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Central *vs.* peripheral Ag(I) coordination in NS_3-open chain and cage ligands

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A series of NS_3-open chain and cage ligands were synthesised and their complexation behaviour towards Ag(I) and Cu(I) studied. Crystal structures show that all open chain ligands form complexes in which the four donor atoms of the ligands coordinate the metal ions in a trigonal pyramidal geometry. For the NS_3-cages, however, the ions are not in the centre of the cage, but show peripheral coordination resulting in polymeric crystal structures. The new NS_3-aromatic cage ligand **18** binds Ag(I) peripherally giving a polymeric structure in the solid state and fluxional behaviour in solution. NMR evidence for equally populated central and peripheral coordination sites is coherent with results from DFT calculations.

Introduction

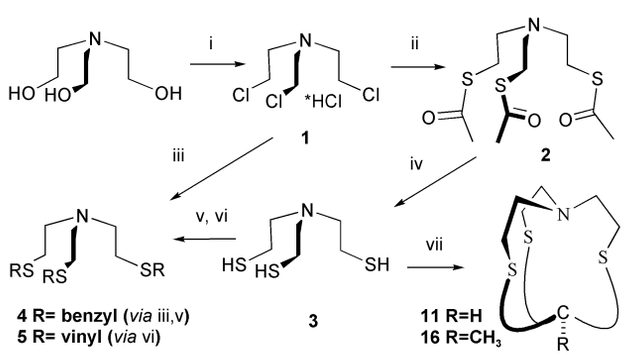
We have previously reported on Ag(I) coordination chemistry of macrocyclic and macrobicyclic ligands.[1–3] Our continuing efforts to synthesise tailor made Ag(I) chelators was induced by the radiation properties of the radioisotope ^{111}Ag. Its decay characteristics such as half life time and type/energy of decay predestine it for applications in radioimmunotherapy.[4] On the other hand, the coordination chemistry of this labile metal ion is difficult to predict. The applicability of ^{111}Ag in biological systems relies to a large extent on the possibility of efficiently encapsulating Ag(I) in very potent ligands. This should prevent the labile Ag(I)-ion from performing transmetallations in the organism. The required encapsulation of coordinated Ag(I) can be achieved *via* complexation by a tight-fit, tailor-made cage ligand. Among the most potent chelators for metal complexation macrocycles and macrobicycles usually outperform open chain ligands by what can be summarized as chelate or cryptate effect. One aspect thereof is the preorganisation of the donor atoms in the ligands scaffold. The majority of stable Ag(I) complexes exhibit a tetradentate coordination sphere, which in most cases is build up by ethylene-bridged donors.[5] Investigations of hexadentate S_6-ligands and their Ag(I) complexes synthesised in our group[2] are in accordance to these findings from literature. Yet, those hexadentate thioether cages and macrocycles have been found to be unfavourable either due to steric restraints in the former and/or a strong preference for tetradentate coordination of Ag(I) in the latter case.[3] This knowledge and the need for chelators that are at least slightly water-soluble led to the development of a series of novel NS_3-compounds.

Recently, Ambundo *et al.* introduced an open chain tetradentate tripodal ligand based on a NS_3 donor set for the complexation of Cu(I).[6] An analogous compound has been described earlier for Cu(II) by Suzuki *et al.*[7] and for Tc(III) by Spies *et al.*[8] Their coordinating properties towards Ag(I) had not been investigated so far, but we expected a comparable coordination chemistry with Ag(I), a higher homologue of Cu(I). In a first section, we present herein several open chain ligands and cage compounds bearing this ethylene-bridged NS_3-moiety. We report on the crystal structure of a mononuclear cationic Ag(I) complex with an extraordinarily flexible open chain ligand and compare it with the related Cu(I) complex. As to approach more potent ligands, we performed DFT calculations on model compounds and followed conclusions of analogy on literature NS_3-ligands.[6–8] This resulted in the synthesis of a novel NS_3-metacyclophane and the investigation of its coordinating properties towards Ag(I), which are presented in a second section of this article.

Results and discussion

NS_3-open chain ligands and NS_3-alkyl cages

Potential starting materials are readily available from triethanolamine. Open chain compounds were synthesised starting from tris(2-chloroethyl)amine hydrochloride[9] **1** (**Caution!** This compound is a strong vesicant! It should only be handled in a hood. Wear protective garments!). General synthetic routes to various ligands described in this paper are given in Scheme 1. Tris(2-benzylsulfanyl-ethyl)amine **4** is isolated from the reaction of **1** and benzyl mercaptane in sodium ethanolate solution



Scheme 1 *Reagents and conditions:* i, $SOCl_2$; ii, $KSCOCH_3$; iii, $C_6H_5CH_2SH$, DMF, Na_2CO_3; iv, $LiAlH_4$, THF; v, $C_6H_5CH_2Cl$, DMF, Na_2CO_3; vi, KOH/DMSO, C_2H_2; vii $RC(CH_2CH_2Cl)_3$, DMF, Cs_2CO_3.

in almost quantitative yield. Alternatively, it is synthesised by reacting tris(2-mercaptoethyl)amine[8] **3** and benzyl chloride in the presence of sodium carbonate.

Together with Cu(I)- or Ag(I)-salts **4** forms white, crystalline solids. ^{1}H-NMR spectra of these compounds indicated symmetrical coordination modes, not excluding fluxional coordination of the metal ion. By variation of counter ions and recrystallisation from acetone/diethyl ether, we succeeded in growing single crystals suitable for X-ray analysis. The structures of both the Cu(I) (Fig. 1) and Ag(I) (Fig. 2) complexes are

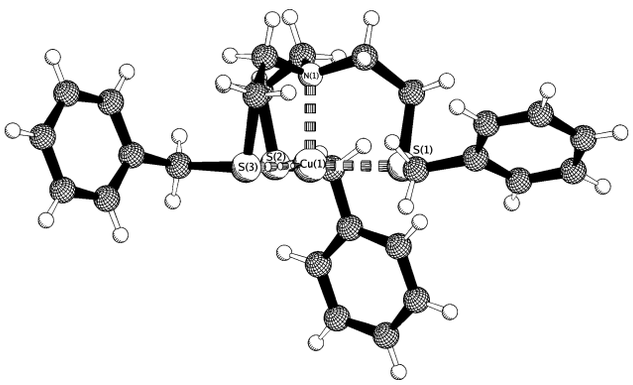


Fig. 1 Crystal structure of [Cu(**4**)]PF_6. The counterion has been omitted for clarity. Selected bond distances (pm) and angles (°): Cu(1)–N(1) 218.8(2), Cu(1)–S(1) 225.61(8), Cu(1)–S(3) 226.92(9), Cu(1)–S(2) 227.01(8); N(1)–Cu(1)–S(1) 90.48(6), N(1)–Cu(1)–S(3) 90.75(7), S(1)–Cu(1)–S(3) 123.45(3), N(1)–Cu(1)–S(2) 90.71(7), S(1)–Cu(1)–S(2) 121.93(3), S(3)–Cu(1)–S(2) 114.58(3).

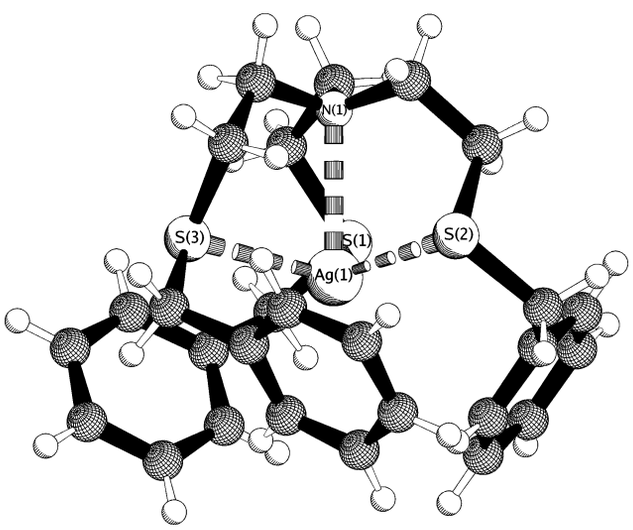


Fig. 2 Crystal structure of [Ag(**4**)]PF_6. The counterion has been omitted for clarity. Selected bond distances (pm) and angles (°): Ag(1)–S(1) 257.37(11), Ag(1)–S(3) 257.97(10), Ag(1)–S(2) 258.58(10), Ag(1)–N(1) 264.21(10); S(1)–Ag(1)–S(3) 113.45(3), S(1)–Ag(1)–S(2) 118.65(3), S(3)–Ag(1)–S(2) 112.32(3), S(1)–Ag(1)–N(1) 77.30(4), S(2)–Ag(1)–N(1) 75.88(2), S(3)–Ag(1)–N(1) 76.71(1).

shown as SCHAKAL plots.[10] The non-coordinating hexafluorophosphate anion is omitted for clarity in both representations. Each metal ion is solely coordinated by one tetradentate NS_3-moiety. A potential coordinative site at the metal centre is left free in the *trans*-position to the nitrogen atom. This site can be occupied by monodentate ligands (*e.g.* tert-butyl isocyanate) resulting in a significant downfield shift of benzylic ^{1}H-NMR-resonances of the Cu(I)-/Ag(I)-bound NS_3-ligand. For Cu(II) complexes this site is usually occupied by additional ligands as reported by Suzuki *et al.*[7]

A shown in Fig. 1, the Cu(I) ion is trigonal-pyramidally coordinated, the complex not being exactly C_3-symmetrical probably due to crystal packaging. A plane is defined by the three sulfur atoms S(1), S(2) and S(3). The copper atom Cu(1) is deflected out of this plane by 3 pm towards the nitrogen atom N(1). Bond lengths are 226 ± 1 pm for all copper–sulfur bonds. Each pair of sulfur atoms forms an angle of 118 ± 4° at the Cu(1) atom. The top of the trigonal pyramid is defined by the nitrogen atom N(1). The bond distance to the metal ion is 219 pm. N(1) forms 90°-angles at Cu(1) with each sulfur atom. A search in the CSD database returned 474 structures with 951 relevant bonds and an average Cu(I)–NR_3 bond length of 210 pm. An average Cu(I)–S bond length of 234 pm is calculated from 89 structures with 280 relevant Cu(I)–S bonds. Compared to these data, the Cu(1)–N(1) bond length of [Cu(**4**)]PF_6 is slightly longer, while Cu(1)–S bond lengths are significantly shorter.

Fig. 2 shows a SCHAKAL plot of the related [Ag(**4**)]PF_6. In contrast to Fig. 1 this representation shows a C_3-symmetrical Ag(I) complex. The Ag(I) ionic radius is 21 pm larger than that for Cu(I). Nevertheless the Ag(I) ion is still complexed due to the flexibility of the open chain ligand. This is reflected in a slight widening of the ligands coordinating cavity. For [Ag(**4**)]-PF_6 sulfur–sulfur distances are 435 pm, while in [Cu(**4**)]PF_6 these donor atoms are only 390 pm apart. The Ag(I) ion is trigonal-pyramidally coordinated with a slight distortion related to the plane defined by the three sulfur atoms S(1), S(2) and S(3). Due to the larger ionic radius the Ag(I) atom is deflected out of this plane by 60 pm, away from the N(1) atom at the top of the trigonal pyramid. The N(1) atom and each sulfur atom hence include angles of 76 ± 1° at Ag(1). The Ag(1)–N(1) bond length is 265 pm. Each of the three sulfur–Ag(1) bonds is 258 pm long. Each pair of sulfur atoms forms an angle of 115 ± 3° at the Ag(1) atom. Again, a search in the CSD database returned 32 structures with 64 relevant bonds and an average Ag(I)–NR_3 bond length of 247 pm. An average Ag(I)–S bond length of 263 pm is calculated from 77 structures with 245 relevant Ag(I)–S bonds. The Ag(1)–N(1) bond is significantly longer than this average. All bonds between Ag(1) and the sulfur atoms compare to the known values. This crystal structure is one of the few with an open chain tetradentate ligand coordinating Ag(I) to form a mononuclear complex. A related tren-derived complex has been reported lately.[11] More complexes are known, that combine tridentate open chain ligands with coordination of the counter ion. In open chain ligands this ethylene-bridged NS_3-building block forms mononuclear Ag(I) complexes even though it provides an environment too narrow to completely encapsulate the Ag(I) atom. The free site in the *trans*-position to the N(1) atom remains the Achilles' heel for applications in radioimmunotherapy. Competing ligands can easily attack at this site leading to transmetallation. ^{1}H-NMR downfield shift of the ligands resonances upon addition of competing ligands (*e.g.* tert-butyl isocyanate) to the complex solution are proof. Anyhow, these results are a strong hint for the excellent suitability of this NS_3-moiety to form well-defined complex compounds of Ag(I).

As discussed previously, cage compounds are expected to form the most stable Ag(I) complexes.[2] So we decided to synthesise small cages to evaluate several building blocks and general routes to cage compounds.

One approach to cage synthesis was to functionalise the open chain NS_3-moiety starting from the trithiol **3**. This functionalised compound could then be subjected to a subsequent ring-closing reaction. Trofimov *et al.* reported a threefold acetylene addition to triethanolamine in a superbasic KOH/DMSO system.[12] Tris(2-vinylsulfanyl)amine **5** was synthesised following an adaptation of this synthesis: acetylene was introduced into a solution of tris(2-mercaptoethyl)amine **3** in KOH/DMSO at 70 °C over 8 h. ^{1}H-NMR signals of both the Cu(I)- and Ag(I)-complexes of this compound imply a coordination as previously observed for **4**. From these experiments we received no evidence for a Ag(I) coordination to the double bond. X-ray analysis of the copper complex confirms this finding. Fig. 3

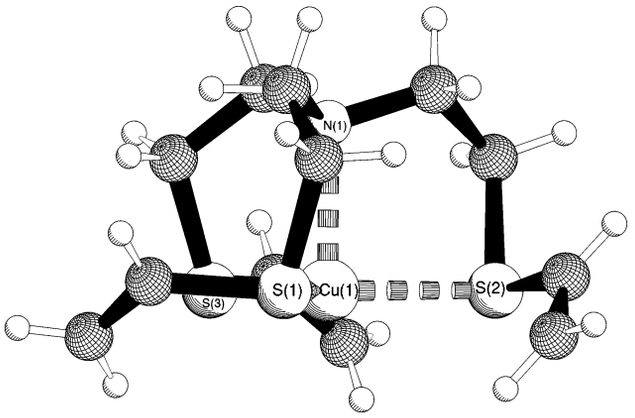
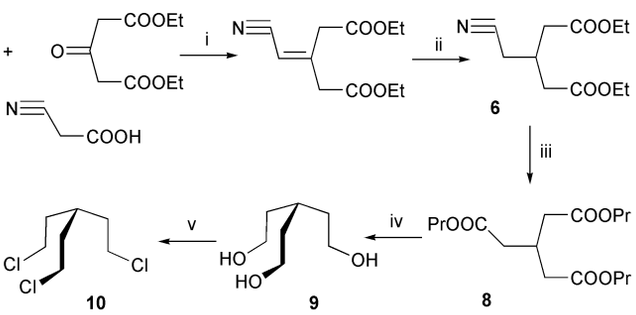


Fig. 3 Crystal structure of [Cu(**5**)]PF_6. The counterion has been omitted for clarity. Selected bond distances (pm) and angles (°): Cu(1)–N(1) 220.6(3), Cu(1)–S(1) 227.30(11), Cu(1)–S(3) 227.38(11), Cu(1)–S(2) 227.52(11); N(1)–Cu(1)–S(1) 90.27(8), N(1)–Cu(1)–S(3) 90.10(8), S(1)–Cu(1)–S(3) 122.10(5), N(1)–Cu(1)–S(2) 89.58(9), S(1)–Cu(1)–S(2) 119.04(4), S(3)-Cu(1)–S(2)118.86(4).

shows a C_3-symmetrical complex with free non-coordinating vinylic double bonds. Bond lengths and angles are similar as reported for [Cu(**4**)]PF_6. It is likely for Ag(I) to have the same coordination mode and to allow template macrocyclisations using these double bonds. Further investigations are underway on this topic and on NS_3-ligands with functionalised phenyl-substituents to form cages.

Cage compounds reported herein were generally synthesised starting from **3** and reacting it with the appropriate alkyl halide under high dilution conditions (Scheme 1). 3-(2-Chloroethyl)-1,5-dichloropentane **10** is a building block previously used in our laboratory for the synthesis of hexadentate thioether cages.[2] We present an improved synthesis of this compound (Scheme 2). Two configuration isomers can evolve from the cyclisation



Scheme 2 *Reagents and conditions:* i, Dean–Stark, toluene, H_2SO_4; ii, Pd/C, H_2; iii, 1. $NaOH_{aq.}$, Δ, 2. propanol, H^+; iv, $LiAlH_4$, THF; v, $SOCl_2$.

reaction of **3** and **10** showing *in*/*out*-isomerism on the bridgehead carbon atom. Besides *in*/*out*-conformation isomers are defined by the position of the free electron pair of the bridgehead amine as described by Alder and East.[13] For purposes of central four-coordinate metal complexation obviously only the *in*-conformation isomers are suitable and referred to throughout this article.

The *in*-isomer has a proton attached to the bridgehead carbon atom pointing into the cage, whereas the bridgehead proton of the *out*-isomer is pointing out of the cage. Isomerisation between both forms is relevant only for cages made of 20-membered rings and larger.[13] Geometry optimisations of both cage isomers were performed on the DFT level using the TURBOMOLE program package.[14] The *in*-isomer was found to be by 40 kJ mol^{-1} lower in energy than the *out*-isomer. Since the final product distribution will nevertheless be kinetically controlled due to irreversible alkylation steps, the energy of activation for this cyclisation step towards the *in*-isomer has to be significantly lower, too. The *in*-isomer is the only reaction product experimentally found. It is obtained in 12% yield by reacting **3** and **10** in DMF with caesium carbonate as base at 55 °C under high dilution conditions. The ^{1}H-NMR signal of the bridgehead proton is shifted to the low-field region of the spectrum. Such a shift can be caused by interaction with the free-electron pair of the bridgehead-amine. This was already a strong hint for having isolated the *in*-isomer. The final proof was given by the crystal structure analysis of the [Ag(**11**)] tosylate. Suitable crystals were grown by overlayering a dilute solution of **11** in acetonitrile with a dilute solution of Ag(I) tosylate in acetonitrile at 5 °C. Colourless crystals appeared at the interface, that were insoluble in most solvents. The insolubility is due to the polymeric crystal structure shown in Fig. 4.

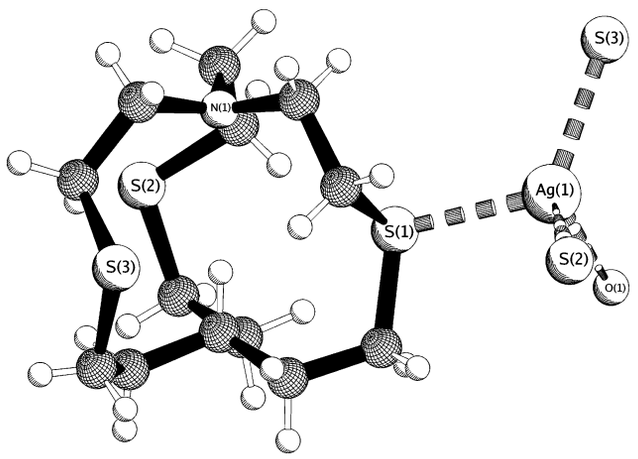
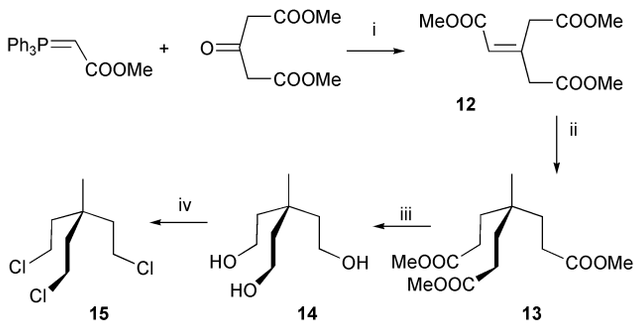


Fig. 4 Extract from the crystal structure of polymeric {[Ag(**11**)]-tosylate}$_\infty$. Except of their coordinating atoms, the counterion and two additional cage ligands have been omitted for clarity. Selected bond distances (pm) and angles (°): Ag(1)–S(1) 253.86(6), Ag(1)–S(3) 255.63(6), Ag(1)–O(1)#1 257.1(4), Ag(1)–S(2)#3 267.76(6); S(1)–Ag(1)–S(3) 118.65(2), S(1)–Ag(1)–O(1)#1 93.70(9), S(3)–Ag(1)–O(1)#1 106.59(9), S(1)–Ag(1)–S(2) 101.724(19), S(3)–Ag(1)–S(2) 118.57(2), O(1)#1–Ag(1)–S(2) 115.26(7). Symmetry transformation used to generate equivalent atoms: #1 $-x+3/2$, $-y$, $z-1/2$.

Each Ag(I) is almost tetrahedrally coordinated by three cages **11** and the counterion. The angles formed by each pair of ligands vary from 94 to 118°. Bond lengths between the Ag(I) atom and the three thioether sulfur atoms are 254 pm. The tosylate oxygen atom is 257 pm apart. This *in*-isomer is unsuitable for central Ag(I) coordination. The cage cavity is occupied by the bridgehead proton leaving no space for the coordination of Ag(I). The *out*-isomer was not accessible through this synthetic pathway and required an alternative synthetic strategy.

A different approach to NS_3 alkyl cages was to sterically overcrowd the bridgehead carbon atom. For steric reasons, the cyclisation step would then necessarily yield the *out*-isomer. We expected a methyl substituent at the bridgehead carbon atom to suit this purpose. A DFT geometry optimisation of both isomers revealed that the *out*-isomer should be significantly lower in energy than its *in*-isomer. The energy difference was calculated to be 110 kJ mol^{-1}.

The preparation of 1,1,1-ethane-triacetonitrile as a precursor of 3-(2-chloroethyl)-1,5-dichloro-3-methylpentane **15** is known in the literature.[15] An expected overall yield of ~1% for this compound is much too low in view of the required amounts of substance for the high-dilution reaction. We had thus to find an alternative synthetic pathway (Scheme 3). The building block 3-(2-chloroethyl)-1,5-dichloro-3-methylpentane **15** was synthesised in several steps from the previously known compound 3-(methoxycarbonyl)-methylpent-2-ene-1,5-dicarboxylic acid-dimethylester **12**.[16] The elementary step is a copper(I)-mediated Grignard addition to the double bond. In analogy to the methyl addition to glutaconic acid dimethyl ester reported



Scheme 3 *Reagents and conditions:* i, C_6H_6, reflux; ii, MeMgI, CuI, TMSCl, Et_2O; iii, $LiAlH_4$, THF; iv, $SOCl_2$.

by Leotta *et al.* in a one-pot reaction, first the enol ester is formed in the presence of TMSCl, Cu(I) and Grignard reagent, then the methyl addition takes place.[17] The yield is low in this step due to the intermediate formation of two enolate esters. After workup, the ester is reduced to 3-(2-hydroxyethyl)-3-methyl-pentane-1,5-diol **14** and reacted to the trichloro building block **15** in 15% overall yield. Starting from building blocks **15** and **3**, the new cage out-7-methyl-4,10,15-trithia-1-azabicyclo[5.5.5]heptadecane **16** was synthesised according to the high-dilution pathway with caesium carbonate as base in DMF at 55 °C. Once again, only one isomer could be isolated from the reaction mixture. A crystal structure analysis of the Ag(I) complex (Fig. 5) confirmed our expectations: the *out*-isomer was

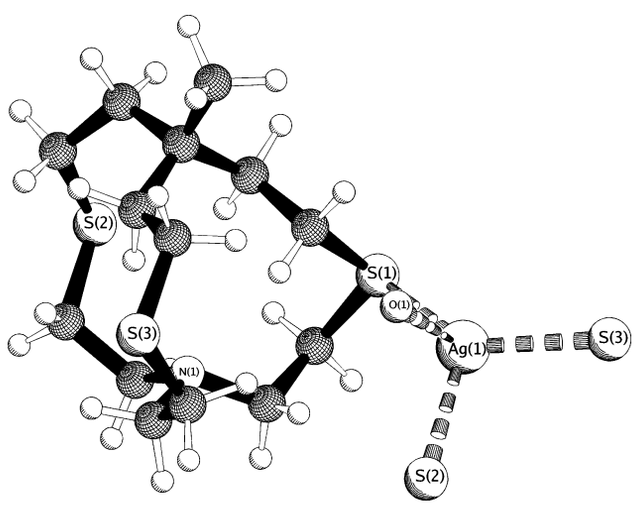


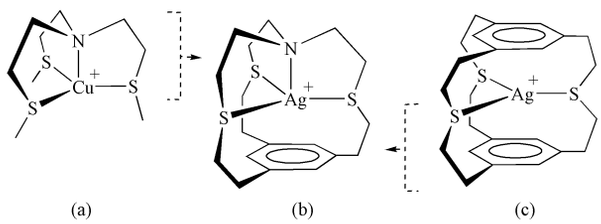
Fig. 5 Extract from the crystal structure of polymeric {[Ag(**16**)]-tosylate}$_\infty$. Except for their coordinating atoms, the counterion and two additional cage ligands have been omitted for clarity. Selected bond distances (pm) and angles (°): Ag(1)–O(1) 248.3(3), Ag(1)–S(1) 249.71(8) Ag(1)–S(3)#1 254.25(8), Ag(1)–S(2)#2 259.63(8); O(1)–Ag(1)–S(1) 98.87(7), O(1)–Ag(1)–S(3)#1 104.53(7), S(1)–Ag(1)–S(3)#1 132.59(3), O(1)–Ag(1)–S(2)#2 75.40(6), S(1)–Ag(1)–S(2)#2 125.03(3), S(3)#1–Ag(1)–S(2)#2 100.74(3). Symmetry transformations used to generate equivalent atoms: #1 $x-1, y, z$; #2 $-x+2, y-1/2, -z+1$.

formed, but apparently the cage is strongly distorted and does not centrally coordinate Ag(I). Each Ag(I) atom is bound by three cages **16** and the tosylate counter ion. The coordinating tosylate oxygen atom occupies the top of the slightly distorted trigonal pyramid with a bond length of 248 pm. It forms angles of 75, 98 and 104° with the three sulfur atoms. Angles of 100, 125 and 132° are formed by the three pairs of sulfur atoms. Bond lengths between the thioether donor atoms and the Ag(I) atom are 250, 254 and 260 pm.

Even though the cage cavity would allow a central Ag(I) coordination, the metal ion is coordinated externally. The energy barrier towards central coordination could neither be overcome by thermal heating, nor microwave irradiation, nor ultrasonic treatment. The cage seems to be too rigid to allow subsequent Ag(I) inclusion. Solely a Ag(I) template synthesis could possibly yield the desired inclusion compound. Yet, in terms of applicability with ^{111}Ag in radioimmunotherapy this approach has to be rejected.

A novel macrobicyclic NS_3-metacyclophane

As shown above with the open chain ligands, this mixed, ethylene-bridged, tripodal NS_3 donor set provides a favourable coordination geometry for Ag(I) and Cu(I) (Scheme 4a). It was



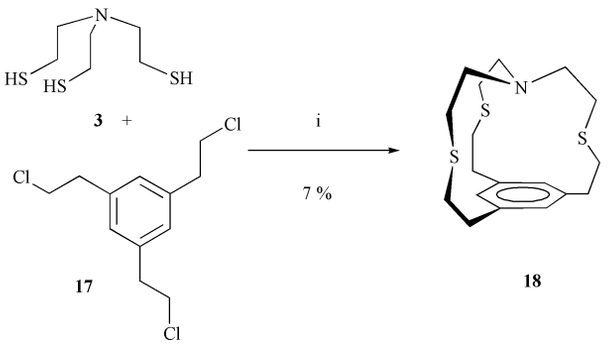
Scheme 4 Complexes (a) and (c) from crystal structures.[6,18] Combined coordinative features of (a) and (c) within the novel complex [Ag^+(**18**)] (b) as derived from DFT calculations.

our aim to use it as a building block in the formation of a corresponding cage type ligand. It was at this stage when Mascal *et al.* recently reported a bis-cyclophane (Scheme 4c) which fully encapsulates Ag(I) by coordination to three thioether sulfur atoms and in addition, sandwich-like η^6-coordination to both benzene rings, thus, providing a fully shielded Ag(I) centre.[18] Combining these two types of coordinative features would lead to a novel cage type ligand (Scheme 4b). Compared to the open chain complex (Scheme 4a), this ligand is expected to more efficiently shield competing ligands from coordinating to the metal atom in the position *trans* to the nitrogen donor atom by blocking this free site. Compared to the bis-cyclophane of Scheme 4c, we expect a better water solubility to act as a chelator for ^{111}Ag in combination with antibodies and a higher stability constant of the resulting Ag(I) complex. We present in this second section the synthesis and the structure of this novel type of ligand. We describe its behaviour with Ag(I) in the light of previously observed Ag(I) complexes resulting in a peripheral type of coordination rather than inclusion in the cage.

As a rational base, molecular modelling calculations on the DFT level supported the possibility of formation of an Ag(I) inclusion complex with **18**, the result being a molecule with approximate C_3 symmetry.[14] The calculated distances from Ag(I) to N and S are 251 and 259 pm, respectively, whereas the distance to the centre of the benzene ring is about 266 pm which is shorter than the 292 pm in Mascal's biscyclophane.[18] The calculated structure of the free ligand indicated the presence of an optimally preorganised coordination sphere for the inclusion of an Ag(I) metal centre. 1-Aza-4,10,15-trithia-7(1,3,5)-;benzenabicyclo-[5.5.5]-heptadecaphane **18** was obtained from a high-dilution reaction of 1,3,5-tris(chloroethyl)benzene **17** synthesised in a multistep reaction according to literature[19] and triethanethiolamine **3** as shown in Scheme 5.

Compound **3** can be prepared from triethanolamine in three steps according to the procedure briefly outlined by Spies *et al.*[8] Reaction of **3** and **17** under high-dilution conditions gave **18** in 7% yield. Single crystals of ligand **18** suitable for X-ray analysis were obtained from $CHCl_3$/diethylether. A SCHAKAL representation of **18** is given in Fig. 6.[10]

The X-ray crystal structure shows that the free electron pair of the nitrogen is pointing out of the cage imposing to the ligand an inside-out conformation. Thus, at least in the solid state, preorganisation, an important factor for formation of stable metal complexes is not given. DFT calculations revealed that the experimentally observed geometry is more favoured than the in-conformation by about 10 kJ mol^{-1}. Such a small



Scheme 5 *Reagents and conditions:* i, Cs_2CO_3, DMF, high dilution, 55 °C.

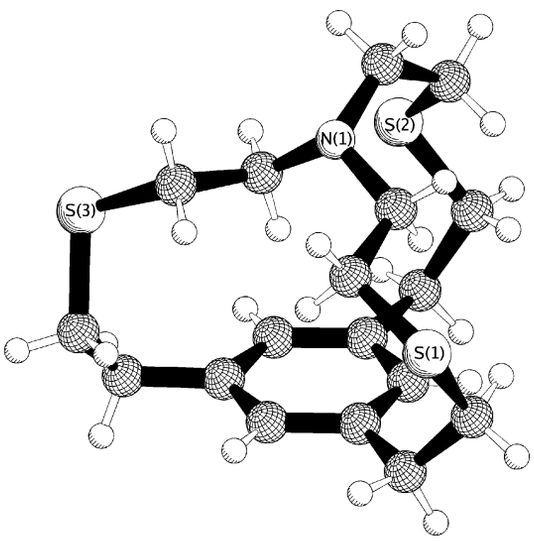


Fig. 6 Crystal structure of the free ligand **18**.

difference allows no prediction to be made about conformational preferences before the ligand synthesis was carried out.

Complex formation between **18** and Ag(I) was achieved by adding a solution of $AgPF_6$ in acetonitrile to a solution of the ligand in the same solvent. A colourless compound of stoichiometric composition [Ag(**18**)]PF_6 was isolated and recrystallised from acetonitrile/diethylether to yield crystals suitable for X-ray structure analysis in quantitative yield. A SCHAKAL representation of the complex unit $[Ag(\mathbf{18})]^+$ is depicted in Fig. 7.

Surprisingly, the Ag(I) cation is not located in the centre of the cage but is disordered with relative site occupancy of 9 : 1 between two peripheral positions. The major form, denoted Ag(1) in Fig. 7, is coordinated to the nitrogen atom N(1), two sulfur atoms S(2), S(3) and a carbon atom C(8) of the benzene ring. The minor form Ag(2) is bound to the nitrogen atom N(1) and three sulfur atoms S(1)#1, S(2) and S(3), where S(1)#1 is an atom from a second ligand molecule. This results in a polymeric solid state structure which resembles earlier results of our group.[2] For Ag(1), bond lengths are 247 pm to the nitrogen atom N(1), 246 pm to the η^1-bonded aromatic carbon atom C(8), and 249 pm to both coordinating sulfur atoms S(2) and S(3) (502 pm to the non-coordinating sulfur S(1)). Bond angles at Ag(1) are 137° between the nitrogen atom and the aromatic carbon atom and 156° between both coordinated sulfur atoms. Since Ag(1) is shifted from the vertical position above the arene carbon atom C(8) towards the aromatic hydrogen atom H(24), the Ag(1)–carbon bond thus forms an angle of 80° with the aromatic plane. The minority of Ag(I) ions, denoted Ag(2), are bridging two cages intermolecularly *via* an Ag(2)–S(1)#1 bond of 273 pm, while both intramolecularly bound sulfur atoms S(2), S(3) are at 250 pm. With a bond length of 278 pm the amine is significantly further away from the Ag(I) atom, as is the arene carbon. At a distance of 294 pm there is only a weak interaction between Ag(2) and this π-system.[20] For Ag(2), bond angles are smaller at the silver centre. The intramolecular sulfur atoms S(2), S(3) form an angle of 154°, while the amine N(1) and the arene C(8) form an angle of 107°. The Ag(I) coordination of **18** corresponds to the regular features of silver-arene interactions with typical bond lengths of 241 ± 5 pm and η^1-coordination mode as stated by Lindeman *et al.*[20] Yet, the presence of two η^1-Ag(I) sites in this X-ray structure is somewhat unusual: the coordination mode in the Ag(1)-position can be regarded as σ-bonding, whereas three-centre two-electron bonding might account for the Ag(2)-position. These structural features are not specific to the solid state.

The broad ^{1}H-NMR-signals at rt in solution indicate a fluxional behaviour with a preference for a peripheral coordination in solution as well (Fig. 8). At low temperature (218 K) there are three sharp signals in the aromatic region with coalescence temperatures of 283 and 288 K. This behaviour could be rationalized by assuming a flip-flop mechanism between peripheral Ag(1) and Ag(2) sites and, at higher temperatures,

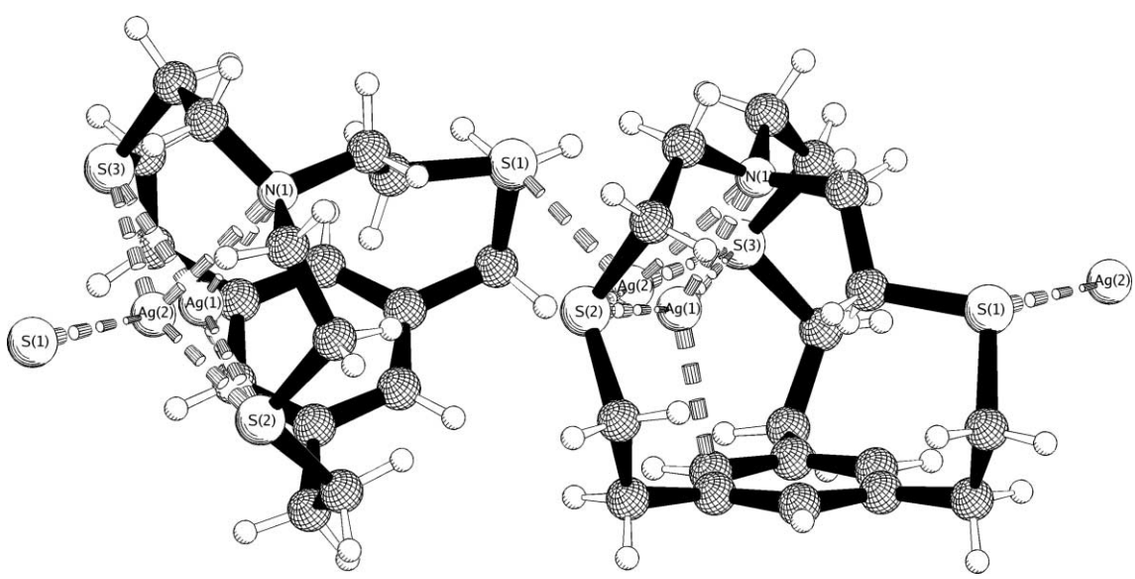


Fig. 7 Extract from the crystal structure of polymeric $\{[Ag(\mathbf{18})]PF_6\}_\infty$. Counterions have been omitted for clarity. Selected bond distances (pm) and angles (°): Ag(1)–S(2) 249.52(8), Ag(1)–S(3) 249.16(8), Ag(1)–N(1) 247.2(3), Ag(1)–C(8) 246.4(3), Ag(2)–S(2) 248.8(3), Ag(2)–S(3) 251.4(3), Ag(2)–S(1)#1 273.0(4), Ag(2)–N(1) 273.0 (2), Ag(2)–C(8) 294.2 (4); N(1)–Ag(1)–C(8) 137.35(10), S(2)–Ag(1)–S(3) 156.24(3), S(2)–Ag(2)–S(3) 154.59(17), N(1)–Ag(2)–S(1)#1 102.88, Ag(1)–C(8)–H(24) 80.53. Symmetry transformations used to generate equivalent atoms: #1 x, $-y + 1/2$, $z + 1/2$.

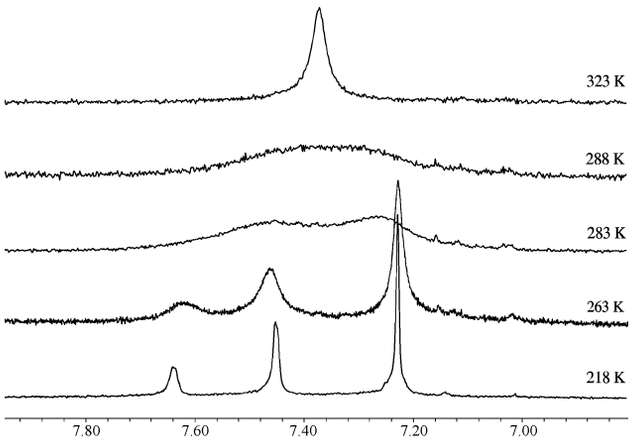


Fig. 8 Temperature dependent NMR of [Ag(**18**)]PF_6 in acetone-d_6.

subsequent rotation of the silver ion within the cage. On the other hand, and assuming that Ag(1) and Ag(2) sites can not be resolved, an equilibrium could exist between two species with either central (Scheme 4b) or peripheral Ag(I)-coordination. The former will show one, the latter two aromatic peaks with intensities of 1 : 2. Even at lower temperatures, peaks at 7.64 and 7.45 ppm are broadened due to exchange. Indeed, these peaks at 7.64 and 7.45 ppm show relative intensities of 1 : 2. With rising temperature, the peak at 7.64 ppm (one proton) shows twice the increase in full width at half-height as the peak at 7.45 ppm (two protons). This is to be expected due to the higher exchange rate of the single proton compared to the two protons. Those two peaks thus belong to one species. The peak at 7.23 ppm (relative intensity 2.8) showing exchange only at elevated temperature consequently belongs to a second species with C_3-symmetry. This can only be rationalised by an isomer with central Ag(I)-coordination. From the relative intensities we can thus deduce a 7% excess of the isomer with peripheral metal ion coordination at 218 K. Heating to 323 K shows a single peak at 7.37, which is exactly the calculated barycentre of the aromatic peaks from the spectrum at 218 K. These experimental results prompted us to perform geometry optimisations starting from the crystal structure with the silver ion in its Ag(1) position. To our surprise the calculated structure of C_1 symmetry was more or less identical with the crystallographically found structure. The proposed C_3-symmetrical complex is energetically less favoured. The energy difference was calculated to be only 0.3 kJ mol^{-1}. Obviously our preliminary conformer analysis yielded only one of the two possible coordination isomers. Note that the calculated energy difference would refer to a 12% excess of the C_1 complex, which is in good accordance with the experimentally found 7%. According to Harris the activation energy for an exchange reaction can be calculated from the coalescence temperature T_c and the initial chemical shift difference $\delta\nu$ of two sharp signals of equally populated species.[21] Neglecting the 7% excess we assumed equal population of peripherally and centrally coordinated Ag(I) complex. We furthermore treated the barycentre of the aromatic resonances at 7.64 and 7.45 ppm as a single hypothetic resonance of the peripheral Ag(I) complex at 7.52 ppm. With these assumptions an activation barrier $\Delta G^{\ddagger} \approx 60$ kJ mol^{-1} can be estimated. Even with the approximations encountered above these similar results encouraged us to pursue our efforts to crystallise the complex with central coordination of the Ag(I) ion, *e.g.* at lower temperatures and in different solvents.

Conclusion

We established the ethylene-bridged NS_3-moiety as a potent donor set for Ag(I) coordination chemistry. Even open chain ligands of this type form mononuclear complexes with the labile Ag(I) ion. Several building blocks from our laboratory have been evaluated for NS_3-cage synthesis. The resulting small cages **16** and **11** from high dilution reactions turned out to be either to strained or the undesirable configuration isomer. All efforts to encapsulate Ag(I) in these cages failed. The introduction of an aromatic building block **17** offered the possibility to enlarge the cage cavity. Concomitant stabilisation of the coordinated silver ion in the metacyclophane **18** through interaction with the π-system was expected and could be proofed by a crystal structure and NMR experiments. Obviously the equilibrium between central and peripheral coordination in [Ag(**18**)]PF_6 affects the thermodynamic and kinetic stability of this complex to a significant extent. The determination of the thermodynamic stability constant by potentiometric titration gave log $K = 11.6$. This is a high value for Ag(I) complexes. Yet, for a labile metal centre such as Ag(I), it is by far too low for applications in biological systems. Ag(I) complexes with macrocyclic ligands such as 18-crown-S_6 (log $K = 12.7$)[1] or 18-crown-N_4S_2 (log $K = 14.6$)[22] have comparable thermodynamic stability constants and showed fast transmetallation to proteins when exposed to human serum.

The novel macrobicyclic NS_3-metacyclophane molecule **18** represents a ligand able to encapsulate cations according to DFT-calculations and experimental results. In the case of Ag(I) however, peripheral coordination in two different conformations in the solid state and interconversion between different species in solution was observed. Whether this unexpected behaviour is mainly a result of the size of Ag(I) or a high strain in the ligand itself is currently under investigation with other metal cations. For applications in radioimmunotherapy with ^{111}Ag(I) this ligand is not suitable due to a relatively low stability constant and thus is likely to undergo rapid transmetallation in serum. Our expectations to having primarily tetradentate NS_3–Ag(I) coordination with additional stabilising η^6-arene interactions were not met.

Experimental

All starting materials were purchased either from Fluka or Aldrich and used without further purification. Technical grade acetylene was bubbled through concentrated sulfuric acid and passed through charcoal filters before being used for the synthesis of **5**. Tris(2-chloroethyl)amine hydrochloride **1** (**Caution!** This compound is a strong vesicant!) was prepared according to literature.[9] **6**, **12** and **17** were synthesised according to published procedures.[16,23,19] Tris(2-thiocarboxyethyl)amine **2** and tris(2-mercaptoethyl)amine **3** were prepared as reported previously.[8] Silver complexes were generally synthesised by adding a solution of the ligand to a solution of the appropriate silver salt in an inert atmosphere at rt and in the dark.

DFT calculations were performed using the RIDFT module of the TURBOMOLE program suite.[14] Geometries were optimised using the BP-86 functional and TZVP basis sets.[24] Total energies in hartree are: *in*-**11**: −1752.9882096; *out*-**11**: −1752.9678205; *in*-**16**: −1798.2914438; *out*-**16**: −1798.3333509; $\mathbf{18}_{C1}$: −1950.6829914; $\mathbf{18}_{C3}$: −1950.6793941; Ag(**18**)$_{C1}$: −2098.8473037; Ag(**18**)$_{C3}$: −2098.8471968.

The stability constant of [Ag(**18**)]PF_6 was determined in methanol solution under an inert atmosphere using a Metrohm 713 pH-meter with a Metrohm Ag/AgCl-reference electrode and a silver electrode. At rt a 0.003 M solution of the ligand **18** was titrated with a 0.0026 M $AgClO_4$ solution. The calibration was performed using 0.1 M and 0.001 M $AgClO_4$. All solutions were prepared using 0.1 M NBu_4ClO_4 in methanol as inert electrolyte and solvent.

NMR spectra were recorded on a Varian Gemini 2000, 300 MHz at room temperature and referred to the residual solvent signal. The chemical shift differences of [Ag(**4**)]PF_6 and [Cu(**4**)]PF_6 upon addition of one equivalent of tert-butyl isocyanate were measured in acetone-d_6 solution at rt. X-ray crystal structure analysis were performed on a STOE IPDS

Table 1 Crystal data and structure refinement

Compound	[Cu(**4**)]PF_6	[Ag(**4**)]PF_6	[Cu(**5**)]PF_6	{[Ag(**11**)]tosylate}$_\infty$	{[Ag(**16**)]tosylate}$_\infty$
Empirical formula	$C_{27}H_{33}CuF_6NPS_3$	$C_{27}H_{33}AgF_6NPS_3$	$C_{12}H_{21}CuF_6NPS_3$	$C_{22}H_{35}AgN_2O_3S_4$	$C_{23}H_{37}AgN_2O_3S_4$
Formula weight	676.23	720.56	483.99	611.63	625.66
Temperature/K	183(2)	183(2)	183(2)	183(2)	183(2)
Crystal system	Triclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P\bar{1}$	$P21/c$	$P21/n$	$P212121$	$P21$
a/Å	9.0477(6)	15.0859(12)	12.3903(10)	8.7597(5)	8.1923(6)
α/°	107.744(8)	90	90	90	90
b/Å	11.6121(8)	11.6960(6)	15.3514(8)	15.1614(11)	13.8066(14)
β/°	98.854(8)	110.803(8)	91.405(9)	90	92.14(1)
c/Å	14.9961(11)	18.1530(13)	10.2517(8)	19.4053(11)	11.973(1)
γ/°	93.950(8)	90	90	90	90
Volume/Å^3	1471.43(18)	2994.2(4)	1949.4(2)	2577.2(3)	1353.3(2)
Z	2	4	4	4	2
Absorption coefficient/mm^{-1}	1.066	0.992 mm^{-1}	1.573 mm^{-1}	1.133 mm^{-1}	1.081 mm^{-1}
Reflections collected	16579	5830	3770	18238	18638
Independent reflections [R(int)]	8014 [0.0311]	5830 [0.0000]	3770 [0.0000]	4991 [0.0244]	6393 [0.0563]
Final R indices: R_1, wR_2 [$I > 2\sigma(I)$]	0.0451, 0.1231	0.0373, 0.0864	0.0438, 0.1184	0.0207, 0.0528	0.0315, 0.0699

Table 2 Crystal data and structure refinement

Compound	**18**	{[Ag(**18**)]PF_6}$_\infty$
Empirical formula	$C_{18}H_{27}NS_3$	$C_{18}H_{27}AgF_6NPS_3$
Formula weight	353.59	606.43
Temperature/K	183(2)	183(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P21/n$	$P21/c$
a/Å	8.9341(6)	13.2112(9)
α/°	90	90
b/Å	15.0765(9)	13.5373(12)
β/°	100.668(8)	115.847(7)
c/Å	13.6182(9)	13.9691(9)
γ/°	90	90
Volume/Å^3	1802.6(2)	2248.4(3)
Z	4	4
Absorption coefficient/mm^{-1}	0.408	1.302
Reflections collected	28591	15549
Independent reflections [R(int)]	4367 [0.0679]	4146 [0.1027]
Final R indices: R_1, wR_2 [$I > 2\sigma(I)$]	0.0392, 0.1038	0.0305, 0.0748

diffractometer. All structures were solved by direct methods using the program SHELXS-97 and refined using the program SHELXL-97.[25,26] Pertinent data are given in Tables 1 and 2.

CCDC reference numbers 186809–186814 and 180039.

See http://www.rsc.org/suppdata/dt/b2/b205287c/ for crystallographic data in CIF or other electronic format.

Tris(2-thiocarboxyethyl)amine 2

Tris(2-chloroethyl)amine hydrochloride (**Caution!** This compound is a strong vesicant! It should only be handled in a hood. Wear protective garments!) (50 g, 0.21 mol) and sodium carbonate (25 g, 0.25 mol) is suspended in 500 ml dry DMF and stirred for several minutes under nitrogen. After addition of potassium thioacetate, the reaction mixture is stirred for 3 h at 50 °C. The solvent is evaporated in vacuum and the remaining dark-brown solid is extracted several times with dichloromethane. The solvent is evaporated to yield the tris(2-thiocarboxyethyl)amine (66.6 g, 0.2 mol, 98%) as a dark brown liquid, suitable for reduction without further purification, δ_H (300 MHz, $CDCl_3$) 2.28 (s, CH_3, 9 H), 2.65 (t, J = 7.2 Hz, CH_2, 6 H), 2.89 (t, J = 7.2 Hz, CH_2, 6 H); δ_C (75.5 MHz, $CDCl_3$) 22.8, 26.1, 48.7, 191.3.

Tris(2-mercaptoethyl)amine 3

Lithium aluminium hydride (7.4 g, 0.2 mol) is suspended in 150 ml absolute THF under dry nitrogen. A solution of tris(2-thiocarboxyethyl)amine (40 g, 0.12 mol) in 100 ml absolute THF is added drop-wise to keep the solution refluxing. The reaction mixture is heated for another hour and hydrolysed after cooling with a minimum amount of degassed water. Carbon dioxide is bubbled through the mixture and the solution is filtered under nitrogen. The remainders are extracted twice with THF under nitrogen. The combined extracts are evaporated to yield the product **10** (10.66 g, 54 mmol, 45%) as a yellow oil, δ_H (300 MHz, $CDCl_3$) 1.74 (s, SH, 3 H), 2.60 (br, SCH_2, 6 H), 2.66 (m, NCH_2, 6 H); δ_C (75.5 MHz, $CDCl_3$) 18.5, 52.6.

Tris(2-benzylsulfanyl-ethyl)amine 4

Sodium (0.83 g, 36 mmol) is dissolved in 50 ml dry ethanol under nitrogen. Tris(2-chloroethyl)amine hydrochloride **1** (2 g, 8.3 mmol) and benzyl mercaptane are added and stirred for 2 h at 50 °C. The solvent is removed under reduced pressure and the residue is extracted several times with dichloromethane. The combined extracts are evaporated to yield **4** (3.69 g, 7.9 mmol, 95%) as a yellow oil, δ_H (300 MHz, $CDCl_3$) 2.38 (t, J = 8.9 Hz, CH_2, 6 H), 2.52 (t, J = 8.9 Hz, CH_2, 6 H), 3.67 (s, CH_2, 6 H), 7.2–7.35 (m, phenyl-H, 15 H); δ_C (75.5 MHz, $CDCl_3$) 24.6, 32.0, 49.2, 122.5, 124.0, 124.3, 133.9.

Tris(2-vinylsulfanyl-ethyl)amine 5

Potassium hydroxide (114 mg, 2 mmol) is suspended in dry DMSO under nitrogen. **3** (3.5 g, 17.7 mmol) is added and for 8 h dry acetylene is bubbled through the reaction mixture at 70 °C. The solvent is removed and the residue is dissolved in dichloromethane and filtered through celite. Evaporation of the solvent yields **5** (2.9 g, 10.5 mmol, 60%) as a yellow oil, δ_H (300 MHz, $CDCl_3$) 2.78 (s, SCH_2 + NCH_2, 12 H), 5.12 (d, J_{trans} = 16.6 Hz, CHH, 1 H), 5.75 (d, J_{cis} = 10 Hz, CHH, 1 H), 6.33 (dd, J_{cis} = 10 Hz, J_{trans} = 16.6 Hz, CH_2CHR, 1 H); δ_C (75.5 MHz, $CDCl_3$) 25.1, 48.8, 106.5, 127.5.

3-Carboxymethyl glutaric acid 7

3-(2-Cyanomethyl)glutaric acid diethyl ester **6** (19.4 g, 85 mmol) is prepared according to Egawa.[23] The oil is added to 100 ml 5 M NaOH solution forming a two phase-system. The mixture is heated and vigorously stirred for 2 h. Evolving ammonia and ethanol are distilled off. After cooling, the clear solution is acidified with 5 M sulfuric acid and evaporated to dryness. The solid is extracted several times with diethyl ether and the combined extracts are dried with sodium sulfate. Evaporation of the solvent yields the product **7** (16.1 g, 85 mmol, 100%) as a white powder, δ_H (300 MHz, d_6-acetone) 2.52 (d, J = 6.3 Hz, CH_2, 6 H), 2.68 (m, CH, 1 H); δ_C (75.5 MHz, d_6-acetone) 23.9, 32.3, 169.

3-(Propyloxycarbonylmethyl) glutaric acid dipropylester 8

3-Carboxymethyl glutaric acid **7** (16.1 g, 85 mmol), 1 ml sulfuric acid, 50 ml benzene and 100 n-propanol are heated over

night in a Dean–Stark apparatus. After cooling, the reaction mixture is diluted with diethyl ether and subsequently washed with water, $NaHCO_3$ solution and water. Evaporation of the dried (with sodium sulfate) solution yields the product **8** (21.6 g, 68 mmol, 95%) as a bright yellow oil, δ_H (300 MHz, $CDCl_3$) 1.92 (t, CH_3, 9 H), 1.61 (q, OCH$_2$CH_2, 6 H), 2.42 (m, CHCH_2, 6 H), 2.77 (m, CHCH$_2$, 1 H), 4.0 (t, OCH_2CH$_2$, 6 H); δ_C (75.5 MHz, $CDCl_3$) 5.9, 17.4, 24.3, 33.2, 61.6, 167.5.

3-(2-Hydroxyethyl)pentane-1,5-diol 9

Lithium aluminium hydride (3.9 g, 0.105 mol) is suspended in 80 ml absolute THF under dry nitrogen. A solution of **8** (21.6 g, 68 mmol) in 100 ml absolute THF is added dropwise to keep the solution refluxing. The reaction mixture is heated for another hour and hydrolysed after cooling with a minimum amount of water. This suspension is filtered and extracted with hot ethanol. The solvent is evaporated to yield the product **9** (4.76 g, 0.029 mol, 98%) as a yellow oil which solidifies after several days, δ_H (300 MHz, $CDCl_3$) 1.42 (dt, J = 6 Hz, CHCH_2, 6 H), 1.5 (m, CH, 1 H), 3.51 (t, J = 6 Hz, CH_2OH, 6 H); δ_C (75.5 MHz, $CDCl_3$) 22.9, 30.7, 55.0.

3-(2-Chloroethyl)-1,5-dichloropentane 10

9 (12.13 g, 82 mmol) and dry pyridine (30 ml) is dissolved in 100 ml dichloromethane. Thionyl chloride is added with stirring and cooling. After gas evolution has ceased the reaction mixture is heated to give a clear yellow solution. Excess thionyl chloride is hydrolysed carefully under cooling. The organic phase is washed with 1 M HCl, water, sodium bicarbonate solution and again water. Drying with sodium sulfate and evaporation of the solvent yields the product **10** (12.52 g, 62 mmol, 75%) as a yellow oil, δ_H (300 MHz, $CDCl_3$) 1.78 (q, J = 6.9 Hz, CHCH_2, 6 H), 1.99 (m, CH, 1 H), 3.56 (t, J = 6.9 Hz, CH_2Cl, 6 H); δ_C (75.5 MHz, $CDCl_3$) 37.7 (CH$_2$Cl), 31.6 (CHCH$_2$), 26.6 (CHCH$_2$).

in-4,10,15-Trithia-1-aza-bicyclo[5.5.5]heptadecane 11

Caesium carbonate (42 g, 0.13 mol) is suspended in 300 ml dry DMF under nitrogen. **3** and **10** are diluted in 300 ml dry DMF each and added dropwise under stirring over 78 h at 55 °C in a nitrogen atmosphere. After completing the addition the reaction mixture is stirred for another hour. The solvent is removed in vacuum and the remaining solid is extracted several times with dichloromethane. Evaporation of the solvent yields a brownish semisolid. Column chromatography over silica with dichloromethane as eluent yields the product **11** (175 mg, 0,6 mmol, 12%) as a white, crystalline solid, δ_H (300 MHz, $CDCl_3$) 1.42 (dt, J = 5.1 Hz, CHCH_2, 6 H), 2.55 (t, J = 4.2 Hz, SCH_2, 6 H), 2.71 (t, J = 5.1 Hz, SCH_2, 6 H), 2.91 (t, J = 4.2 Hz, NCH_2, 6 H), 3.23 (m, CH, 1 H); δ_C (75.5 MHz, $CDCl_3$) 23.8, 29.0, 31.6, 33.8, 55.7.

3-(Methoxycarbonyl)methyl-3-methyl-pentane-1,5-dicarboxylic acid-dimethylester 13

Iodomethane (130 g, 0.92 mol) was added dropwise to a stirred suspension of magnesium turnings (22 g, 0.92 mol) in absolute diethyl ether (500 ml) to keep the reaction mixture refluxing. It was heated for 20 min to complete the reaction. The cooled Grignard solution is filtered to a suspension of Cu(I) iodide in 700 ml diethyl ether in a 1500 ml Schlenk tube. The mixture is stirred at room temperature until it shows an almost black colour and is subsequently cooled to −150 °C. After slow addition of trimethylchlorosilane (117 ml, 0.92 mol) 3-(methoxycarbonyl)-methylpent-2-ene-1,5-dicarboxylic acid dimethylester **12** is rapidly added. The mixture is stirred at this temperature for 1 h and then allowed to warm up over night. The green suspension is carefully hydrolysed with saturated ammonium chloride solution. After extraction with ethyl acetate the organic phase was washed several times with ammonia and brine. Drying with sodium sulfate and evaporation of the solvent yields a yellow oil. The methylated product **13** (7.4 g, 0.03 mol, 20%) can be isolated by fractional distillation at 3.5×10^{-2} mbar and 91 °C over a 30 cm Vigreux column, δ_H (300 MHz, $CDCl_3$) 1.16 (s, CR$_3$CH_3, 3 H), 2.6 (s, CH_2, 6 H), 3.63 (s, OCH_3, 9 H); δ_C (75.5 MHz, $CDCl_3$) 20.7, 29.5, 32.0, 46.8, 167.3.

3-(2-Hydroxyethyl)-3-methyl-pentane-1,5-diol 14

Lithium aluminium hydride (1.7 g, 45 mmol) is suspended in 70 ml absolute THF under dry nitrogen. A solution of **13** (7.4 g, 30 mmol) in 50 ml absolute THF is added dropwise to keep the solution refluxing. The reaction mixture is heated for another hour and hydrolysed after cooling with a minimum amount of water. This suspension is filtered and extracted with hot ethanol. The solvent is evaporated to yield the product **14** (4.76 g, 29 mmol, 98%) as a yellow oil, which solidifies after several days, δ_H (300 MHz, $CDCl_3$) 1.16 (s, CR$_3$CH_3, 3 H), 1.37 (m, CH_2, 6 H), 3.48 (m, OCH_2, 6 H); δ_C (75.5 MHz, $CDCl_3$) 12.2, 27.9, 26.3, 53.4.

3-(2-Chloroethyl)-1,5-dichloro-3-methylpentane 15

14 (4.76 g, 29 mmol) and dry pyridine (30 ml) is dissolved in 100 ml dichloromethane. Thionyl chloride is added with stirring and cooling. After gas evolution has ceased the reaction mixture is heated to give a clear yellow solution. Excess thionyl chloride is hydrolysed carefully under cooling. The organic phase is washed with 1 M HCl, water, sodium bicarbonate solution and again water. Drying with sodium sulfate and evaporation of the solvent yields the product **15** (5 g, 23 mmol, 80%) as a yellow oil, δ_H (300 MHz, $CDCl_3$) 0.99 (s, CH_3, 3 H), 1.78 (t, J = 6.6 Hz, CH_2CH$_3$, 6 H), 3.50 (t, J = 6.6 Hz, CH_2Cl, 6 H); δ_C (75.5 MHz, $CDCl_3$) 20.0, 32.1, 35.4, 37.7.

out-7-Methyl-4,10,15-trithia-1-aza-bicyclo[5.5.5]heptadecane 16

Caesium carbonate (40 g, 0.12 mol) is suspended in 300 ml dry DMF under nitrogen. **3** and **15** are diluted in 300 ml dry DMF each and added dropwise under stirring over 60 h at 55 °C in a nitrogen atmosphere. After completing the addition the reaction mixture is stirred another hour. The solvent is removed in vacuum and the remaining solid is extracted several times with dichloromethane. Evaporation of the solvent yields a brownish semisolid. Column chromatography over silica with dichloromethane as eluent yields the product **16** (20.5 mg, 0.07 mmol, 0.3%) as a white, crystalline solid, δ_H (300 MHz, $CDCl_3$) 0.88 (s, CH_3, 3 H), 1.94 (t, J = 6.9 Hz, CH_2CH$_3$, 6 H), 2.55 (t, J = 4.5 Hz, SCH_2, 6 H), 2.78 (t, J = 4.5 Hz, SCH_2, 6 H), 2.94 (t, J = 6.9 Hz, NCH_2, 6 H); δ_C (75.5 MHz, $CDCl_3$) 25.3, 26.1, 28.0, 29.2, 36.6, 54.7

1-Aza-4,10,15-trithia-7(1,3,5)-benzenabicyclo[5.5.5]-heptadecaphane 18

Caesium carbonate (59 g, 0.18 mol) is suspended in 1000 ml dry DMF under nitrogen. **3** and **17** are diluted in 500 ml dry DMF each and added drop-wise under stirring over 96 h at 55 °C in a nitrogen atmosphere. After completing the addition the reaction mixture is stirred for another hour. The solvent is removed under reduced pressure and the remaining solid is extracted several times with dichloromethane. Evaporation of the solvent yields a brownish semisolid. Column chromatography over silica with a mixture of dichloromethane, diethylether and ethyl acetate (4 : 4 : 1) as eluent yields an oily, brownish product after removal of the solvent. This residue is dissolved in hot ethanol, filtered and stored at −15 °C over night to yield **18** (2.6 mg, 7.4 mmol, 7%) as a white, crystalline solid, δ 2.37 (m, CH_2, 12 H), 2.92 (m, CH_2, 12 H), 7.03 (s, phenyl-H, 3 H); ^{13}C ($CDCl_3$): δ 29.7, 32.0, 32.6, 50.2, 124.6, 136.3; calc. for $C_{18}H_{27}NS_3$: C, 61.14; H, 7.70; N, 3.96%; found: C, 61.11; H, 7.56; N, 3.77%.

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