Unexpected polymeric string formation between Ag(I) and a homoleptic thioether cage: synthesis and crystal structure of [R,R′-S$_6$tricosane] and {[Ag(R,R′-S$_6$hexacosane)]TsO}$_\infty$

Roger Alberto,*[a] Daniela Angst,[a] Ulrich Abram,[b] Kirstin Ortner,[b] Thomas A. Kaden[c] and August P. Schubiger[a]

[a] *Center for Radiopharmacy, Paul Scherrer Institute, CH-5232 Villigen, Switzerland. E-mail: ariel@aci.unizh.ch*
[b] *Forschungszentrum Rossendorf, Institute of Radiochemistry, D-01062 Dresden, Germany*
[c] *Department of Inorganic Chemistry, University of Basel, CH-5067 Basel, Switzerland*

Received (in Basel, Switzerland) 29th April 1999, Accepted 13th June 1999

The large cavity homoleptic thioether cages [R,R′-S$_6$tricosane] (1-hydroxymethyl-9-methyl-3,7,11,15,18,22-hexathiabicyclo[7.7.7]tricosane) (1) and [R,R’-S$_6$hexacosane] (1-hydroxymethyl-10-methyl-3,8,12,17,20,25-hexathiabicyclo-[8.8.8]hexacosane) (2) have been synthesized and the structures of 1 and of the complex {[Ag(2)]TsO}$_\infty$ have been elucidated, the latter showing a polymeric string structure with Ag$^+$ coordinated by three different cages.

The radionuclide ^{111}Ag has excellent decay properties for applications in radioimmunotherapy.[1] For applications of the labile Ag(I) in organisms, this metal center has to be efficiently shielded in order to prevent transchelation from cancer specific antibodies to serum proteins. For this purpose, a number of thia- and thia-aza macrocycles of various ring size providing high selectivity and/or stability have been prepared for Ag(I).[2–6] However, although the corresponding silver complexes are of relatively high thermodynamic stability,[7] Ag(I) was found to transchelate rapidly to other coordinating sites in serum. Ligand exchange at d^{10} metal centers often occurs *via* an associative or interchange associative mechanism.[8] Only efficient shielding of Ag$^+$ might allow the protection of Ag(I) against incoming ligands. We therefore prepared thio-cages with large cavities in order to encapsulate Ag$^+$ and to profit from the well known high kinetic stability of the corresponding metal complexes.[9]

Although a number of homoleptic thio-cages have been published, their coordination chemistry is far less well investigated than that of their aza- or thia-aza-homologues. The only structurally characterized inclusion complex of a homoleptic thio-cage is that of Co(II) and ligand **4**. Additionally, a similar structure of the Co(III) complex with ligand **3** has been concluded from ^{1}H NMR measurements.[10,11] We have prepared the two cages **1** and **2** by a novel route and investigated their coordination chemistry with Ag(I) (Scheme 1).

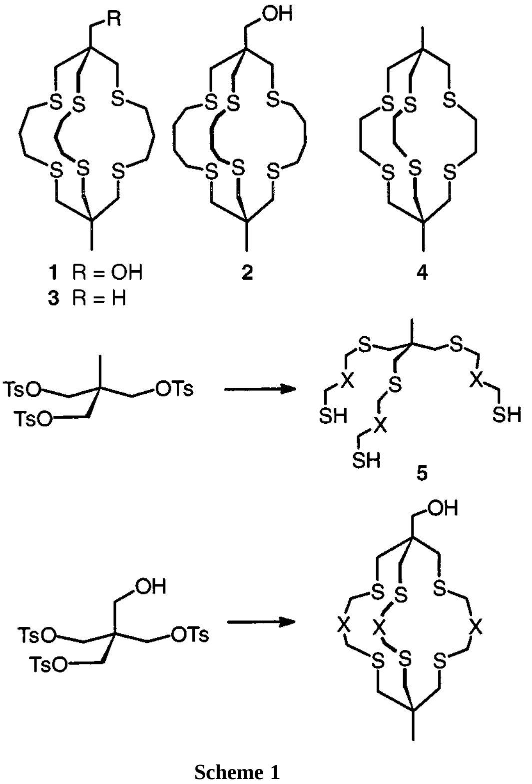
The syntheses presented here are principally different from published methods but also involve adaption of the conventional synthesis for macrocyclic thioethers with a Cs$_2$CO$_3$ mediated ring closure step.[11] The -SH groups are located on the larger fragment of the [1+1] bicyclisation, whereas the leaving groups are on the small cap. The yields for such bicyclisations are relatively high and reach up to 30%. The hydroxymethyl groups have been attached to allow subsequent covalent binding of **1** or **2** to proteins. Ligand **3** was prepared according to the same procedure. Reaction yield, rate of formation and behaviour of **3** are very similar to **1**. ^{1}H NMR data of **3** are in full agreement with the published ones.[10]

Structure optimization of **1** by simple molecular modelling calculations predicts a structure with predominant *exo*-orientation of the lone pairs which is confirmed by the X-ray structure of **1** (Fig. 1).[12]

The structure of **3** was determined as well. The basic framework of the two ligands is essentially the same, showing that the influence of the functional group is negligible in regard to the orientation of the lone pairs.

Although no X-ray structure of a metal complex with **1** has been described to date, the ^{1}H NMR spectrum of the Co(III) complex of **3** clearly shows the metal center to be encapsulated.[13] Since Co(III) forms highly inert complexes, rapid transchelation between different donors, resulting in a fully symmetrical ^{1}H NMR spectrum, can be excluded (even on the NMR timescale). Thus, **1** and **3** are able to reorganize their conformation from *exo*- to *endo*-sulfur lone-pairs, as required for inclusion of the metal. Obviously, the relatively small Co(II) ion is able to penetrate a 16-membered ring of **1** and to coordinate additionally to the sulfur atoms of the bicyclic backbone (oxidation to Co(III) was done after inclusion). The highly symmetrical ^{1}H NMR spectrum rationalizes an octahedral coordination geometry.

Ag(I) is much larger than Co(II) (ionic radii 129 *vs*. 89 pm) and probably not able to penetrate the formal 16-membered ring in **1**. This assumption is supported by the X-ray structure of the Ag(I) complex with [16]aneS$_4$ recently published.[14] This ligand coordinates only through one sulfur to Ag(I) resulting in a three dimensional polymer. In contrast, the X-ray structure analysis of [Ag([18]aneS$_6$)]$^+$ clearly demonstrated that, when the ring is enlarged, the Ag$^+$ can slip inside and the ligand wraps around it.[15]



Scheme 1

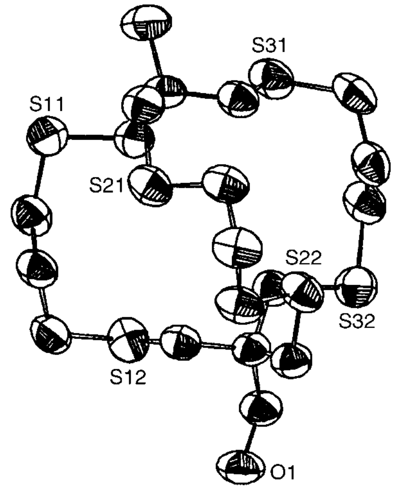


Fig. 1 ORTEP plot of (1-hydroxymethyl-9-methyl-3,7,11,15,18,22-hexathiabicyclo[7.7.7]tricosane) (**1**).

We have enlarged the propylene backbone in **1** to butylene in **2**. Molecular modelling calculations gave a reasonable coordination geometry for [Ag(**2**)]$^+$ without significant steric interactions between hydrogen atoms from the backbone or from the cap. The ^{1}H NMR of **2** shows 6 signals. Complexation with different Ag$^+$ salts shifts the resonances by about 0.1 ppm towards lower field but leaves the pattern unchanged. The exhibition of 6 different H's indicates either an inclusion of the metal ion (pseudo-symmetry retained) or a fast fluxionality between different coordination sites.

Several modes of external coordination can be expected, *i.e.* by one, two, three or four sulfur atoms from one ring in the bicyclic ligand which is known in the literature for tridentate thio crowns where Ag$^+$ is found to bind at least to two different macrocycles.[16] X-Ray structure analysis exhibits an unexpected polymeric string structure (Fig. 2). Three cages are coordinated to one Ag(I) center by one thioether ligand atom. Thus, each cage is coordinated to three Ag$^+$ atoms. The distorted tetrahedral geometry around the Ag$^+$ center is completed by the coordination of one counter-ion (tosylate).[17] The highly symmetrical ^{1}H NMR spectrum thus comes from a fast exchange between the different coordinating sites.

Monodentate coordination only is unexpected. Analysis of the solid state structure of **1** or calculated models of **2** reveals that preorganization could favour bidentate external coordination by two sulfur atoms from two different backbones under formation of a six-membered chelate in **1** or in **2**. Six-membered chelates with Ag(I) and sulfur are disfavoured compared to five-membered rings.[18] Indeed, the Cambridge Crystallographic Database does not contain any Ag(I) complex with a six-membered thioether chelate. However, a number of crown thioethers with propylene backbones were found to coordinate in a monodentate fashion to Ag(I) resulting in comparable polymeric structures as in [Ag(**2**)]$^+$.[5,14,16]

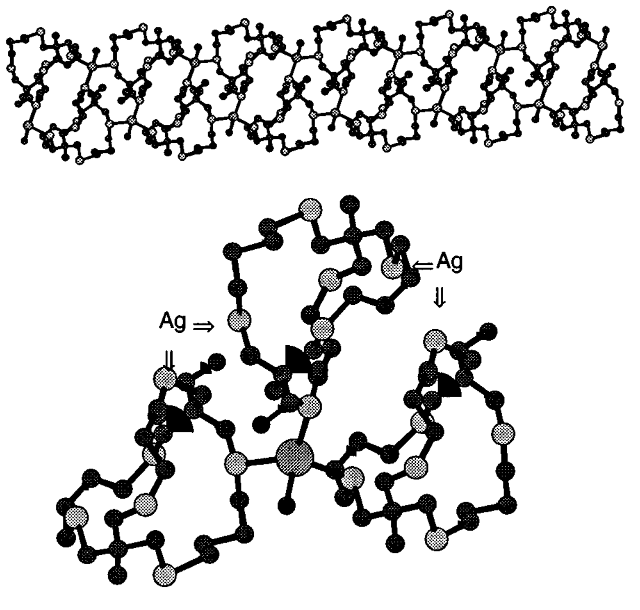


Fig. 2 Part of the polymeric string structure of {[Ag(**2**)]TsO}$_\infty$. The coordinated tosylate anions are omitted for clarity (above). Excerpt of the structure, depicting three cages coordinated to one Ag$^+$ (below).

To exclude the possibility that the product is a kinetic intermediate and to overcome high reorganization energies for the encapsulation, we exposed [Ag(**2**)]$^+$ to ultrasound or microwave heating. In neither case was it possible to obtain a 1:1 complex of Ag$^+$ encapsulated in cage **2**.

In the case of radioactive ^{111}Ag, where the metal concentrations are extremly low, similar behaviour was not observed. Chromatographic investigations (the only possible analytical method) exhibits only free ^{111}Ag$^+$, demonstrating the low ability of a monodentate thioether to compete with coordinating solvents.

Although thio-cages can kinetically stabilise labile metal centers, their coordination chemistry, in particular with late transition metals, is not routine. The steric requirements and the electronic properties of a metal center demand a perfectly tailored framework of backbones and donor atoms.

Notes and references

1 P. A. Schubiger, R. Alberto and A. Smith, *Bioconjugate Chem.*, 1996, **7**, 165.
2 T. Gyr, H. R. Mäcke and M. Hennig, *Angew. Chem., Int. Ed. Engl.*, 1997, **109**, 2869.
3 R. Alberto, W. Nef, A. Smith, Th. A. Kaden, M. Neuburger, M. Zehnder, A. Frey, U. Abram and P. A. Schubiger, *Inorg. Chem.*, 1996, **11**, 3420.
4 J. A. R. Hartman, E. J. Hintsa and S. R. Cooper, *J. Chem. Soc., Chem. Commun.*, 1984, 386.
5 A. J. Blake and M. Schröder, *Adv. Inorg. Chem.*, 1990, **35**, 1 and references cited therein.
6 A. J. Blake, M. A. Halcrow and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1992, 2803.
7 L. D. Pettit and H. K. J. Powell, *IUPAC Stability Constants Database*, Academic Software, 1994.
8 H. Diebler, *Pure Appl. Chem.*, 1969, **20**, 93.
9 B. Dietrich, J. M. Lehn and J. P. Sauvage, *J. Chem. Soc., Chem. Commun.*, 1970, 1055; L. R. Gahan, T. W. Hambley, A. M. Sargeson and M. R. Snow, *Inorg. Chem.*, 1982, **21**, 2699; A. M. Sargeson, *Pure Appl. Chem.*, 1986, **58**, 1511 and references cited therein.
10 P. Osvath and A. M. Sargeson, *J. Chem. Soc., Chem. Commun.*, 1993, 40.
11 J. Bute and R. M. Kellog, *J. Org. Chem.*, 1981, **46**, 4481; R. E. Wolf Jr., J. R. Hartman, L. A. Ochrymowycz and S. R. Cooper, *Inorg. Synth.*, 1989, **25**, 122.
12 *Crystal data* for **1**: $C_{19}H_{36}OS_6$, MW = 472.84, colourless plates, monoclinic, $P2_1/c$, a = 18.186(4), b = 26.587(4), c = 10.255(2) Å, β = 101.16(1)° , V = 4864(1) Å^3, Z = 8, 9737 reflections, 5657 with $F > 2\sigma(F)$ used for refinement: R = 0.0553, wR_2 = 0.1381.
13 P. Osvath, A. M. Sargeson, B. W. Skelton and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1991, 1036.
14 A. J. Blake, W.-S. Li, V. Lippolis and M. Schröder, *Chem. Commun.*, 1997, 1943.
15 A. J. Blake, R. O. Gould, A. J. Holder, T. I. Hyde and M. Schröder, *Polyhedron*, 1989, **4**, 513.
16 H.-J. Küppers, K. Wieghardt, Y.-H. Tsay, C. Krüger, B. Nuber and J. Weiss, *Angew. Chem., Int. Ed. Engl.*, 1987, **6**, 575; P. J. Blower, J. A. Clarkson, S. C. Rawle, J. R. Hartman, R. E. Wolf, R. Yagbasan, S. G. Bott and S. R. Cooper, *Inorg. Chem.*, 1989, **28**, 4040.
17 *Crystal data* for **2**: $C_{29}H_{49}AgO_4S_7$, MW = 793.97, monoclinic, $P2_1/c$, a = 10.707(4), b = 17.737(4), c = 19.081(8) Å, β = 103.61(2)°, V = 3522(2) Å^3, Z = 4, μ(Mo-Kα) = 0.1020 cm^{-1}, 5807 reflections, 1661 with $F > 2\sigma(F)$ used for refinement: R = 0.0695, wR_2 = 0.0671. CCDC 182/1329. See http://www.rsc.org.suppdata/cc/1999/1513/ for crystallographic data in .cif format.
18 R. E. Wolf Jr., J. R. Hartman, J. M. E. Storey, B. M. Foxman and S. R. Cooper, *J. Am. Chem. Soc.*, 1987, **109**, 4328.

Communication 9/03455B