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George A. Forsyth[a]; Joyce C. Lockhart[a]
[a] Department of Chemistry, Bedson Building, The University, Newcastle-upon-Tyne, England

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Macrocyclic thioether design by molecular modelling

GEORGE A. FORSYTH and JOYCE C. LOCKHART*

Department of Chemistry, Bedson Building, The University, Newcastle-upon-Tyne, England, NE1 7RU

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Two trithiamacrocycles have been designed by molecular modelling to have preorganised endodentate sulfur donor atoms. These new macrocycles have five- and six-membered saturated heterocycles inserted into 2,5,8-trithia[9]-*m*-benzenophane; molecular dynamics simulations suggest that the endo forms will be rigid on a nanosecond timescale. Optimum metal-sulfur distances which the new ligands will accommodate lie between 2.76 Å and 2.95 Å, suggesting they will be particularly suitable for a large soft metal ion such as silver(I).

INTRODUCTION

Macrocyclic thiocrowns have been intensively studied as hosts for the softer metal ion guests[1,2]. As noted by Cooper[3], the dithioethane unit SCCS, which is the most common building block for such thioethers, has a conformational preference to have its sulfurs anti rather than gauche, and CSCC gauche rather than anti. The resulting free macrocycles thus tend to have their sulfurs pointing exo to the ring, but must reorganise to have these sulfurs pointing endo in order to complex metal ions; this requires an energy penalty. The only such crown known to crystallise with all sulfurs endo is trithiacyclononane[4] (9S3, **1**, Fig. 1) which is too small to encapsulate a metal ion but gives excellent fac coordination. Molecular mechanics studies suggest an optimum M-S bond length of 2.27 Å or 2.29 Å, depending on ligand conformation[5], or 2.31 Å.[6] However, 9S3 is fluxional on a very rapid timescale[7], flexing between two all-endodentate conformations at roughly 60 ps intervals at 450 K. It is not clear whether this can be regarded as 'preorganised' although it is often claimed to be so. The concept of preorganisation originally proposed by Cram[8] and coworkers[9,10] was not specific with regard to the kinetic and thermodynamic criteria which might define the concept. The operational criterion[10] was that the conformation in the crystal of the host should remain the same before and after guest complexation. There is no guarantee that a host in solution will retain the form it took in the crystal; indeed this point is specifically made in ref. 10 (p. 59). Thus it is important to define the solution structure which is the relevant one for complexation of a guest. What are the kinetic and thermodynamic requirements for preorganisation? Thermodynamically, the implicit requirement is that the lowest energy host conformer accessible must have the same shape as in its host-guest complex. This should lead to the strongest possible interaction in thermodynamic terms. The kinetic question is how long the host conformer must retain this shape in solution? In complexation reactions, the host (ligand) and guest (metal ion) meet at the collision rate and the complexation is usually fast, within 10^{-8} s (but see the Eigen scale for typical values for a range of metals[11]). Thus conformations stable for around 1 – 10 ns would be preorganised for such a complexation. This should suffice to complex a guest ion of the correct dimensions without prior shape change. We have considered the question of fluxionality on the ps to ns timescale, using Molecular Dynamics,[7,12] and on the NMR timescale,[13] in relation to its importance as a pre- or post-equilibrium process which may affect the metal-ligand coordination. We describe in this paper our attempts to design a ligand which should have the correct dimensions to complex the large soft metal ion Ag(I), and which should remain preorganised on a much longer timescale than does 9S3.

The macrocycle 2,5,8-trithia[9]-*m*-benzenophane, **2**, (Fig. 1), has been demonstrated to be specially selective for silver in ion-selective electrode formulations.[14,15] A recent molecular dynamics study of this ligand[12] has shown the ring to be flexible, easily able to adopt an exodentate conformation, which is found in the crystal structure[16], and an endodentate conformation, calculated to be only 0.06 kcalmol^{-1} lower in energy than the exodentate form[12]. It was hypothesised that this could give

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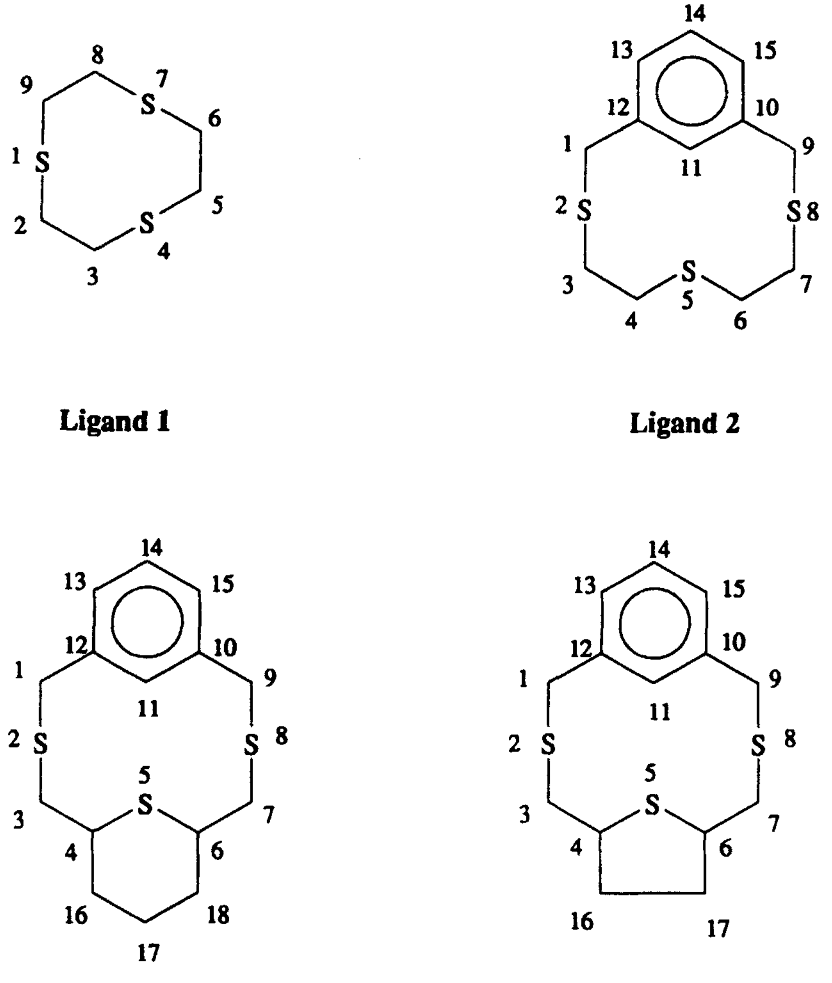
*Corresponding author:



Ligand 1

Ligand 2

Ligand 3

Ligand 4

Figure 1 Diagrams and numbering schemes of ligands **1** to **4**

pseudo-axial coordination to large soft ions. In view of our interest in the complexation and transportation through aqueous and organic media, and across liquid membranes, of silver ions, we chose this ligand, **2**, which has sulfurs spaced appropriately to bind larger ions, e.g. silver ions, as the starting point of the design. A rigid derivative of this ligand would provide a critical test of the relative timescale of fluxionality (or rigidity) required to render a molecule preorganised, information of great value for future design processes. For this reason, the design of new ligands was based on the endo form of **2**.

The design of new ligands is often accomplished by the strategic positioning of methyl and other groups to hinder torsional rotations.[17,18,19] A recent example is (R,R,R)-4,8,12-trimethyl-1,5,9-trioxadodeca-2,6,10-trione[20] although here the intended donor atoms are in fact the ester oxygens. An example of similar substitution in crown ether chemistry predating Pedersen is the synthesis (non-stereospecific) of tetramethyl twelve-crown-4 by Lewis et al.[21] Dale[22] has shown that the oxygen-donor 12-crown-3 may be conformationally restricted by the insertion of gem-dimethyl substituents on the middle carbon of each set of three. In thiamacrocycle chemistry, where the usual motif is more energetically favoured with CSCC gauche,[3] Cooper suggests the modification of lengthening the bridge between sulfurs from 2 to 3 carbons, with gem-dimethyl substitution on the middle carbon will force the SCC(Me)C torsions from anti to gauche, and the CSCC(Me) torsions from gauche to anti.[3] There is experimental evidence that such substitution has an overall thermodynamic effect on the behaviour of 14S4.[3,23,24] Izatt and coworkers estimate an improvement in the enthalpy of interaction of Cu(II) with substituted 14S4 of ca. 1–2 kcalmol^{-1} for each gem dimethyl pair. Another method of designing conformationally-restricted ligands is the incorporation of small alicyclic units into the backbone,[25] which is nature's device for the rigid backbone of the steroids. Bell, Choi and Harte show how ring inversion can be prevented by adding another ring to N donors of the aza macrocycle triazadodecane.[26] Now we present a new suggestion for conferring rigidity on macrocycles.

Inspection of the topography of the endodentate form of 2,5,8-trithia[9]-*m*-benzenophane suggests that replacing the C(4)S(5)C(6) thioether unit with a saturated heterocycle, such as tetrahydrothiin or tetrahydrothiophene, would, in effect, force the derived ligands **3** and **4** (see Fig 1) to adopt an endodentate conformation, and thus preorganise the 3 sulfur atoms in the required binding position. Such a ligand would still not be rigidly locked into only one possible conformation, as the two other thioether units, C(1)S(2)C(3) and C(7)S(8)C(9), are theoretically able to adopt an exodentate conformation. Thus, it was necessary to establish whether the lowest-energy conformation of the new ligands would have the three sulfur atoms in the endodentate conformation. Also, the creation of chiral centres at carbons C(4) and C(6) must be addressed: there should be four distinct isomers of such a ligand, the RR, SS, RS and SR forms, each of which should be investigated.

METHOD

In the investigation of the conformational space of molecules there are three commonly used techniques, *viz.* Monte Carlo, molecular dynamics and a systematic search. The efficiency of these methods in locating minimum conformations has been widely discussed[27 - 34]. For a small macrocycle such as **3** or **4**, a systematic search technique is the most comprehensive method available. The Elastic Bond option in QUANTA[35] was used.

Computational Details

Version 21.3 of the commercial version of CHARMm[36] was used to perform all computational calculations. All calculations and visual analyses were done on a Silicon Graphics IRIS 4D20. Charges were assigned to atom types (thioether sulfur, SE; aliphatic carbon, CT; aromatic carbon, C6R; aliphatic or aromatic hydrogen, HA) using the charge templates option of the Molecular Editor of QUANTA, which assigns charges compatible with the CHARMm force field. Each conformation was first minimised using 25 steps of the Steepest Descents minimiser, then by the Adopted-Basis-Newton-Raphson minimiser (ABNR) until convergence was reached (when the first derivative of the energy was 0.1 kcalmol^{-1}). For non-bonded interactions, a cut-off distance, beyond which such interactions are excluded, of 12 Å was chosen. The remaining non-bonded parameters were chosen as described previously[7]. Conformations that were selected for molecular dynamics simulations were heated for 6 ps, equilibrated for 10 ps, and given a 500 ps simulation. The appropriate CHARMm parameters for the heating process were:

IHTFRQ	200
TEMINC	10
NSTEP	6000
FIRSTT	0.0
FINALT	300.0

for equilibration:

IEQFRQ	20
NSTEP	10000

and for simulation:

NSTEP	500000

The remaining parameters were assigned as described previously.[7]

RESULTS AND DISCUSSION

2,5,8-Trithia[9]-*m*-benzenophane

The Elastic Bond chosen was C(12)-C(1). Each rotatable torsion was assigned possible values -60°, 60° or 180° which are values typically found for C-C-S-C and S-C-C-S bonds. Thus, with 8 rotatable bonds a total of 3^8 (6561) conformations are possible. Many of these conformations have unrealistic geometries for the macrocycle, with the Elastic Bond, C(12)-C(1), adopting values, in some cases, in excess of 10 Å, and so are not of interest. These unwanted conformations were screened out by monitoring the interatomic distance of the atoms adjacent to those of the Elastic Bond, the C(13). . .S(2) distance, and selecting only those conformations for which this distance would allow a feasible C(12)-C(1) bond length. If the C(13)-C(12)-C(1)-S(2) torsion angle is anti, and thus the atoms C(13) and S(2) are at their maximum separation, the C(13). . .S(2) distance is 4.1 Å, so by screening out those conformations where this distance is in excess of 5.5 Å, the remaining conformations should encompass every available conformation of the macrocycle. A small increment, in this case 1.4 Å, should allow for the inclusion of conformations that have torsional values noticeably different from the values used for the conformational search. At first, the Elastic Bond distance (C(1). . .C(12)) was monitored, and a cut-off distance of 2.8 Å used to exclude unrealistic conformations. On comparison with the published MD study, some low energy conformations that were located in the MD study were not found in the systematic search. By selecting the non-bonded distance S(2). . .C(13) with 5.5 Å as the cut-off, some conformations with quite large C(1). . .C(12) distances were obtained. However, graphical inspection of a few showed that slight torsional adjustments to the ring could allow the C(1). . .C(12) distance to have a more acceptable value. Using this method, 504 conformations were selected for minimisation, resulting in 69 unique conformations. In the lowest-energy conformation (10.68 kcalmol^{-1}), the S(2)C(3)C(4)S(5) and S(5)C(6)C(7)S(8) torsion angles were anti, and the three sulfur atoms exo, the same conformation as the crystal structure,[16] shown as A in Fig. 2. The endo form (B in Fig. 2) was only 0.03 kcalmol^{-1} higher in energy than the exo form. There were many conformations within 10 kcalmol^{-1} of the exo form, which might all exist, in whatever small proportions, in the thermodynamic ensemble. The energies of the ten lowest-energy conformations are shown in Table 1. For the purpose of this study, the conformation of interest for the new design was the one with the three sulfur atoms in an endo form (and the S(2)C(3)C(4)S(5) and S(5)C(6)C(7)S(8) torsion angles in a gauche conformation).

The first attempt at preorganisation replaced the C(4)S(5)C(6) unit of the endo form of **2** with tetrahydrothiin.

Ligand 3

RR Isomer: Using the conformational search technique described above, the Elastic Bond corresponding to that used for **2** was defined as C(1) – C(12). Thus there were 6 rotatable bonds, and 729 possible conformations. A cut-off distance of 5.5 Å was used for the C(13). . .S(2) distance, and 123 conformations were selected for minimisation. In the lowest-energy conformation (11.58 kcalmol^{-1}, shown as C in Fig. 2), the sulfur atoms were in an endodentate conformation. The backbone of this conformation superimposes exactly on the endo form of the 'parent' ligand, thus the sulfur atoms are in their coordinating position. The comparison in Table 2 shows that the equivalent torsion angles in the compounds (**2**)B and (**3**)C have identical values. The next conformation of **3** (D in Fig. 2) has an energy of 12.20 kcalmol^{-1}, and the C(1)S(2)C(3) thioether unit is pointing up, in an exo position; both thioether units, C(1)S(2)C(3) and C(7)S(8)C(9), were exo in the next conformation (E, Fig. 2), which has an energy of 14.94 kcalmol^{-1}. So it is not possible to say that this, the RR isomer, is locked into the desired conformation, where the three sulfur atoms are in an endo form, although the desired conformation will predominate in the thermodynamic ensemble. Table 1 lists the energies of the ten lowest-energy conformations found. A molecular dynamics simulation was of use in predicting the flexibility of the endo form, C. This conformation was used to initiate a 500 ps MD simulation, at 300 K. Throughout the entire simulation the ligand remained in its endo conformation, although the thioether units C(1)S(2)C(3) and C(7)S(8)C(9) were seen to deviate slightly from their initial positions. The S(2). . .S(8) distance fluctuated between 4.4 Å and 5.4 Å. The simulation demonstrates that the desired conformation of the RR isomer of **3** is, at 300 K, quite inflexible.

SS Isomer: This isomer is a mirror-image of RR, thus the lowest-energy conformation is again the desired conformation.

RS Isomer: The conformational search procedure used was exactly the same as that described for the RR isomer. Again, the lowest-energy conformation, (F in Fig. 2, 12.84 kcalmol^{-1}), has the three sulfur atoms in the required (endo) position. When the equivalent sulfur atoms in the endo form of **2** are superimposed, there is good agreement, and it can be seen in Table 3 that the interatomic S. . .S distances in the two conformations ((**2**)B and (**3**)F) are very close. The next conformation, G in Fig. 2, with one sulfur endodentate, has an energy of 14.38 kcalmol^{-1}, and so will occur less frequently than the equivalent conformation of the RR isomer. The energies of the ten lowest-energy conformations are listed in Table 1. In a 500 ps MD simulation, at 300 K, the endo form again retains its shape for the entire simulation.

SR isomer: In the lowest-energy conformation (H, Fig. 2, 14.64 kcalmol^{-1}) again, the sulfur atoms are all endodentate, in the required position, as can be seen in the interatomic S. . .S distances. A visual comparison of this conformation with the endo form of **2** also showed that the sulfurs were well aligned. The next conformation, (I in Fig. 2) with one sulfur exo, has a significantly higher energy, 18.58 kcalmol^{-1}. Thus, of all the isomers of ligand **3**, the H conformer of the SR isomer dominates to a greater degree its thermodynamic ensemble (see Table 1 for the energies of the lowest-energy conformations). The MD simulation did not result in any significant conformational alterations.

The results of the minimisations on the RR(SS), SR and RS isomers show that the lowest-energy conformation of **3** for each isomer is the desired conformation, with the three sulfur atoms endodentate, and with very similar interatomic sulfur-sulfur distances to those in the endo form of **2**. Substituting the heterocycle has not locked this conformation to the extent of excluding all other conformations at room temperature, although the SR isomer is the almost exclusive component of its thermodynamic ensemble at this temperature. The MD simulations demonstrate the inflexibility of the endo forms of

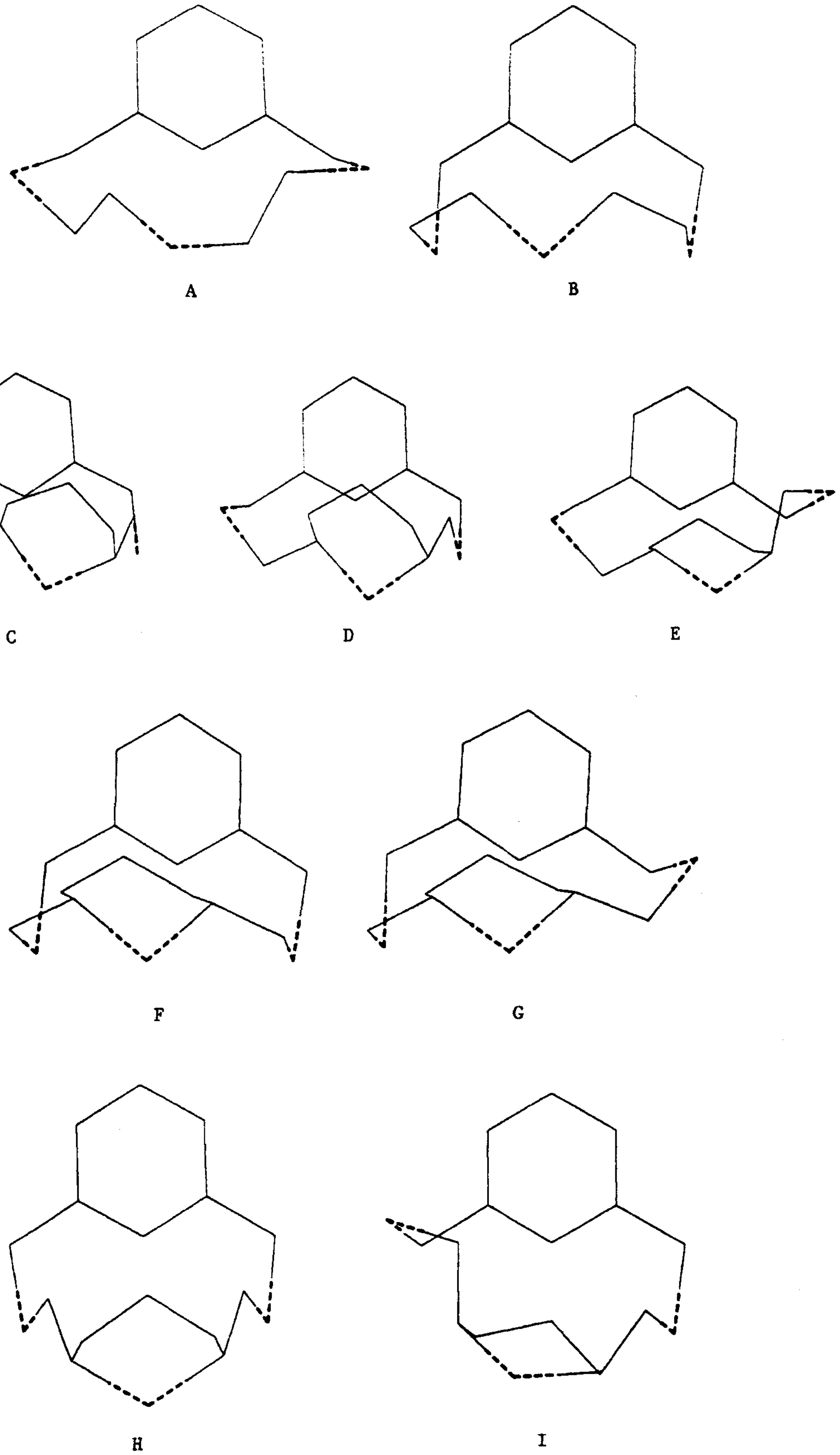


Figure 2 Conformations A and B of ligand **2**, and C to I of ligand **3**

Table 1 The energies of the ten lowest-energy conformations of ligands **2, 3** and **4**.

	energy/kcalmol^{-1}						
Conformer	*L2(B)*	*L3(RR)*	*L3(RS)*	*L3(SR)*	*L4(RR)*	*L4(SR)*	*L4(RS)*
1	10.68	11.58	12.84	14.64	20.21	17.89	20.46
2	10.71	12.20	14.38	18.58	21.14	20.00	21.12
3	11.43	14.94	15.92	18.71	22.20	20.06	21.12
4	11.61	15.66	17.99	18.88	22.85	20.84	21.62
5	11.95	17.31	18.01	18.93	23.01	20.97	22.43
6	12.96	17.36	18.78	19.53	23.49	21.95	24.65
7	13.11	18.13	19.18	20.04	23.50	22.58	26.87
8	13.32	18.38	19.22	20.94	24.30	22.76	26.83
9	14.24	18.90	19.86	21.03	24.86	22.77	27.14
10	15.34	19.30	20.08	21.47	23.38	23.18	27.34

Table 2 Torsion angles in ligands **2, 3** and **4**.

Torsion Angle/°	*L2(B)*	*L3(RR)*	*L3(RS)*	*L3(SR)*	*L4(RR)*	*L4(SR)*
C(13)C(12)C(1)S(2)	-144	-144	-144	-148	-146	-154
C(12)C(1)S(2)C(3)	75	75	80	62	73	66
C(1)S(2)C(3)C(4)	-90	-90	-75	-172	86	-164
S(2)C(3)C(4)S(5)	-55	-55	-47	61	-51	62
C(3)C(4)S(5)C(6)	180	180	171	87	-168	93
C(4)S(5)C(6)C(7)	-71	-71	-171	-87	-86	-114
S(5)C(6)C(7)S(8)	-59	-59	48	-61	-48	-44
C(6)C(7)S(8)C(9)	158	158	75	172	150	159
C(7)S(8)C(9)C(10)	-65	-65	-80	-62	-62	-59
S(8)C(9)C(10)C(11)	-40	-40	-36	30	-42	-33
Energy/kcalmol^{-1}	10.71	11.58	12.84	14.64	20.21	17.89

the isomers at 300 K, and it is likely that, at this temperature, these conformations will not undergo any significant changes.

The next attempt at preorganisation replaced the central C(4)S(5)C(6) unit of the endo form of 1 with tetrahydrothiophene.

Ligand 4

RR isomer: The Elastic Bond for the conformational search was C(1) – C(12), and the distance monitored to exclude unwanted conformations was S(2). . .C(13). The cut-off distance was 5.5 Å. In the lowest-energy conformation (J, Fig. 3, 20.21 kcalmol^{-1}) located by the search, the three sulfur atoms were all endodentate, as required, and superimposed well on equivalent atoms in the endo form of **2**, no S. . .S separation being more than 0.2 Å. The next conformation (K, Fig. 3) has an energy of 21.14 kcalmol^{-1}, and has the sulfur atom S(2) exodentate. Table 1 lists the energies of the ten lowest-energy conformations. The endo form of this ligand was used to initiate a 500 ps MD simulation, at 300 K, and inspection showed that this conformation did not undergo any significant conformational change.

Table 3 Interatomic S . . . S distances in **2, 3** and **4**.

Distance	*2(B)*	*RR(3)*	*SR(3)*	*RS(3)*	*RR(4)*	*SR(4)*
S(2)—S(5)	3.195	3.195	3.075	3.328	3.131	3.206
S(2)—S(8)	4.854	4.854	4.990	4.652	5.003	4.811
S(5)—S(8)	3.232	3.232	3.076	3.328	3.011	3.044

SS Isomer: This isomer is the mirror image of the RR isomer, so its lowest energy conformation again meets the requirements for metal binding.

SR isomer: Exactly the same conformational search procedure that was used for the RR isomer was applied to this isomer. The lowest-energy conformation (L, Fig. 3, steric energy 17.89 kcalmol^{-1}) is the desired conformation, with all three sulfur atoms endodentate, and the interatomic separation of these sulfurs is very similar to that seen in the endo form of **2**. The next conformation, with S(2) exodentate, (M, Fig. 3) has a noticeably higher energy, 20.00 kcalmol^{-1}. The energies of the ten lowest-energy conformations are shown in Table 1. The 500 ps

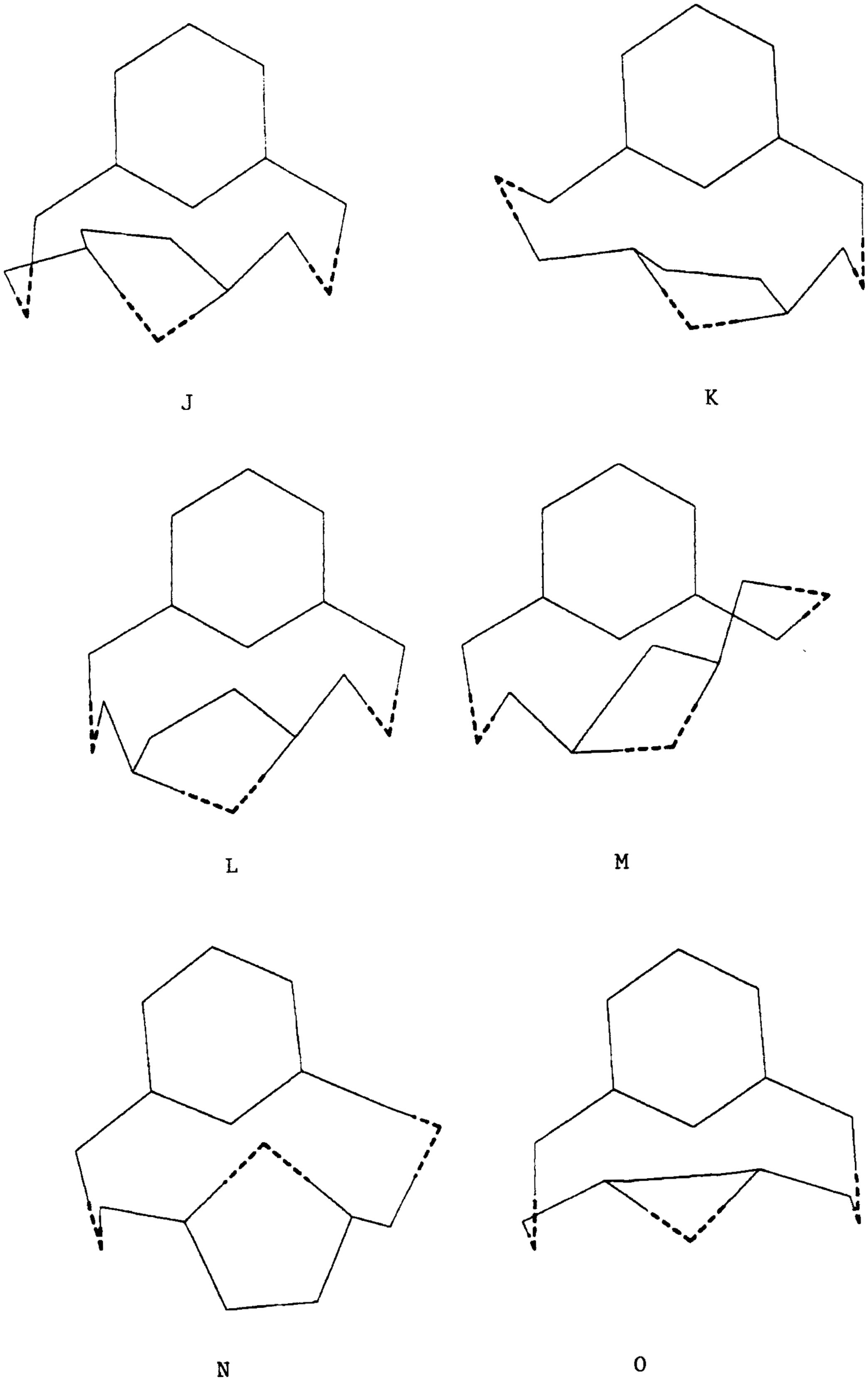


Figure 3 Conformations J to O of ligand **4**

300 K molecular dynamics simulation showed that the lowest-energy conformation of this isomer did not undergo any significant change, with the sulfur atoms S(2) and S(8) moving only very slightly.

RS isomer: The lowest-energy conformation (N in Fig. 3, 20.46 kcalmol^{-1}) located by the conformational search has one sulfur in an exo conformation, thus this isomer of ligand **4** does not meet the requirements for binding to silver. The energy of the desired conformation, (O in Fig. 3) with the sulfur atoms endo, is 28.45 kcalmol^{-1}, so it is unlikely that this conformation will be seen (see Table 1 for the ten lowest-energy conformations).

Unlike ligand **3**, where each of the isomers meets our specifications for the arrangement of the sulfur atoms, only the RR(SS) and SR isomers of **4** are suitable. The molecular dynamics simulations performed on RR and SR suggest the lowest-energy conformations will retain the desired conformation at 300K.

Replacing the C(4)S(5)C(6) unit of **2** with the unsaturated heterocycle thiophene was investigated (ligand **5**). In the lowest energy conformation of this macrocycle (11.73 kcalmol^{-1}) the two aromatic rings are approximately parallel, and the two thioether sulfurs are exo. The conformation with these two sulfurs endo has an energy of 14.28 kcalmol^{-1}. With such a difference in energies, the endo form of this macrocycle will not occur in significant quantities in the population of **5**. Substituting bulky alkyl groups (*t*-butyl) on either ring did not force the endo form to have a lower energy than the exo form, but actually accentuated the energy difference between the two conformations.

The numbering scheme for ligand **2** was preserved in the numbering of ligands **3** and **4** to facilitate geometric comparisons (Tables 2 and 3). In the crystal structure of **2** (conformation A), the SCCS torsions are anti, but in the isomers of **3** and **4** that are detailed in Table 2, these SCCS torsions have been forced gauche (as seen in the endo conformer, B, of **2**) by the ring fusion. The behavior of the CCSC torsions is dependent on the nature of the ring junctions, thus the C(3)C(4)S(5)C(6) and C(4)S(5)C(6)C(7) torsions are both gauche in the SR isomers of **3** and **4**, but in the RR isomers one torsion is anti and the other gauche; in the RS isomer of **3** each torsion is anti. Cooper's empirical rules (3) should be amended for such new steric situations. In Table 3 are collected the interatomic S. . .S distances for all the lowest-energy conformers of the isomers of **3** and **4** in the endo form, which are comparable to those of the starting, endo, conformer of ligand **2**.

Macrocycle hole size

In order to calculate the optimum metal-sulfur distance for ligands **3** and **4**, the method of Drew et al[37] was used. The M-S bond stretching force constant used was 2500 kcalmol^{-1} Å^{-2}, making it the predominant term in energy calculations. This is of the order of ten times the value that might be expected for this term. The macrocycle must then adjust to meet the optimum bond length, and the resulting steric energy is an indication of the strain induced in the macrocycle by fitting with the enforced bond length. By varying the bond length and minimising each time, it is possible to calculate which M-S distance causes the least strain in the macrocycle. For the SR isomer of ligand **3** in an octahedral ML_2 complex, the M-S bond length was increased from 2.2 Å to 3.5 Å in steps of 0.1 Å. In the region of least strain further minimisations were performed at intervals of 0.05 Å. From the resulting plot of Energy versus M-S distance (Figure 4), this method suggests an optimum bond distance of 2.80 Å. For the SR isomer of **4** in octahedral environment, the optimum M-S distance is 2.76 Å. In the case of ML complexes of the SR isomers of **3** and **4**, the optimum M-S bond lengths are 2.95 Å and 2.90 Å respectively.

Few metal ions consistently adopt M-S bond lengths similar in magnitude to the optimum values calculated above for ligands **3** and **4**. In the Cambridge Crystallographic database[38] there are four examples of silver bonded solely to thioether sulfur in an octahedral environment: two crystal structures of silver sandwiched by two 1,4,7-trithiacyclononane ligands, (CCDC codes FIJTOH[39] and FITDOB[40]); bis [2,5,8-trithia[9]-*o*-benzenophane-S,S′,S″]silver perchlorate (VOZNIH);[41] and [1,4,7,10,13,16-hexathiacyclooctadecane]silver hexafluorophosphate (KAZWUD)[42]. Bond distances range from

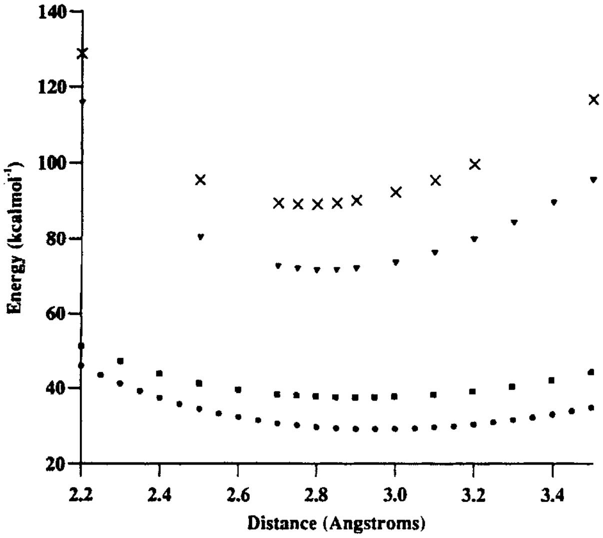


Figure 4 Plot of M-S distance versus steric energy for ML_2 and ML complexes.
Top curve: octahedral $ML_{SR}L_{SR}$, ligand **4**
Second curve: octahedral $ML_{SR}L_{SR}$, ligand **3**
Third curve: ML_{SR}, ligand **4**
Fourth curve: ML_{SR}, ligand **3**

2.666 Å (KAZWUD) to 2.787 Å (VOZNIH); the average Ag-S distance is 2.734 Å. Two crystal structures were located with mercury in a similar bonding environment, both with 9S3 (KIFCAD[43] and VEXGEK[44]). Hg-S distances vary from 2.669 Å (VEXGEK) to 2.728 Å (KIFCAD); the average Hg-S distance is 2.687 Å. Gold(II) forms a distorted octahedral complex with 9S3[45] elongated in one axial direction: the long Au-S distances are 2.839 Å; the shorter distances are 2.462 Å and 2.452 Å. In thallium[46,47] and lead[48] complexes with thioether macrocycles the M-S distances are significantly longer than Ag-S distances, ranging from 3.092 Å to 3.114 Å in Tl(9S3), 3.164 Å and 3.205 Å in Tl(18S6), and 3.015 Å to 3.129 Å in bis(1,4,7-trithiacyclononane-S,S′,S″)-bis(perchlorato-O)-lead(II). No lead complexes were found where lead coordinated only to thioether sulfur in an octahedral environment.

Thus, silver approximates well to the geometric requirements for ligands **3** and **4** in an octahedral ML$_2$ environment or in an ML species.

Parameterisation for Ag(I)

To demonstrate how silver might bind to the new ligands **3** and **4** it was necessary to derive a force field for silver, the parameters for which are given in Table 4. The application of molecular mechanics to metal complexes is the subject of two recent reviews.[49,50] Due to the unpredictability of metal coordination and the wide range of geometries involving metals, parameterisation for metals in molecular mechanics remains a persistently troublesome issue. One method of deriving good parameters is to decide on a very specific metal coordination, in this case silver bonding only to thioether sulfur, and to choose force field parameters that result in the best fit to available crystal structures. To this end a crystal structure search was performed, using the Cambridge Crystallographic database,[38] looking for silver in the appropriate bonding environment. Mixed-donor complexes that included thioether sulfurs were omitted from the search. Structures with one ligand bridging two or more silvers were excluded. Only those crystal structures with one silver ion were selected. Inspection of the endo form of the ligands shows that they are ideally suited either for octahedral coordination, in an AgL$_2$ complex, or for tridentate coordination, in an AgL complex; in the Database only seven silver-thioether complexes that fitted the search criteria were located, the four octahedral complexes described above and three tetrahedral complexes. The octahedral set were used to determine the consensus geometries used in the force field.

Table 4 Force field parameters for octahedral Ag(I) structures.

Parameter	*Force constant*	*Value*
Ag-S	250.0 kcalmol^{-1}	2.75Å
S-Ag-S (*trans*)	30.0 kcalmol^{-1}rad^{-2}	170.0°
S-Ag-S (*cis*)	30.0 kcalmol^{-1}rad^{-2}	90.0°
Ag-S-C	40.0 kcalmol^{-1}rad^{-2}	103.5°

Octahedral Ag(I)

FITDOB crystallised together with an (Ag[9S3]) trimer, which possibly induced the highly distorted octahedral coordination sphere of Ag[9S3]$_2$; the trans S-Ag-S angles all deviate markedly from the ideal 180° and certain C-S-Ag angles are significantly greater than expected. Even using the very specific criteria described above, inspection of the silver coordination sphere reveals a very wide range of geometries. For example, bond distances range from 2.666 Å (KAZWUD) to 2.787 Å (VOZNIH). No systematic description of the distortion could be found which would fit all of the four structures (e.g. axial compression is inapplicable) hence the choice of only one bond distance parameter and relatively low force constant to describe the Ag-S distance in the force field. Also, 'non-bite' angles (see Fig. 5 for definition) range from 90.09 to 116.01° (FITDOB), and Ag-S-C angles from 96.76° (FIJTOH) to 113.48° (VOZNIH). The force field for silver was derived by slightly adjusting the consensus bond length and angle values, and their relevant

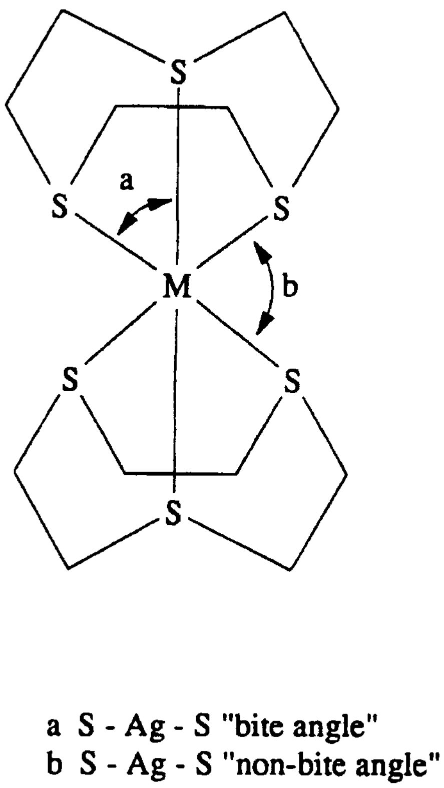


Figure 5 Definition of 'bite' and 'non-bite' angles

force constants, until the four crystal structures were reproduced. Because of the wide range of trans S-Ag-S angles seen in the four crystal structures that were used to derive the geometric terms of the force field for silver, a value of 170° was most suitable. Torsional barriers to rotation around the Ag-S bond were assumed to be zero. A charge of +0.5 was assigned to silver. Calculations were also performed which assigned a charge of 0 and +1 to silver, but varying the charge had no effect on the geometries of the minimised complexes, only on their energies. A similar result has been noted before,[51] with those authors questioning the entire rationale of including electrostatic interactions. A van der Waals radius of 1.72 Å was calculated by Bondi[52] for silver. The r_{min} values 1.0, 1.5, 2.0 and 2.5 Å were tested in this work and a 'hardness' value, E_{min} of -0.05 kcalmol^{-1}. The geometries of the minimised structures were slightly affected. The r_{min} value of 1.5 Å was used subsequently, this value being the most compatible with the CHARMm force field. It is also close to a previously calculated value[53]. The final version of the parameters is listed in Table 4. Comparisons of the crystal structures and their minimisations showed that the minimised structures are generally in good agreement with the crystal structures, except in certain geometries in FITDOB, where the crystal structure is distorted from an octahedral complex. Comparing the AgS_6 unit of the crystal structures with the minimised structures validates the terms derived for the force field: the overall r.m.s. deviations were FIJTOH 0.085; FITDOB 0.349; KAZWUD 0.102, VOZNIH 0.046. The high r.m.s. deviation seen for FITDOB is caused by the huge distortion from an octahedral geometry seen in the crystal structure. It was not possible to reproduce exactly all the Ag-S bond distances in the 4 crystal structures, although the average minimised Ag-S bond length, 2.728 Å, is very close to the average distance in the crystal structures, 2.734 Å; no minimised value deviates by more than 0.065 Å from the corresponding crystal structure value. The Ag-S-C angles are all well reproduced, to within 3° except Ag-S(4)-C(9) in VOZNIH, which is 108.74° in the crystal structure, and 113.07° when minimised. Given the great diversity of S-Ag-S values observed in the crystal structures, the minimised values are fairly reasonable approximations.

This force field was then used to predict the geometry of an octahedral complex with ligands **3** and **4**. Using the four isomers (RR, SS, RS, SR) of ligand **3**, there are ten possible combinations for an octahedral complex ($AgL_{RR}L_{RR}$, $AgL_{RR}L_{SS}$, etc). With the three isomers (RR, SS, SR) of **4**, there are 6 possible combinations for an octahedral complex (the fourth isomer, RS, has only two endodentate sulfurs, as shown in conformer N of Figure 3, and so it was not included).

Ligand 3: Although the ligands underwent little change on minimisation when forming octahedral complexes, the pairings exhibited a wide range of energies, which are shown in Table 5. (The combinations of the SS isomer with itself and with the SR and RS isomers are equivalent to the $AgL_{RR}L_{RR}$, $AgL_{RR}L_{SR}$, and $AgL_{RR}L_{RS}$ pairings, so are omitted from the table.) Inspection of this table shows that $AgL_{SR}L_{SR}$ has the lowest steric energy, 72.09 kcalmol^{-1} (Fig. 6), even though the free SR isomer has the highest global minimum energy of the isomers. The nearest combination to $AgL_{SR}L_{SR}$ is $AgL_{SR}L_{RR}$ (75.30 kcalmol^{-1}), then $AgL_{RR}L_{RR}$ (78.89 kcalmol^{-1}). The CHARMm energy of the coordinated macrocycle in $AgL_{SR}L_{SR}$ (computed for this conformation but omitting the metal ion) is 17.82 kcalmol^{-1} more strained by 3.18 kcalmol^{-1} than the ground state ligand; this is similar to the degree of strain in each ligand in $AgL_{RR}L_{RR}$, which is 3.66 kcalmol^{-1}. On coordination to silver, the $AgL_{RS}L_{RS}$ combination has the highest energy, 101.06 kcalmol^{-1}. Each ligand is strained by 7.53 kcamol^{-1}, which is mainly caused by silver coordinating to S(5), and distorting the S(5)C(6)C(18) and S(5)C(4)C(16) angles from 107.27°, seen in the free ligand, to 103.80° in one coordinated ligand and 103.89° in the other. It seems that the SR isomer is best suited to forming an octahedral complex because, although it is not significantly less strained than the RR isomer, the strain induced by forming an AgL_2 complex is significantly less than in any other pairing. In $AgL_{SR}L_{SR}$, the strain induced by complexation to silver is equivalent to the difference between the total steric energy of the complex and the global minimum energy of the macrocycles, which is (72.09 – (2×14.68)) kcalmol^{-1}, *i.e.* 42.73 kcalmol^{-1}. For $AgL_{RR}L_{SR}$, the strain of complexation is (75.30 – (11.58 + 14.68)) kcalmol^{-1}, which is 49.04 kcalmol$_{-1}$, and for $AgL_{RR}L_{RR}$ it is 55.75 kcalmol^{-1}. The minimised complex $AgL_{SR}L_{SR}$ is compressed in one axial direction: the silver-sulphur distances, 2.741 Å and 2.738 Å, are shorter than the other Ag-S distances, which ranges from 2.759 Å to 2.761 Å. In the four crystal structures used to derive the force field, the average Ag-S distance is 2.734 Å, compared with 2.753 Å in the modelled

Table 5 Steric energies of octahedral complexes of silver with **3** and **4**.

	energy/kcalmol^{-1}	
complex	*L=3*	*L=4*
$AgL_{RR}L_{RR}$	78.892	107.834
$AgL_{RR}L_{RS}$	89.287	—
$AgL_{RR}L_{SR}$	75.300	97.818
$AgL_{RR}L_{SS}$	78.935	107.788
$AgL_{RS}L_{RS}$	101.059	—
$AgL_{RS}L_{SR}$	85.055	—
$AgL_{SR}L_{SR}$	72.086	88.995

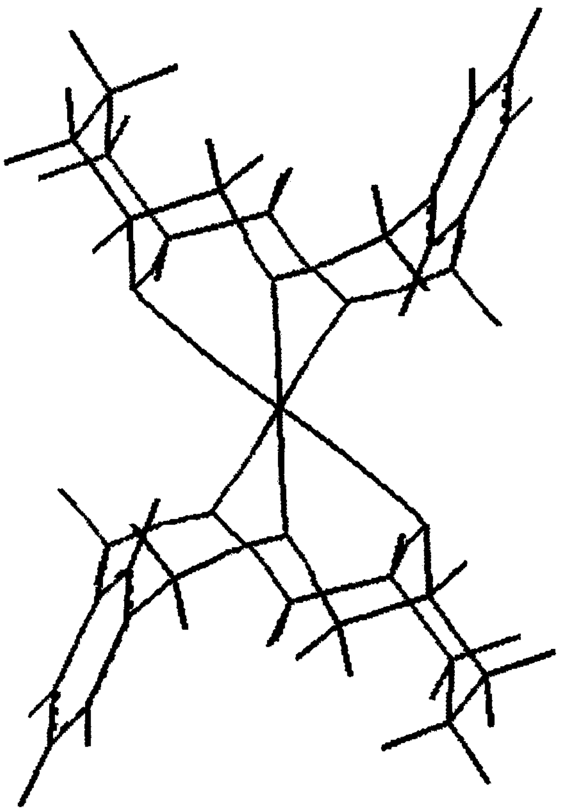


Figure 6 Octahedral complex of $AgL_{SR}L_{SR}$, ligand 3 Colour Plate III

$AgL_{SR}L_{SR}$ structure.

Ligand 4: On coordination to silver in octahedral geometry, there was again little change in the geometry of the macrocycle. The steric energies of the pairings are listed in Table 5. (Combinations of the SS isomer with itself and with SR are equivalent to $AgL_{RR}L_{RR}$ and $AgL_{RR}L_{SR}$, so are omitted from the table.) The least strained pairing is $AgL_{SR}L_{SR}$, which has an energy of 88.99 kcalmol^{-1}, which compares with an energy of 97.82 kcalmol^{-1} for the next combination, $AgL_{RR}L_{SR}$. The SR isomer in the $AgL_{SR}L_{SR}$ complex has a CHARMm energy of 24.58 kcalmol^{-1} and so is strained by 6.69 kcalmol^{-1} which is less than the strain in the coordinated RR isomer (7.26 kcalmol^{-1}) in $AgL_{RR}L_{SR}$. The steric energy of complexation in $AgL_{SR}L_{SR}$, as calculated for the equivalent complex of 3, is 53.21 kcalmol^{-1}, whereas for $AgL_{RR}L_{SR}$ it is 59.72 kcalmol^{-1}. Thus, the most favored pairing is $AgL_{SR}L_{SR}$ for this ligand. Again, the octahedron is slightly flattened: the Ag-S(5) and Ag-S(5A) distances are 2.733 Å and 2.736 Å, less than the other Ag-S distances (2.758 Å to 2.761 Å).

1:1 Complex

The force field parameters arrived at above were used to deduce a possible geometry for this complex. It was assumed that silver would coordinate to all three sulfur atoms. When in the chosen starting geometry silver was deliberately bonded to only two sulfur atoms, the third sulfur after minimisation was still less than 3 Å from silver, and it seems unlikely that the sulfur would preferentially not coordinate to silver in these circumstances.

Table 6 Steric energies of AgL complexes with **3** and **4**.

	energy/kcalmol-1	
complex	*L=3*	*L=4*
AgL_{RR}	30.762	44.773
AgL_{RS}	38.797	
AgL_{SR}	30.020	37.903

Ligand 3: The energies of the minimised structures are given in Table 6 (AgL_{SS} is equivalent to AgL_{RR} so is omitted). The lowest energy complex is AgL_{SR}, 30.02 kcalmol^{-1}, which is slightly lower than AgL_{RR}, which has an energy of 30.76 kcalmol^{-1}. The energy of the SR isomer (computed for the conformer in the complex, with the metal ion removed) is 17.07 kcalmol^{-1}, and is thus strained by 2.43 kcalmol^{-1}, which is very similar to the strain in the RR isomer, 2.46 kcalmol^{-1}. The strain of complexation, measured by the difference in energy between the minimised complex and the energy minimum of the free ligand is 19.19 kcalmol^{-1} for AgL_{RR} but only 15.38 kcalmol^{-1} for AgL_{SR}. Thus, the AgL_{SR} complex is slightly more (energetically) favorable than AgL_{RR}. Geometries of this complex do not differ significantly from those in the octahedral complex.

Ligand 4: The AgL_{SR} complex has a significantly lower energy, 37.90 kcalmol^{-1} (Fig. 7), than AgL_{RR} 44.77 kcalmol^{-1}. Although the degree of strain in each ligand is

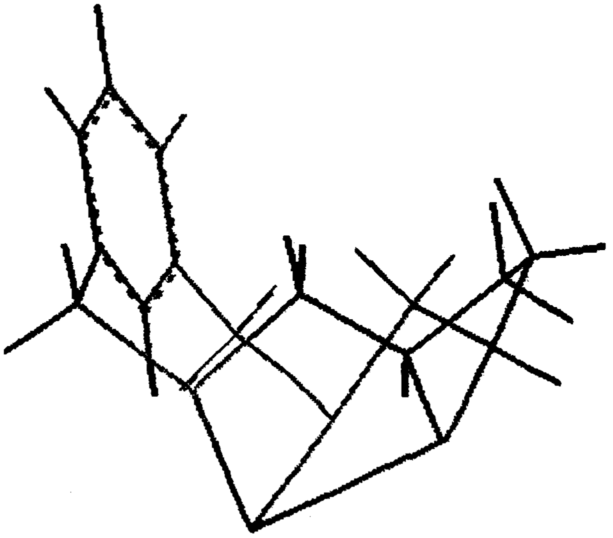


Figure 7 Complex of Ag(I) with SR isomer of ligand 4 Colour Plate IV

similar (5.12 kcalmol^{-1} in L_{SR}; 5.64 kcalmol^{-1} in L_{RR}), the energy arising from complexation to silver is significantly lower in AgL_{SR} (20.01 kcalmol^{-1}) than in AgL_{RR} (24.56 kcalmol^{-1}), so again, AgL_{SR} seems to be the favoured complex.

Tetrahedral Ag(I)

Although the new ligands were designed to coordinate in an octahedral or tridentate way, as described above, the possibility of a tetrahedral complex forming was not discounted. The inherent inflexibility of the tetrahydrothiin-containing segment of the macrocycle, atoms S(2) to S(10), means that any strain in the complex can only be relieved by forcing one ligand into a highly strained conformation. Thus it seems highly unlikely that ligand **3**, or **4**, would preferentially form a tetrahedral complex with silver, by coordinating via S(2) and S(10). If silver coordinated via S(2) and S(5), any strain induced by the tetrahedral complex might be relieved by the segment C(6)C(9)S(10)C(11) undergoing a conformational change, which might occur more readily than forcing the benzene ring into a strained position, as happened in the first attempt to deduce the geometry of the tetrahedral complex. Minimisation resulted in an obviously less strained complex, but this time both ligands had to adopt relatively strained conformations to accommodate tetrahedral complexation. The strain in the ligands was relieved by changes in the torsion angle C(6)C(9)S(10)C(11). These minimisations suggested that ligands **3** and **4** would not coordinate to silver to form a tetrahedral complex.

CONCLUSION

The new thioether macrocycles **3** and **4** described above should, according to Molecular Dynamics simulations, be preorganised in the required (endo) conformation. The conformation of the SR isomer of each ligand is tuned for binding silver(I) in preference to other metal ions.

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