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

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The synthesis of the [18]-N_4S_2 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 [111]Ag-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 [67]Cu (ref. 1) and ^{90}Y,[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]-N_2S_4,[3] N_2O_4,[4] S_2O_4,[5] and N_4O_2 [6] for certain transition metal ions including silver(I) (except for N_4O_2). 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]-N_4S_2 system has been examined.

Reaction of ethylenediamine with thiodiglycollic anhydride in CH_2Cl_2 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	$-\Delta H$/kJ mol^{-1}	$T\Delta S$/kJ mol^{-1}
(**1a**) N_4S_2	14.1	77.0	+3.3
(**1b**) $N_4S_2Me_4$	14.6	102.1	−18.7
(**6a**) N_4O_2	11.2	—	—
(**6b**) $N_4O_2Me_4$	13.4	84.3	−7.8
(**7a**) N_2O_4[a]	10.0	51.4	+5.7
(**7b**) S_2O_4[a]	10.3	64.0	−5.3
(**7c**) O_6[b]	4.6	38.3	−12.1
(**8**) N_2S_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, H$_2$O, I = 0.1 NMe$_4$NO$_3$).

Ligand	pK_1	pK_2	pK_3	pK_4	log K_{AgL}	log K_{AgLH}	log K_{AgLH_2}	log K_{AgLH_3}
(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 ($\pm$0.10). [b] pH-metric data were analysed by SCOGS-2 and SUPERQUAD.
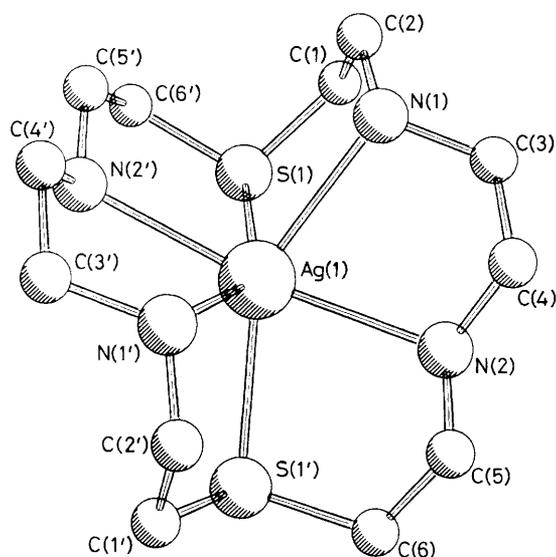

Figure 1. Structure of [(1a)·Ag]$^+$ in the crystal. Selected bond lengths (Å) and bond angles (°): Ag–S(1) = 2.658(5), Ag–N(1) = 2.589(10), Ag–N(2) = 2.553(11); S(1)–Ag–N(1) 75.9(3), S(1)–Ag–N(2) 113.2, S(1)–Ag–S(1′) 124.5(2), N(1)–Ag–N(1′) 104.3(4), N(2)–Ag–N(2′) 164.3(5).

187 °C, 76%) and reduction with BH$_3$·THF (THF = tetra-hydrofuran) afforded the tetra-amine (4) as a colourless oil (71%). Tosylation [TsCl/py (Ts = OSO$_2$C$_6$H$_4$Me-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 Cs$_2$CO$_3$ gave the cycle (1c) (m.p. 254—6 °C, 62%). Detosylation under reductive conditions (Li/NH$_3$/THF–MeOH) permitted the isolation of the tetra-amine (1a) (m.p. 88—9 °C, 64%) and Eschweiler–Clarke methylation gave the corresponding ter-tiary amine (1b) (m.p. 43—44 °C, 56%).

Admixture of (1a) and silver nitrate (1:1 in MeOH) followed by addition of NH$_4$PF$_6$ led to isolation of the colourless crystalline complex (following slow solvent evapor-ation). The crystal structure† revealed that the complex possessed crystallographically imposed C_2 symmetry with the silver cation lying on the symmetry axis. The silver ion is hexaco-ordinated by the N$_4$S$_2$ donor atoms in a distorted octahedral geometry (Figure 1). The pair of ligands which are

(a)

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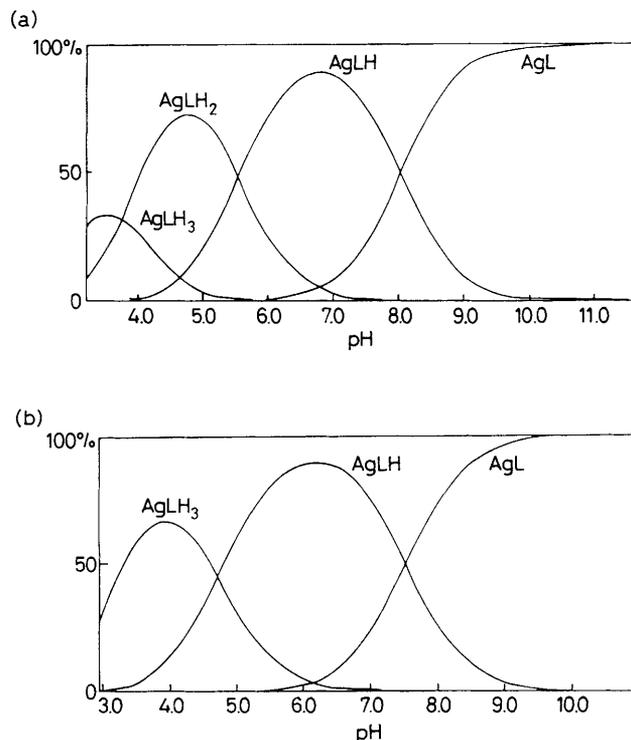
Figure 2. Species distribution plots for (a) [(1a)·AgH$_n$] and (b) [(1b)·AgH$_n$] (lower).

(1) a; R = H
b; R = Me
c; R = Ts

(2) X = OEt
(3) X = NH$_2$

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

(6) a; R = H
b; R = Me
c; R = Ts

(7) a; X = NH
b; X = S
c; X = O

(8)
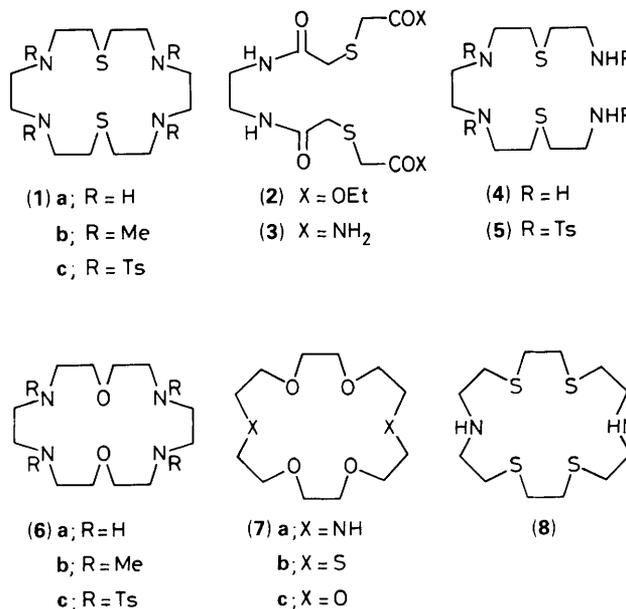
most nearly trans-disposed are the C_2-related nitrogen atoms N(2) and N(2') at 164.3(5)°. Considering these atoms as the axial sites, S(1) and N(1') are displaced below the equatorial plane by 0.68 and 0.82 Å respectively with their C_2-related counterparts displaced equally above this plane. Surprisingly, 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 reported[8] 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 conformations[7] 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 NMe_4NO_3) 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, Cs_2CO_3), (20%), followed by detosylation (HBr, AcOH, PhOH).