

Synthesis, Solution Stability, and Crystal Structure of Aza-thia Macrocyclic Complexes of Silver(I)

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The synthesis of the [18]-N₄S₂ coronand is reported with the crystal structure of the silver complex and determinations of complex stability in both methanol and water.

During the course of studies directed towards the synthesis of kinetically inert silver(I) complexes, a series of mixed donor [18]-ring coronands have been compared. A motivation for this work was the desire to find a ligand which bound silver(I) sufficiently quickly (≤ 2 h) in aqueous media (pH 4–7, 298–310 K) to yield a complex that was stable with respect to silver loss *in vivo* permitting its use in ¹¹¹Ag-based radioimmunotherapy ($t_{1/2} = 179$ h, mean range in tissue = 1.1 mm, max energy = 1.04 MeV). Although considerable progress has been made with other metallic therapeutic radioisotopes, notably ⁶⁷Cu (ref. 1) and ⁹⁰Y,² there are no reports of complexes of silver(I) which possess sufficient stability with respect to acid, or metal-catalysed dissociation to permit their use *in vivo*. Earlier studies have defined the binding abilities of [18]-N₂S₄,³ N₂O₄,⁴ S₂O₄,⁵ and N₄O₂⁶ for certain transition metal ions including silver(I) (except for N₄O₂). Given the enthalpic donor atom preference of silver for S > NH > O, and bearing in mind the unfavourable entropy of complexation introduced by incorporation of a sulphur atom into macrocyclic ligands,⁷ the [18]-N₄S₂ system has been examined.

Reaction of ethylenediamine with thiodiglycolic anhydride in CH₂Cl₂ followed by esterification (EtOH/HCl) yielded the diamide (2) (m.p. 93–94 °C, 27%). Condensation with ammonia in ethanol gave the tetra-amide (3) (m.p. 186–

Table 1. Thermodynamic parameters for silver complexes of [18]-monocycles (298 K, MeOH).

Ligand	log K_s /mol ⁻¹ dm ³	–ΔH/kJ mol ⁻¹	TΔS/kJ mol ⁻¹
(1a) N ₄ S ₂	14.1	77.0	+3.3
(1b) N ₄ S ₂ Me ₄	14.6	102.1	–18.7
(6a) N ₄ O ₂	11.2	—	—
(6b) N ₄ O ₂ Me ₄	13.4	84.3	–7.8
(7a) N ₂ O ₄ ^a	10.0	51.4	+5.7
(7b) S ₂ O ₄ ^a	10.3	64.0	–5.3
(7c) O ₆ ^b	4.6	38.3	–12.1
(8) N ₂ S ₄ ^a	13.7	83.2	–5.0

^a Data from ref. 11. ^b Data from ref. 12. ^c Errors on log K are typically (±0.1) or less, and for ΔH ±0.3 kJ mol⁻¹, or less.

Table 2. Protonation constants for the ligands and binding constants for silver complexes of (1)^a (298 K, H₂O, *I* = 0.1 NMe₄NO₃).

Ligand	pK ₁	pK ₂	pK ₃	pK ₄	log K _{AgL}	log K _{AgLH}	log K _{AgLH₂}	log K _{AgLH₃}
(1a)	9.26	8.45	5.81	4.88	10.4 (7.91)	9.05 (5.40)	6.00 (3.94)	4.13
(1b)	8.82	8.35	4.13	3.71	9.47 (7.41)	8.06 (4.60)	4.31	

^a Values in parentheses refer to protonation constants of the complexes (± 0.10). ^b pH-metric data were analysed by SCOGS-2 and SUPERQUAD.

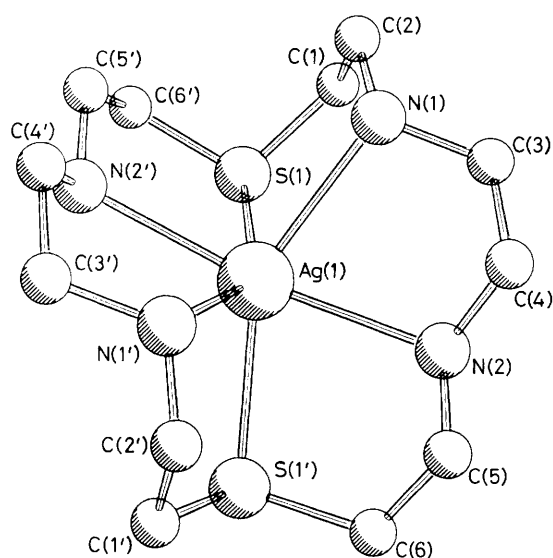


Figure 1. Structure of [(1a)·Ag]⁺ in the crystal. Selected bond lengths (Å) and bond angles (°): Ag–S(1) = 2.658(5), Ag–N(1) = 2.589(10), Ag–N(2) = 2.553(11); S(1)–Ag–N(1) 75.9(3), S(1)–Ag–N(2) 113.2, S(1)–Ag–S(1') 124.5(2), N(1)–Ag–N(1') 104.3(4), N(2)–Ag–N(2') 164.3(5).

187 °C, 76%) and reduction with BH₃·THF (THF = tetrahydrofuran) afforded the tetra-amine (4) as a colourless oil (71%). Tosylation [TsCl/py (Ts = OSO₂C₆H₄Me-*p*)] yielded the tetra-tosylamide (5) (m.p. 131–133 °C, 56%) and co-cyclisation with 1,2-bis(toluene-*p*-sulphonato)ethane in dimethylformamide (DMF) in the presence of Cs₂CO₃ gave the cycle (1c) (m.p. 254–6 °C, 62%). Detosylation under reductive conditions (Li/NH₃/THF–MeOH) permitted the isolation of the tetra-amine (1a) (m.p. 88–9 °C, 64%) and Eschweiler–Clarke methylation gave the corresponding tertiary amine (1b) (m.p. 43–44 °C, 56%).

Admixture of (1a) and silver nitrate (1:1 in MeOH) followed by addition of NH₄PF₆ led to isolation of the colourless crystalline complex (following slow solvent evaporation). The crystal structure[†] revealed that the complex possessed crystallographically imposed C₂ symmetry with the silver cation lying on the symmetry axis. The silver ion is hexaco-ordinated by the N₄S₂ donor atoms in a distorted octahedral geometry (Figure 1). The pair of ligands which are

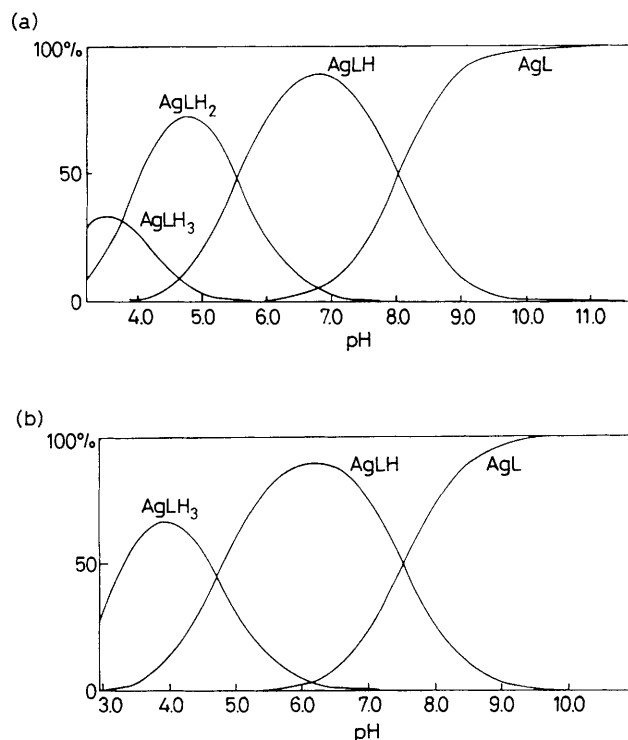
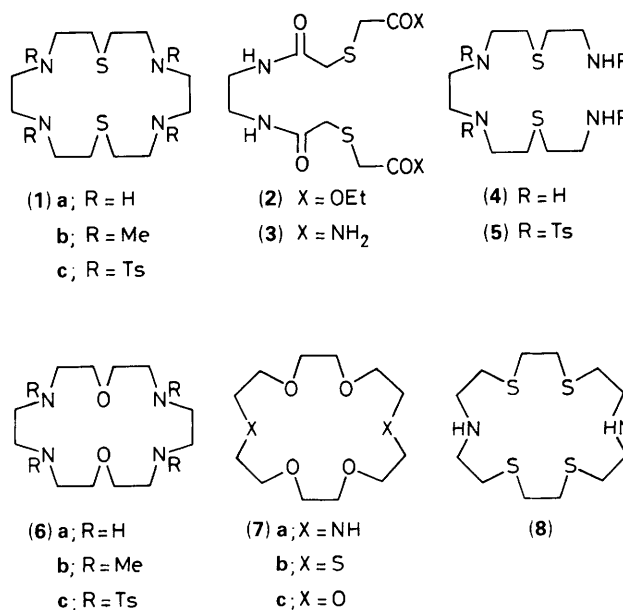


Figure 2. Species distribution plots for (a) [(1a)·AgH_n] and (b) [(1b)·AgH_n] (lower).



[†] Crystal data for [C₁₂H₂₈N₄S₂Ag]⁺PF₆[−]: orthorhombic, *Pbcn*, *a* = 10.859(22), *b* = 20.247(26), *c* = 9.742(10) Å, *U* = 2142(6) Å³, *D_c* = 1.691 g cm^{−3}, *Z* = 4, *F*(000) = 1103.8, μ(Mo-*K*_α) = 12.46 cm^{−1}. Refinement converged at *R* = 0.072, with evidence of some disorder in the PF₆ counterion. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

most nearly trans-disposed are the C_2 -related nitrogen atoms N(2) and N(2') at 164.3(5)°. Considering these atoms as the axial sites, S(1) and N(1') are displaced below the equatorial plane by 0.68 and 0.82 Å respectively with their C_2 -related counterparts displaced equally above this plane. Surprisingly, none of the secondary amines participate in any hydrogen bonding to either cation or anion: the shortest contact is from N(1)–H(1) to F(3) of a symmetry related PF_6^- anion [N(1) $\cdots$ F(3) = 3.32; H(1) $\cdots$ F(3) = 2.40 Å]. There are very few reports of structural determinations of silver complexes of [18]-ring coronands. A dimeric complex with the pyridine– NS_2O_3 cycle has been reported⁸ and the silver complex of [18]- S_6 has been defined,⁹ with two short (2.666 Å) and four longer (2.781 Å) silver–sulphur bonds.

The enthalpy of complexation of (1a), (1b), (6a), and (6b)‡ was measured by calorimetric methods in anhydrous MeOH, and stability constants were determined potentiometrically,¹⁰ thereby permitting calculation of the entropy of complexation. Values are given in Table 1 and a comparison has been made with values measured, by similar methods, in previous work with other [18]-ring mixed donor coronands.¹¹ Certain trends are apparent; sulphur donors in the ring give rise to favourable enthalpies of complexation but this is offset by the unfavourable entropy change [via (1a) vs. (6a); (7a) vs. (7b); (7a) vs. (8); (1b) vs. (6b)]. This phenomenon is associated with the propensity of sulphur lone pairs in the free ligand to adopt exodentate conformations⁷ in the free ligand and hence an unfavourable conformational re-ordering is necessary prior to metal ion complexation. *N*-Methylation leads to enhanced enthalpies of complexation [NMe vs. NH: (1a) vs. (1b)] but markedly unfavourable entropies of complexation. Evidently for [(1b)·Ag]⁺ in order to minimise non-bonding N–Me/–N–Me interactions, the ring has deformed into a markedly different conformation from that of the free ligand.

The protonation and silver complexation equilibria for (1a) and (1b) have also been studied in aqueous solution (198 K, *I* = 0.1 NMe₄NO₃) using pH-metric methods (Table 2). The protonated silver complexes have good stabilities compared to the parent complex, because loss of one nitrogen binding site does not greatly impair silver complexation. Such a situation

may be contrasted with the more dramatic loss of binding that occurs on protonation of silver complexes of poly-aza cryptands.¹³ Species distribution plots as a function of pH are given (Figure 2): it is evident that at pH < 5, dissociation of silver will occur indicating that these silver complexes will not be sufficiently stable *in vivo* for any practical use. It remains a considerable challenge to devise a silver-ligand system that possesses sufficient stability at low pH to minimise decomplexation, yet may be formed quickly (≤ 2 h) under ambient physiological conditions.

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‡ The coronand (6a) was prepared by co-cyclisation of ethylenediamine ditosylamide with 3-oxa-1,5-bis(toluene-*p*-sulphanato)pentane (DMF, Cs₂CO₃), (20%), followed by detosylation (HBr, AcOH, PhOH).