In this context it is noted that the X-ray structures of the 1 : 1 (Ag^+: L) complexes, where L = **1** with X = S, Y = O,[4] X = S, Y = NH[7] and X = S, Y = S[8] (all 17-membered rings) confirm coordination of all five macrocyclic ring donors to silver in each case (with no other ligands present in the coordination sphere). A third observation, was that the presence of a $NHCH_2CH_2XCH_2CH_2$ NH (X = O or S) donor atom sequence, rather than the corresponding sequence with X = NH, also promotes enhanced silver discrimination; even though the absolute log *K* values tend to be smaller when X = O. Finally, in a number of studies by us and others,[9] it has been well documented that *N*-benzylation of a secondary amine donor in a variety of aza macrocyclic systems leads to enhanced discrimination for silver over a range of transition and post-transition metal ions—behaviour we have previously termed 'selective detuning'.[10] For example, it has been reported that *N*-benzylation of the nitrogen donors in a number of mixed nitrogen–oxygen donor macrocycles leads to enhanced metal ion discrimination for Ag(I) within the transition and post transition metal ions mentioned previously.[11,12]

Related behaviour to the above has been reported for the tetra-*N*-benzylated derivative of cyclam (tbc), which shows both substantial affinity and selectivity for Ag(I).[13] For example, in bulk liquid (water–dichloromethane–water) membrane transport experiments[14] it was found that silver (as its perchlorate) was the only cation transported by tbc relative to the perchlorates of lithium, sodium, potassium, ammonium, caesium, barium, lead, calcium, magnesium, cobalt, nickel, copper and zinc under the conditions employed.

In the present study, the design and synthesis of the dibenzyl-*N*-substituted, 17-membered ring **2** (which contains a S_3N_2-donor set as well as a desired-N–S–N-donor atom sequence) was carried out based on all four design elements mentioned earlier. Macrocycle **2** was prepared by direct *N*-benzylation of its unsubstituted precursor **1** (X = Y = S) using benzyl bromide in acetonitrile in the presence of sodium hydrogen carbonate as base.‡

Stability constants for the 1 : 1 complexes of **2** with Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Ag(I) and Pb(II) were investigated potentiometrically by the pH titration method in 95% methanol

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Table 1 Log *K* values for the 1 : 1 complexes of **1** (X = Y = S) and **2** in 95% methanol ($I = 0.1$, Et_4NClO_4) at 25.0 °C

Ligand	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Ag(I)	Pb(II)
1[a,b]	<3.5	[c]	8.1	~3.3	[c]	12.4	~3
2	<3	<3	3.6	<3	<3	8.7	~3

[a] X = Y = S. [b] Values from ref. 2–4. [c] Precipitation or slow approach to equilibrium prevented log *K* determination.

(I = 0.1, Et_4NClO_4; 25.0 °C) under identical conditions to those described previously;[9] use of this solvent system allowed comparison with the log *K* values determined previously.

The results are summarised in Table 1. As for its non-dibenzylated derivative **1** (X = Y = S), **2** shows clear discrimination for Ag(I) over the remaining six metals, with the silver complex being at least 10^5 more stable than any of the remaining complexes investigated. In particular, Ag(I)/Cu(II) discrimination is almost an order of magnitude higher for the latter ligand even though (and as expected) steric[15] and electronic influences on *N*-benzylation of **1** (X = Y = S) result in a general reduction of the respective log *K* values for the complexes of **2**. Once again the results provide an example of 'selective detuning' of the type described previously.[9,10] A rationale for *N*-alkylation in related macrocyclic systems favouring monovalent over divalent metal-ion binding has been presented elsewhere.[16,17]

As might be predicted, the ESI mass spectrum of a mixture of **2** and Ag(I) nitrate in a methanol–acetonitrile mixture yielded a peak corresponding to formation of the 1 : 1 complex, AgL^+ (L = **2**) and a solid complex of this stoichiometry was isolated as its hexafluorophosphate salt on reaction of silver hexafluorophosphate with **2** in acetonitrile–dichloromethane.§

Bulk membrane (H_2O–$CHCl_3$–H_2O) transport studies across a pH gradient were performed employing **2** as the ionophore in a 'concentric cell' apparatus described previously.[18] The aqueous source phase was buffered at pH 4.9 and contained an equimolar solution of the nitrate salts of Co(II), Ni(II), Zn(II), Cu(II), Cd(II), Pb(II) and Ag(I), each at a concentration of 1×10^{-2} M. The chloroform phase contained **2** at 1×10^{-3} M. The aqueous receiving phase was buffered at pH 3.0 ± 0.1 and the transport runs were terminated after 24 h; these are identical conditions to those employed previously.[19]

Sole transport selectivity for Ag(I) was observed; that is, silver was transported with a flux corresponding to 137×10^{-7} moles per 24 h while no transport of the other six metals present in the source phase occurred.

The X-ray structure of [Ag**2**]PF_6·CH_3CN (Fig. 1) shows that the Ag(I) ion is bound to all donor atoms of **2** in the complex cation and adopts a 'tight' (see the space-filling representation given in Fig. 2), distorted trigonal bipyramidal geometry.¶ This is in keeping with the presence of the strong ligand to silver coordination inferred from the solution studies. Interestingly, there is an acetonitrile molecule present in the lattice but it is not coordinated despite the known affinity of this solvent for Ag(I).

Based on the results from previous studies aimed at elucidating the factors underlying Ag(I) ion discrimination, we have carried out the rational design and synthesis of the new macrocyclic ligand **2**. While theory dictates that stability and transport behaviour need not necessarily parallel each other, for the present system this was found to occur. In both cases, **2** shows substantial discrimination

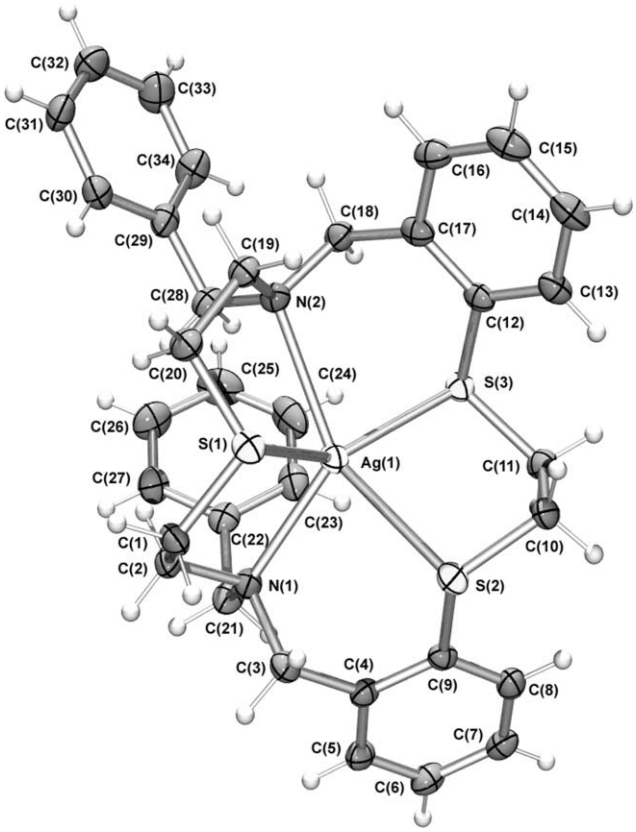

Fig. 1 An ORTEP plot of the [Ag**2**]$^+$ cation in [Ag**2**]PF_6·MeCN shown with 50% probability ellipsoids. Solvent acetonitrile and counter-ion omitted for clarity.

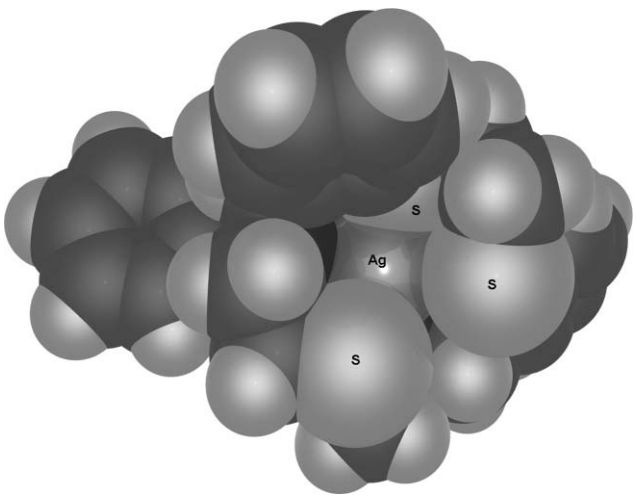

Fig. 2 A space-filling depiction of the X-ray structure of the complex cation in [Ag**2**]PF_6·MeCN.

for silver over the other six transition and post transition metal ions investigated. Apart from the prospect of employing **2** for the sensing or separation of Ag(I), the study serves to exemplify the use of a stepwise strategy for the rational design of a ligand system that, in the present case, results in significantly enhanced discrimination for Ag(I).

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Notes and references

‡ *Synthesis of* **1** (*X* = *Y* = *S*): This was prepared by a modification of a previously described method.[1] 2,2-Diaminoethylthioether (257.9 mg, 2 mmol) was dissolved in absolute ethanol (250 ml) and added dropwise over a period of 3 h to a solution of 2,2′-ethane-1,2-diyl(thio)bisbenzaldehyde (609.5 mg, 2 mmol) in absolute ethanol (600 ml). The reaction mixture was refluxed for 3 h, then sodium borohydride added with minimum delay (1.0 g, 25 mmol) and refluxing continued for 12 h. The solvent was removed on a rotary evaporator and the resulting solid was dissolved in dichloromethane (50 ml) and 1 M sodium hydroxide solution (15 ml) was added. The mixture was shaken and the organic layer was removed and the sodium hydroxide solution was again extracted with dichloromethane (50 ml). The combined organic extracts were washed with saturated sodium chloride (20 ml), then taken to dryness on a rotary evaporator. The resulting white solid was recrystallised from acetonitrile (493 mg, 63%). ^{1}H NMR ($CDCl_3$) δ 2.13, br s, 2H, NH; 2.73–2.77, m, 4H, SCH_2CH_2N; 2.84–2.88, m, 4H, SCH_2CH_2N; 3.23, s, 4H, SCH_2CH_2S; 3.87, s, 4H, $ArCH_2$; 7.18–7.34, m, 8H, C_6H_4. ^{13}C NMR ($CDCl_3$) δ 32.9, 33.9, 48.2, 52.3, 126.9, 127.9, 130.6, 130.8, 134.2, 140.7. These data correspond to those reported previously for this compound; the above procedure resulted in a significantly enhanced yield over that reported for the existing preparation. § *Synthesis of* **2**: Sodium hydrogen carbonate (1.32 g, 15.7 mmol) was added with stirring to a solution of **1** (X = Y = S) (0.350 g, 0.8 mmol) in acetonitrile (50 ml) and the mixture was heated to reflux. Benzyl bromide (0.306 g, 1.79 mmol) in acetonitrile (75 ml) was added dropwise over 1.5 h. The reaction mixture was filtered and the filtrate was taken to dryness on a rotary evaporator. The solid that remained was partitioned between water (50 ml) and dichloromethane (100 ml). The organic layer was separated and the water layer was washed with a further 2 × 50 ml of dichloromethane. The combined organic fractions were backwashed with water (50 ml), dried over anhydrous sodium sulfate, filtered, and the solvent removed on a rotary evaporator. The resulting solid was recrystallised from acetone–methanol (1 : 1) containing small amounts of acetonitrile and dichloromethane (Yield, 0.326 g, 63.8%). (Found: C, 69.87; H, 6.18; N, 4.85%. $C_{34}H_{38}N_2S_3$ requires C, 69.48; H, 6.55; N, 4.73%). ^{1}H NMR ($CDCl_3$) δ 2.58–2.63, m, 4H, SCH_2CH_2N; 2.71–2.76, m, 4H, SCH_2CH_2N; 3.16, s, 4H, SCH_2CH_2S; 3.56, s, 4H, $C_6H_5CH_2$; 3.73, s, 4H, $ArCH_2$; 7.14–7.43, m, 18H, arom. ^{13}C NMR ($CDCl_3$) δ 28.7, 33.9, 54.4, 57.0, 57.7, 126.1, 126.8, 127.4, 128.1, 128.6, 129.8, 130.0, 135.1, 139.3, 140.5. MS ESI (methanol): m/z = 571.2 (M + H)$^+$; when Ag(I) nitrate was added to the ligand sample the ESI (methanol–acetonitrile) spectrum also yielded a peak at m/z = 679.3 corresponding to (M + Ag)$^+$. *Synthesis of* [Ag(**2**)]PF_6·0.5CH_3CN: $AgPF_6$ (53 mg, 0.21 mmol) in acetonitrile (4 ml) was added to **2** (118 mg, 0.21 mmol) in dichloromethane (2 ml). Diethyl ether vapour was slowly diffused into this solution to yield needle-like crystals which were filtered off and washed with diethyl ether. These crystals were crushed and dried under vacuum before microanalysis. (143 mg, 84%). Mp 126–128 °C. MS (ESI): m/z = 679.3 (M + Ag)$^+$ (Found: C, 49.84; H, 4.98; N, 4.03%. $C_{34}H_{38}AgF_6N_2PS_3$·0.5CH_3CN requires C, 49.80; H, 4.72; N, 4.15%). ^{1}H NMR (CD_3CN) δ 2.63–2.69, m, 4H, SCH_2CH_2N, 2.95–3.00, m, 4H, SCH_2CH_2N, 3.36, s, 4H, SCH_2CH_2S, 3.66, s, 4H, $C_6H_5CH_2$, 3.70, s, 4H, $C_6H_4CH_2$, 7.19–7.50, m, 18H, aromatic. ^{13}C NMR (CD_3CN) δ 27.16, 30.04, 51.24, 56.49, 57.76, 124.98, 125.92, 127.86, 128.40, 129.21, 130.24, 131.94, 133.42, 134.27, 135.77. Crystals of X-ray quality were obtained on slow evaporation of an acetonitrile solution of the above product.

¶ *X-Ray structure determination*: [Ag**2**]PF_6·MeCN. Formula $C_{36}H_{41}AgF_6N_3PS_3$, *M* 864.74, Monoclinic, space group $P2_1/c$ (#14), *a* 9.1249(14) Å, *b* 24.720(4) Å, *c* 16.670(3) Å, β 101.913(3), *V* 3679.3(10) Å, D_c 1.561 g cm^{-3}, *Z* 4, crystal size 0.348 × 0.158 × 0.120 mm, colourless, prism, temperature; 150(2) K, λ(MoKα) 0.71073 Å, μ(MoKα) 0.823 mm^{-1}, T(SADABS)$_{min,max}$ 0.777, 0.906, 2θ = 56.64°, *hkl* range −12 12, −32 32, −22 21, *N* 36352, N_{ind} 8880(R_{merge} 0.0501), N_{obs} 6610($I > 2\sigma(I)$), N_{var} 452, residuals* $R1(F)$ 0.0383, $wR2(F^2)$ 0.0894, GoF(all) 1.016, $\Delta_{min,max}$ −0.314, 0.608 e$^-$ Å^{-3}. *$R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$ all reflections $w = 1/[\sigma2(F_o^2)+(0.0406P)^2 + 1.5802P]$ where $P = (F_o^2 + 2F_c^2)/3$. CCDC reference number 616061. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613636m

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